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3. Effects of ovarian hormone therapy on skeletal and extraskeletal tissues in women

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Abstract • Résumé

Objective: To present recent evidence on the use of ovarian hormone therapy (OHT) for osteoporosis and outline safe and effective regimens.

Options: Estrogen alone, estrogen and progestins, progestins alone; various treatment regimens.

Outcomes: Fracture and loss of bone mineral density in osteoporosis; increased bone mass, prevention of fractures and improved quality of life associated with OHT.

Evidence: Relevant clinical studies and reports, including the Nurses' Health Study and the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, were studied with emphasis on recent prospective, randomized, controlled trials. Current clinical practice was determined by survey.

Values: Reducing fractures, increasing bone mineral density and minimizing side effects of treatment were given a high value.

Benefits, harms and costs: Proper management of osteoporosis minimizes injury and disability, improves quality of life and reduces the personal and social costs associated with the condition. OHT is the front-line pharmaceutical therapy for prevention and treatment of osteoporosis in post-

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menopausal women. In those who are able and willing to comply with therapy, OHT prevents bone loss and fractures. Hormone therapy may also decrease risk of coronary artery disease. Cyclic progestin protects against endometrial cancer in patients receiving estrogen. Potential harms include breast cancer and endometrial cancer related to dosage and duration of therapy. Mastalgia and especially resumption of menstrual bleeding affect compliance.

Recommendations: Use of OHT should be considered as early as possible in the perimenopausal period for women at increased risk of osteoporosis. Guidelines are provided for assessment of osteoporosis risk. Physicians and their patients should take into account the absolute and relative contraindications to OHT. Women with a uterus should be given estrogen in combination with a progestin. Ideally, therapy would be continued for a minimum of 10 years beyond menopause for maximum bone protection. Women using OHT should be carefully monitored and evaluated for possible adverse events. This should include regular screening mammography, breast examination and, for some, endometrial surveillance. Specific dosages and treatment regimens are outlined.

Validation: These recommendations were developed by the Scientific Advisory Board of the Osteoporosis Society of Canada at its 1993 Consensus Conference. They take note of the Menopause Consensus Statement of the Society of Obstetricians and Gynaecologists of Canada (May 1994).

Sponsors: Sponsors of the 1993 conference included Merck Frosst Canada Inc., Procter & Gamble Pharmaceuticals Canada Inc., Rhône-Poulenc Rorer Canada Inc., Eli Lilly Canada Inc., Sandoz Canada Inc., Ciba-Geigy Canada Ltd., Ortho-McNeil Inc., the Dairy Bureau of Canada, Wyeth-Ayerst Canada Inc. and Lederle Laboratories.

There are still some major areas of uncertainty regarding the use of ovarian hormone therapy (OHT). However, treatment with estrogen after menopause prevents bone loss and fractures, and OHT is the front-line pharmaceutical intervention for both prevention and treatment of osteoporosis in postmenopausal women. Majority opinions are available on the role of progestational agents and the effect of OHT on the incidence of heart disease and breast cancer, but more evidence is needed. The members of the Scientific Advisory Board of the Osteoporosis Society of Canada (OSC) await the outcome of long-term randomized controlled trials of OHT, such as the Women's Health Initiative in the United States, with great interest, and hope that the key issues of heart disease prevention and breast cancer risks will be resolved. Until these prospective studies are completed, we believe that the following report summarizes the best available evidence on which to base recommendations to our patients.

Health care workers and their patients must understand that OHT, except for women with premature menopause, is not simply a replacement, but rather an active treatment taken for specific purposes. When hormone therapy is chosen to manage problems related to menopause, the method of prescribing the drugs should be tailored to the problem being addressed. In the case of osteoporosis prevention and treatment, the aim is not to replicate the premenopausal cycles of estrogen and progesterone, but to provide the lowest and safest level of ovarian hormone dosage that will protect against osteoporotic fracture. Other regimes may be more appropriate for shorter-term management of symptoms of menopause. Menopause is a natural event and, based on current knowledge, the majority of women do not require treatment with estrogen and progesterone for symptomatic relief.

Osteoporosis and menopause

Osteoporosis occurs when the normal processes of bone formation and bone resorption become unbalanced and resorption exceeds formation. These processes are complex and are influenced by a number of hormonal, metabolic and lifestyle factors. Low levels of ovarian hormones (estrogen and, possibly, progesterone) are recognized as key factors in the development of osteoporosis, whether caused by surgical removal of the ovaries or through the natural decline in estrogen and progesterone production during menopause.

It is now clear that conjugated equine estrogen (CEE) therapy, given at a minimal effective dose of at least 0.625 mg/d (or its equivalent), increases or preserves bone density in all areas of the skeleton that have been studied. More important, the risk of osteoporotic fractures of both wrist and hip is reduced by 50% to 60% in women who begin estrogen therapy within the first 3 years of menopause and who continue therapy for 6 to 9 years.[1,2] Vertebral fractures are also significantly reduced.[3,4]

In preventing fractures due to osteoporosis, OHT with estrogen (and progestin in women with a uterus) should be given for a minimum of 5 to 10 years after the last menstrual period to obtain the most benefit. More recent evidence suggests that hormone therapy given to women many years past menopause also appears to have a beneficial effect on bone.[5,6] Further research is needed before progestins alone can be recommended for the prevention of osteoporosis.

The OSC is convinced that hormonal therapy is currently the most effective preventive strategy against osteoporosis for women immediately following menopause.

Nevertheless, hormonal therapy is not widely ac-

cepted in Canada, largely because of perceived risks, undesirable side effects, inconvenience and poor information. The Scientific Advisory Board has evaluated the risks and benefits of using hormone therapy in light of currently available evidence and made recommendations based on that evidence.

Ovarian hormone therapy in younger women

Our current understanding is that women need 35 to 40 years of reproductive hormone levels for optimum bone health. Women with hypogonadism at any age prior to menopause are at increased risk for osteoporosis and should be given OHT at least until the average age of menopause (50 years). At that point a decision can be made about continuation of the therapy.

In addition to premature menopause, women with gonadal dysgenesis (Turner syndrome and other variants), prolactin-producing pituitary tumours and hypothalamic disturbances of reproduction need therapy. Although all agree that those with permanent impairment of reproduction need full OHT, there has been no consensus on therapy for reversible disturbances related to stress, dieting and overexercise, which are commonly untreated or are treated with oral contraceptives. Although prospective observational studies[7] suggest that oral contraceptives may be of benefit, no randomized controlled trials have been carried out. A recent double-blind, randomized, placebo-controlled trial[8] has shown that cyclic medroxyprogesterone, 10 mg/d for 10 days a month, increases spinal bone density (measured by dual-energy x-ray absorptiometry) in physically active women of normal weight with hypothalamic menstrual cycle disturbances ranging from amenorrhea to regular cycles with short luteal phases ($n = 61$, $p = 0.004$). Women with these hypothalamic changes need therapy because, despite normal weight, good exercise and good dietary intake of calcium, the placebo-treated women lost an average of 2% per year of their spinal bone.[8]

Endometrial cancer

The use of estrogen alone significantly increases the risk of endometrial cancer. This risk increases with dose and duration of use. After 5 or more years of use, there is at least a fivefold increase in risk of endometrial cancer.[9]

The best available evidence shows that cyclic progestin, given in doses of 5 to 10 mg/d of medroxyprogesterone acetate (MPA) (or an equipotent progestin) for 12 to 14 days each month, prevents the development of endometrial hyperplasia and endometrial carcinoma. Adequate endometrial surveillance should also be carried out if lower doses or durations of progestins are used. At present, the endometrial biopsy is the method of choice to evaluate the endometrium. However, vaginal ultrasound, hysteroscopy and dilatation and curettage (D and C) can also be used. More evidence is required to determine whether alternative progestin regimens, such as those using lower-dose cyclic or continuous combined progestin, are equally effective in preventing endometrial cancer.[10–14]

Breast cancer

Probably the most significant deterrent to more prevalent use of postmenopausal OHT is the fear of increased risk of breast cancer. Unfortunately, reports in this area are conflicting, and it is difficult to make a conclusive statement regarding the relation between breast cancer risk and the use of estrogen, alone or in combination with a progestin. Data from the Nurses' Health Study (representing 12 years of follow-up in 30 000 women) did reveal an increased risk of breast cancer among women still taking estrogen compared with women who had never taken estrogen. However, no increase was observed in women who had previously taken postmenopausal estrogen but who had discontinued therapy.[15]

The authors of one of two meta-analyses examining this issue concluded that the risk of breast cancer was increased only after 15 years of estrogen use, but not after a shorter period.[16] In contrast, the author of the second meta-analysis stated that 0.625 mg or less of CEE per day did not increase the risk of breast cancer in postmenopausal women.[17]

Based on our current knowledge, it can be said that after 15 or more years of hormone therapy there may be an increased relative risk of breast cancer of 1.2 to 1.3.[9] It is possible that higher doses of estrogen (i.e., more than 0.625 mg CEE/d) may be associated with a higher relative risk of breast cancer. The concomitant use of progestin has not been shown to have either a beneficial or an adverse effect on risk of breast cancer. In summary, the relation between estrogen use and breast cancer risk remains controversial. More long-term, carefully controlled studies are required to settle the issue.

Coronary artery disease

Over the past 10 years, evidence has pointed to a protective effect of hormone therapy with respect to coronary artery disease (CAD). To date there have been no published randomized, double-blind, placebo-controlled studies of the effects of estrogen therapy on CAD risk. Therefore, findings must be interpreted cautiously.[18] Nevertheless, meta-analysis of available studies indicates a lower rate of CAD risk among estrogen users than among nonusers.[9,19]

More long-term studies of the role of hormone therapy in CAD are needed. Randomized, placebo-con-

trolled studies are underway in the United States. In the meantime, women should be encouraged to make healthy lifestyle choices, such as ensuring optimal calcium intake, reducing fat intake, eliminating tobacco use, exercising regularly and avoiding obesity to reduce their risk of developing CAD and to help preserve bone.

Hormonal regimens

For women with an intact uterus, a progestin should be added to estrogen in OHT to prevent the development of endometrial hyperplasia and carcinoma. The current recommendation of the OSC's Scientific Advisory Board is to give estrogen continuously and combine it with cyclic progestin taken on days 1 to 12 of each month. Another commonly prescribed North American regimen is to give estrogen from day 1 to day 25 of the month, along with a progestin given from day 12 or day 14 to day 25. Mastalgia (breast tenderness) may be reduced with a brief estrogen-free interval. However, this regimen may result in a return of vasomotor symptoms during the hormone-free period, and it is possible that some bone benefits may be lost during this interval. The rationale for an estrogen-free interval would be to control mastalgia, if that is a problem on the continuous estrogen regime, or perhaps to provide a more predictable cycle of bleeding.

Current consensus is that estrogen alone is appropriate for women who have had a hysterectomy. Recent evidence suggests that progesterone may also have a beneficial effect on bone,[20] but further research is needed in this area. The available evidence suggests that 0.625 mg of CEE or its equivalent is the minimum effective dosage required to prevent osteoporosis.[21,22]

Compliance

The addition of cyclic progestin to either a continuous or cyclic estrogen regime will result in regular withdrawal bleeding in 50% to 80% of women. Bleeding becomes less prevalent with increasing duration of treatment.[11] Withdrawal bleeding may be undesirable for some women and is one of the major reasons for women discontinuing OHT. Therefore, regimens that do not promote withdrawal bleeding may be considered. Lack of bleeding may be achieved by using a continuous, combined estrogen/progestin regime.

In North America this regimen of continuous, combined OHT is usually prescribed as 0.625 mg of CEE (or its equivalent) and 2.5 mg MPA per day. Although more than 40% of women receiving this therapy experience irregular breakthrough bleeding for the first 3 to 6 months of therapy, subsequently the endometrium is usually rendered atrophic and most patients become amenorrheic by the 12th month.[22] The continuous, combined regimen has not been as extensively studied as the cyclic regimens, but is often most acceptable to the woman who is well past menopause and who does not wish to resume cyclic menstrual bleeding. This approach will also usually decrease the incidence of troublesome breakthrough bleeding. Accordingly, the continuous, combined approach is ideal in the older woman for secondary prevention of osteoporosis, as it has been shown to maintain beneficial effects on bone.[23]

Timing of hormone therapy

Studies indicate that osteoporosis is best prevented if hormone therapy is initiated at the time of menopause and continues for at least 5 to 10 years. Menopause is defined as the last menstrual period. Levels of follicle-stimulating hormone in the blood can be helpful in defining onset of menopause in the woman without a uterus. When these begin to rise above the base-line level and are greater than 20 or 30 IU/L, the diagnosis of menopause is certain.

In women who are identified as being at increased risk of osteoporosis, hormone therapy (usually with cyclic progesterone to control flow) should be considered even before menopause; that is, in the perimenopause stage, when average levels of ovarian hormones and gonadotropins are beginning to rise. Longer-term therapy (more than 10 years) is likely required to achieve maximum benefit for the prevention of osteoporotic fracture.[24] However, because the risk of breast cancer may increase with more than 10 to 15 years of hormone use, long-term therapy must be carefully scrutinized and evaluated on an individual basis, always bearing in mind the risk to benefit ratio. This is especially important in patients with premature ovarian failure and early menopause, as long-term use of OHT for the maintenance of bone health becomes paramount.

Individual evaluation

Hormone therapy is one of several factors that contribute to bone health. Therefore, OHT should be considered after a physician has carefully reviewed a woman's complete health history, carried out a physical examination and weighed the potential benefits and risks with the particular patient. Because there are definite contraindications for some women and because some women will avoid the problem of osteoporosis without the use of this therapy, the OSC does not recommend the use of OHT for all postmenopausal women. According to the Menopause Consensus Statement of the Society of Obstetricians and Gynaecologists of Canada,[25] all physicians prescribing OHT should be aware of the updated absolute and relative contraindications. A history of thromboembolism and uterine cancer are no longer absolute contraindications to estrogen therapy.

Absolute contraindications to estrogen therapy[25]

- unexplained vaginal bleeding
- active liver disease
- carcinoma of the breast
- active vascular thrombosis

Relative contraindications to estrogen therapy[25]

- migraine headaches
- history of thromboembolism
- familial hypertriglyceridemia
- uterine leiomyomas (fibroids)
- endometriosis
- gall bladder disease
- uterine cancer
- strong family history of breast cancer
- chronic hepatic dysfunction

Summary

Osteoporosis is a common bone disorder in postmenopausal women, resulting in decreased bone strength and increased susceptibility to fracture. It is a major health problem in Canada, causing fractures, disability, pain and deformity in a growing number of people. Hip fractures related to osteoporosis are a serious problem in older populations, resulting in death in 12% to 20% of cases and disability in up to 75% of surviving patients. Osteoporosis affects approximately one in four women after menopause, and it is estimated that as many as two million Canadians may be at a risk of osteoporotic fracture during their lifetime.

Further research is necessary to confirm more precisely the benefits and risks of OHT in the postmenopausal period. In the meantime, the OSC recognizes that Canadians need and deserve current scientific information upon which to base decisions relating to their own health.

Despite the recognized limits of our current knowledge, the Scientific Advisory Board believes that it is possible, based on current evidence, to make recommendations for the use of OHT to help protect against osteoporosis. Continued and intensified research will allow these recommendations to be revised periodically in light of scientific advances.

Conclusions

- Women and their physicians should discuss the use of OHT as early as possible in the perimenopausal period.
- Older women with low bone density may gain benefit from hormone therapy even years after menopause. More long-term data are needed to determine whether there is a limit to the time after menopause that hormone therapy should be considered.
- A dosage of 0.625 mg of CEE (or its equivalent) per day is the minimum level to achieve a beneficial effect on bone; lower doses (0.3 mg/d) may be beneficial if a calcium supplement (1500 mg/d) is given concurrently, but this requires confirmation.
- Estrogen therapy alone (without a progestin) is appropriate for women who have had a hysterectomy. For women with a uterus, estrogen should be given in combination with a progestin.*
- Together with daily estrogen, progestins may be given cyclically or continuously to reduce the risk of endometrial hyperplasia. A cyclic regimen should consist of MPA (or equivalent) at 5 to 10 mg/d, taken from day 1 through 12 to 14 of each month. For some patients with mastalgia, a pill-free interval may be beneficial; for example, CEE at 0.625 mg/d from day 1 to 25, and Provera (MPA) from day 12 or 14 to 25. A continuous progestin regimen using 2.5 mg of MPA/day, together with daily estrogen (0.625 mg of CEE), has been shown to render the endometrium atrophic by 6 months. Within 12 months 95% of women will be amenorrheic.
- OHT should be continued for a minimum of 10 years beyond menopause for maximum bone protection. If there is no strong indication for discontinuing hormone therapy, it should be continued for up to 15 years or even longer. However, further long-term data are needed to assess the safety and efficacy of longer-term OHT, especially regarding risk of breast cancer.
- The OSC does not recommend OHT for all postmenopausal women. However, those judged to be at increased risk of osteoporosis should be encouraged to consider OHT. Although precise estimates of osteoporosis risk for each person are not possible, several factors associated with increased risk have been identified. These include early menopause, physical inactivity, strong family history of osteoporosis, heavy alcohol intake, poor calcium nutrition and cigarette smoking. Women of Caucasian or Asian ethnic origin have a higher risk than black women. The best predictor of osteoporosis risk is the measurement of bone density.
- OHT is considered to be of extreme importance for women with premature menopause (autoimmune, surgically or medically induced) and young women with hypogonadism of any cause, because of the serious adverse skeletal effects of long-term estrogen deficiency. This includes women with hyperprolactinemia, Turner syndrome and diet-, weight- or exercise-related hypothalamic amenorrhea or menstrual dysfunction.

**One of us (J.C.P.) believes that benefits are derived from progesterone in many tissues and, therefore, it is indicated for postmenopausal women who have had a hysterectomy. The majority position is expressed above.*

- If OHT is being used in the prevention or treatment of osteoporosis, women should be carefully monitored and evaluated for possible adverse events. Routine screening mammography should be carried out regularly, according to provincial guidelines. Breast examination should be part of a regular assessment by a physician and women should be taught breast self-examination techniques. Endometrial surveillance is important, and appropriate hormonal withdrawal bleeding should be noted. Any unscheduled uterine bleeding should be appropriately investigated.
- Physicians are urged to keep abreast of current concepts in hormone therapy and menopause. The benefits of OHT for the prevention of osteoporotic fractures are well established. It is important for physicians to be aware of ongoing changes in knowledge and practice.

Since the 1993 consensus conference, a 3-year randomized, double-blind, placebo-controlled trial of various commonly used OHT schedules and doses has been published.[26] Subjects in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial received placebo or oral conjugated estrogen therapy, alone or with cyclic or continuous MPA or natural progesterone. The effect of treatment on cardiovascular risk factors (lipid profile, fibrinogen, blood pressure, insulin), as well as endometrium and bone were studied.

All forms of hormone therapy improved lipid profile (increased HDL cholesterol and lowered LDL cholesterol levels) and lowered fibrinogen levels, although medroxyprogesterone significantly blunted the increase in HDL cholesterol levels. Unopposed estrogen therapy produced a high incidence of endometrial hyperplasia requiring investigation or therapeutic intervention. The results of effects on bone density have only been reported in abstact form; an increase in bone density of 5% to 6% was found in all treatment groups among subjects who took at least 80% of their assigned treatment.[27] Based on this analysis, there was no difference in bone density between those taking estrogen alone and those taking estrogen plus progestin.

In another report, which was widely publicized in the lay press, investigators from the Nurses' Health Study reported a relative risk ratio for breast cancer that was higher than previous estimates.[28] They suggested that the relative risk might be as high as 1.46 for women currently taking estrogen or estrogen plus progestin for more than 5 years. Progesterone use neither increased nor reduced this risk. Oddly, past use of estrogen, for as long as 10 years or more, was not associated with any increase in risk. Clearly, there is a need for a randomized, prospective, controlled clinical trial to settle the issue of risk of breast cancer for women given estrogen–progestin therapy, and we await the results of the Women's Health Initiative with great interest.

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