the second trimester would give clinicians adequate time to plan further tests and treatment. This approach has the potential for routine use in non-sensitized RhD-negative pregnant women. There is scope for application of this method for the diagnosis of many disorders involving single genes.

REFERENCES

Oestrogen deficiency: An important risk marker for fractures

Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, Ettinger B. (Departments of Medicine and Epidemiology and Biostatistics, University of California, San Francisco; Department of Medicine, Veterans Affairs Medical Center and the Division of Epidemiology, School of Public Health, University of Minnesota and the Division of Research, Kaiser Permanente Medical Care Program, Oakland, California.) Endogenous hormones and the risk of hip and vertebral fractures among older women. *N Engl J Med* 1998;339:733–8.

SUMMARY
Oestrogen deficiency causes bone loss in post-menopausal women, thus increasing the risk of hip and vertebral fractures. Hormone replacement therapy (HRT) is the most important and common therapy for prevention of bone loss and its long term effects reduce the risk of osteoporotic fractures by 50%. However, high concentrations of circulating unopposed oestrogens are associated with a risk of endometrial and breast carcinoma. Hence, there is a continuous search for the minimum effective dose for reducing bone loss. Could a baseline data of circulating hormones, before the occurrence of fractures, be a predictive marker for the risk of hip and vertebral fractures and will it give an indication of the minimum effective dose of oestrogen that may suffice to prevent bone loss in elderly women? To answer this, Cummings et al., in a prospective study of osteoporotic fractures, investigated the baseline serum hormone concentration in women more than 65 years of age and followed them for 5.9 years for the occurrence of hip and vertebral fractures. The baseline values in 133 women who subsequently had hip fractures and 138 women who later got vertebral fractures were compared with randomly selected controls from the same cohort. The risk of hip and vertebral fractures increased substantially in women with undetectable serum oestradiol concentrations (5 pg/ml). Surprisingly, there was no effect of increasing serum oestradiol concentrations on the risk of fracture among women who had detectable concentrations at baseline, all of whom had a relative risk of having a fracture of 0.3 to 0.5 compared with women having undetectable concentrations. This suggests that the current recommended oestrogen dose, particularly for women over 65 years of age, may be higher than the dose required to maintain skeletal health; and a much lower dose of oestrogen may suffice to prevent osteoporosis. On the other hand, there was a linear relationship between serum concentration of sex hormone binding globulin (SHBG) and the risk of fracture. Women with both undetectable serum oestradiol and SHBG > 1 μg/dl had a much higher relative risk of hip and vertebral fractures. Low serum 1,25-dihydroxy vitamin D concentration (23 pg/ml) also indicated a higher risk of hip/vertebral fracture. An association between high serum oestrone concentrations and increased risk of vertebral fracture in this study is surprising because oestrone has effects that are similar to, though weaker than oestradiol. This may be due to lower conversion of oestrone, produced from adrenal androstenedione, to oestradiol in the post-menopausal state.

Undetectable baseline serum oestradiol concentrations and high SHBG levels in women 65 years or older appear to be good markers for the risk of hip and vertebral fractures.

COMMENT
Oestrogen is important for bone preservation and its deficiency causes bone loss in women. Hormone replacement therapy for the prevention and treatment of osteoporosis is being used increasingly.1 In 1941, Albright first related the prevalence of hip and vertebral fractures with post-menopausal gonadal deficiency and there is a large body of evidence to support this hypothesis.2 The loss of bone mineral density (BMD), particularly in the parts of the skeleton with a relatively trabecular bone content, is known to accelerate with a decline in ovarian function. This loss of BMD increases the likelihood of fractures of the hip and spine. A positive therapeutic effect of oestrogen on increasing skeletal mass and decreasing fracture rates has been demonstrated.4 Daily oral doses of 0.625 mg of conjugated equine oestrogens or oestrone, 0.5 mg or higher dose of 17β oestradiol, raising the
plasma oestradiol concentration levels to at least 40 pg/ml (147 pmol/L) or more are generally thought to be necessary for preventing bone loss.6,7 However, a higher concentration of circulating unopposed oestrogens is associated with a risk of endometrial hyperplasia, endometrial carcinoma and breast carcinoma.8,9 Thus, there is an urgent need to arrive at the lowest effective dose, specifically for women >65 years of age, which would effectively reduce the risk of fracture without increasing the risk of breast and endometrial carcinoma. This study has shown that even barely detectable levels of circulating oestrogen may be effective in reducing the risk of hip and vertebral fractures, while this risk substantially increased in women with undetectable concentration levels. Thus suggesting that in older women the risk of fracture could be reduced with even low dose oestrogen replacement therapy.

Although many studies have shown the vital role of oestrogen in bone preservation, the exact mode of action is not clear. Complete absence of oestriol has been shown to cause death of osteocytes10 which are responsible for repair of microscopic bone damage and the presence of oestriol helps to maintain the viability of osteocytes. Functional oestrogen receptors11,12 and oestrogen receptor-related protein13 have been identified in bone cells. Oestrogens may block the action of cytokines that promote the transformation of progenitor cells into osteoclasts14 which in turn are responsible for resorption of calcified bone and cartilage.

Another important marker of ‘risk for fracture’ in this study was the concentration of the sex hormone binding globulin (SHBG) in blood. In serum, unconjugated oestradiol exists mainly bound to SHBG and albumin and only a small (1%-3%) fraction is unbound.15 It is generally agreed that only non-protein bound steroid hormones are biologically active and that the serum SHBG capacity regulates the amount of free oestradiol.16 In this study, a linear relationship between serum concentration of SHBG and the risk of fracture was seen. SHBG binds both androgens and oestrogen and higher levels would presumably decrease the bioavailability of both hormones to skeletal tissue.

Other associations with the risk of fracture were less striking, although there was an increased risk of hip fractures in women with low serum concentration levels of free testosterone and 1,25-dihydroxy vitamin D. Curiously, high serum levels of oestrone, which has effects similar to, though weaker than oestradiol, were associated with an increased risk of vertebral fractures. In post-menopausal women, the ovaries no longer produce significant amount of oestrogen or progesterone. The only source of oestrone in post-menopausal women is from peripheral conversion of androstenedione. In turn, oestrone is converted to oestradiol. One of the important points raised by this study is that the serum oestradiol concentration necessary to protect against fractures is quite low, implying that low dose oestrogen might be used to prevent osteoporosis in women who are more than 65 years of age. Recent studies have confirmed that 0.3 mg of conjugated equine oestrogen or esterified oestrogen can prevent bone loss.17,18 This study thus suggested that the current recommended oestrogen doses may be higher than those required to maintain skeletal health. Lower doses are likely to be more acceptable to women because they cause fewer side-effects.

In conclusion, low serum oestradiol concentration levels and high serum SHBG appear to be good markers of ‘risk for fracture’. The measurement of these markers might improve the current methods of treatment by instituting therapy before osteoporosis has occurred.

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