

# Estrogens as first-choice therapy for osteoporosis prevention and treatment in women under 60

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## ABSTRACT

A case is made for estrogens to be the first-choice therapy for the prevention and treatment of osteoporosis in women below the age of 60 years. Estrogens produce a dose-related increase in bone density and also, by their effect on collagen, have a beneficial effect not only on the bone matrix but the intravertebral disc. Bisphosphonates do not have that effect upon the disc. Estrogens are also associated with other beneficial effects upon mood, vasomotor symptoms, pelvic atrophy, sexuality and quality of life. The data from the Women's Health Initiative (WHI) study are used as a justification for not using estrogens but the neglect of estrogen therapy by physicians antedated this and other studies by many years. Subsequent publications from the WHI study show that hormone replacement therapy, particularly estrogens alone, is not associated with the excess side-effects found in the older population. The substantial but non-significant decrease in heart attacks, breast cancer and mortality in women under the age of 60 taking estrogens alone should persuade the advisory bodies to revise their judgment on the benefits and safety of hormone replacement therapy in this population.

In spite of the evidence that estrogens produce the greatest, the most prolonged and most predictable dose- and duration-dependent increase in bone density<sup>1</sup> and have been shown to be effective in preventing osteoporotic fractures of the hip and spine in a study of low- and mixed-risk women<sup>2</sup>, their use has been relegated to second-line therapy by advisory bodies. It has become even unacceptable therapy in the minds of bone physicians and rheumatologists. This is principally the result of the post Women's Health Initiative (WHI) recommendations that hormone replacement therapy (HRT) should be used as a short-term treatment for menopausal symptoms, using the lowest dose for the shortest time necessary and that it may be used as a second-line treatment for

osteoporosis for those who are unable to tolerate other drugs such as bisphosphonates<sup>3</sup>. Virtually all advisory bodies reinforced this proscriptive advice but a further review of the available data does not support this view, particularly in women under the age of 60 years, as estrogens are effective, safe and have many other health advantages.

There may be a sincere anxiety about safety but, in reality, the physicians' objection to HRT antedated the WHI studies by many years. Could it be that bone physicians like psychiatrists were not comfortable with the minor side-effects of HRT such as mastalgia, bleeding, and the premenstrual syndrome-type symptoms of progestogen intolerance, which could be dealt with by any competent general practitioner<sup>4</sup>? All health

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professionals are products of their teaching and training, with pelvic examinations and ultrasound investigations being unfamiliar territory for physicians dealing with osteoporosis. The misinterpretation of the WHI data served to justify this gap in their practice and has been used to virtually exclude the use of estrogens for the treatment of low bone density. These data, together with the breast cancer data from the equally criticized Million Women Study<sup>5</sup> and the low cost of once-weekly Fosamax, have enabled the National Institute for Health and Clinical Excellence (NICE) committee to virtually ignore hormones from their assessment.

Although the benefits of lifestyle changes on the skeleton may be less dramatic, they should not be ignored and patients should, of course, be given advice on alcohol, smoking and exercise as well as calcium and vitamin D supplementation. But in this article, the additional advantages of estrogen therapy will be discussed.

Any treatment by hormones should recognize that different symptoms and indications need different hormones in different doses by different routes, depending on the age and surgical status of the woman<sup>6</sup>. These may include progestogen and testosterone as well as estrogen. Transdermal estrogens produce a better endocrine and coagulation profile than oral therapy; daily progestogen may be less safe than sequential and is not required in women after hysterectomy; that may be safer still. Older patients usually need a smaller dose of these hormones. Transdermal testosterone can be added for the common menopausal problems of loss of libido and loss of energy. Therapy should be individualized, as the 'one dose fits all' treatment of asymptomatic 50–79-year-olds used in the WHI study was the cause of all the confusion. It was a study of considerable clinical incompetence from which women, now denied HRT for various problems such as perimenopausal depression, sexual problems and osteoporosis, continue to suffer.

Typical menopausal symptoms of flushes, night sweats, insomnia, tiredness together with pelvic atrophy causing dyspareunia and recurrent cystitis respond well to low-dose estrogens. Depression, loss of libido and other quality-of-life issues usually are helped with estrogens, often with the addition of testosterone<sup>7</sup>. In fact, most patients on the correct dose and mixtures of hormones feel so well that they are unwilling to discontinue HRT after 10 years, even after they claimed to be aware of the putative risks<sup>8</sup>. The advisory bodies have not considered these quality-of-life issues that are

so important for the woman's choice of continuation of therapy. There is similar support from well-informed professionals in that 80% of female gynecologists or wives of gynecologists in Sweden continue to take estrogens in spite of the WHI reports<sup>9</sup>. Hence, there is a reluctance for these gynecologists to prescribe bisphosphonates as first-choice therapy or women to take such therapy if coexistent symptoms are thought to be responsive to estrogens. Further clarity of the risk-benefit ratio is required to solve the dilemma in this under-60 age group.

In the first 5 years after the menopause, women lose 30% of their skin thickness and collagen<sup>10</sup>. This is also evident in collagen loss most notably from ligaments, tendons, nails, the intervertebral discs and the bone matrix. It has been shown that estrogens can replace the missing skin collagen and skin thickness<sup>11</sup> but how does the skeletal system benefit from preservation or replacement of collagen?

Histomorphometric studies of biopsies of osteoporotic women taken before and after 6 years' percutaneous estradiol, when the spinal bone density has increased by 28%, showed a 26% increase in collagen in cancellous bone and a 7% increase in cortical bone<sup>12</sup>. There was also an increase in intermediate and mature collagen cross-links, indicating continuing collagen production<sup>13</sup>. Similar biopsy studies of patients with a mean increase in vertebral bone density of 29% over 6 years showed an increase in wall thickness, volume of cancellous bone and trabecular thickness. The repair of the micro fractures of osteoporotic bone is strongly suggested by the increase in trabecular buds and the decrease in trabecular ends<sup>12</sup>. This indicates that the therapy is not merely thickening broken trabeculae but new strong bone is being produced. All of these quantifiable beneficial changes have a direct significant correlation with the plasma estradiol levels achieved during therapy. There are no such studies of bone histology showing comparable benefits from bisphosphonates.

More recent work on the intervertebral disc is equally reassuring. The discs are 100% collagen and make up one-quarter of the length of the spine. Studies performed have shown that estrogens protect the spine by maintaining the size of the individual and total disc space and the length of the spine<sup>14</sup>. Bisphosphonates do not.

There remains debate whether the increase in bone density is maintained after cessation of HRT. Banks and colleagues, offering no appropriate data from their single-questionnaire Million

Women Study, claim that the skeletal benefits are lost 'rapidly'<sup>15</sup>. This is surprising as even 5 years of a moderate estrogen dose will increase bone density by 6–10%. The bone mass will decrease by 1–3% per year but there will not be any accelerated loss. Bagger and colleagues<sup>16</sup> provide follow-up data from four previous trials, reporting that 2–3 years of estradiol therapy produced a higher bone density and lower fracture rate than in the placebo group 5 and 12 years after stopping therapy.

On this evidence, HRT would seem to have a better effect on flesh and bone, general well-being, mood and sexuality than non-hormonal options. But is it safe?

The optimism of HRT has been challenged by the WHI<sup>2</sup> and Million Women Study<sup>5</sup>, which revealed an increase in breast cancer and surprisingly an increase in heart attacks and strokes when all but one of 30 case-control studies indicated a considerable decrease in heart attacks. Indeed, the data on heart attacks had been so convincing that the primary and secondary prevention of coronary disease became a principal indication for HRT, particularly in the USA.

The data collection from a single questionnaire of the Million Women's Study is so eccentric and has been so severely criticized that it is difficult to judge the value of any of the conclusions from these papers<sup>17</sup>, but certainly the study over-estimated the risk of breast cancer, as the extrapolation of these data from a single questionnaire is unsound regardless of the size of the study.

On the other hand, the epidemiology of the WHI study as a randomized, controlled study was sound but the investigators chose asymptomatic patients of the wrong age, with 22% starting therapy over the age of 70, using the wrong dose and coming to the wrong conclusions<sup>6</sup>. Even though the Prempro combination of Premarin 0.625 mg and Provera 2.5 mg as continuous therapy is not an available or ideal preparation, there was still an excellent result in patients who

start this therapy below the age of 60, with fewer heart attacks occurring, a slight insignificant increase in breast cancer and a significant reduction in fracture of the hip and spine, colon cancer and mortality<sup>17</sup>.

It seems from various studies that progestogen in HRT preparations is the risk factor for breast cancer. Thus, the estrogen-only arm of the WHI study showed a significant decrease in osteoporotic fracture and a considerable yet insignificant decrease in breast cancer, heart attacks and mortality<sup>18</sup>. As 97% of our patients on HRT start this therapy below the age of 60, this is the important reference group in our clinical practice. Thus, there should be no proscription on the use of estrogens, particularly estrogens alone, for the prevention and treatment of osteoporosis in women under the age of 60 and advisory bodies should revise their statements about this group<sup>4</sup>.

Estrogens should be the correct first-line therapy in women under the age of 60 and the less effective bisphosphonates, which are not without long-term side-effects, should be used in women where there is the rare contraindication to estrogen therapy or those that are non-responders. It is reported that 25% of women are unsuitable for or do not have an increase in bone density with the use of bisphosphonates. This is a very rare occurrence in patients using HRT.

The rejection of estrogens as a simple safe and effective therapy in patients below the age of 60 is incorrect. It is also clear that the thrombogenic potential of Prempro, with its continuous daily progestogen and oral estrogen, is not reproduced by the use of transdermal estradiol<sup>19</sup>. It is even possible that the future treatment for the older patient with osteoporosis may be by this non-oral route of estradiol as much as by non-hormonal preparations with their own side-effects.

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