Published in final edited form as:
Clin Obstet Gynecol. 2013 December ; 56(4): 722–729. doi:10.1097/GRF.0b013e3182a8ae55.

Premenopausal Bone Health: Osteoporosis in Premenopausal Women

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Abstract

This article will discuss the diagnosis of osteoporosis in premenopausal women and the evaluation and management of those with low-trauma fractures and/or low bone mineral density. As secondary causes (glucocorticoid excess, anorexia nervosa, premenopausal estrogen deficiency, and celiac disease) are commonly the underlying cause of osteoporosis in this population, treatment of the underlying condition should be the focus of management. Additional management options, generally reserved for those with major or multiple fractures and/or ongoing bone loss, will also be described.

Keywords

premenopausal women; osteoporosis; bone mineral density; pregnancy-associated osteoporosis; lactation- associated osteoporosis; idiopathic osteoporosis

Premenopausal Women With a History of Low-trauma Fracture

The diagnosis of osteoporosis in premenopausal women is most secure when there is a history of low-trauma fracture(s) in the absence of other causes of bone fragility such as malignancy or osteomalacia.[1,2] A low-trauma fracture is defined as a fracture that occurs with trauma equivalent to a fall from a standing height or less. Such fractures (excluding those of the digits) may be a sign of decreased bone strength, irrespective of whether bone mineral density (BMD) is frankly low.

Several studies have shown that fractures before menopause predict postmenopausal fractures.[3–5] In the Study of Osteoporotic Fractures, women with a history of premenopausal fracture were 35% more likely to experience fractures during the early postmenopausal years compared with women without a history of premenopausal fracture.[3] These findings suggest that certain life-long risk indicators such as fall frequency, neuromuscular protective response to falls, bone mass, or various aspects of bone quality can affect the life-long incidence of fractures.[4]

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The authors declare that they have nothing to disclose.

BMD Testing in Premenopausal Women

Several cross-sectional studies have reported lower BMD by dual energy x-ray absorptiometry (DXA) in premenopausal women with fractures. Premenopausal women with Colles fractures have been found to have significantly lower BMD at the nonfractured radius,[6] lumbar spine, and femoral neck[7] compared with controls without fractures. Female military recruits with stress fractures were also found to have lower BMD than controls.[8] However, in contrast to postmenopausal women, there are no longitudinal prospective studies relating BMD by DXA to incident fractures in premenopausal women. Because of this, and also because fracture rates are much lower in premenopausal than postmenopausal women,[3,4,9] the predictive relationship between BMD and short-term fracture incidence is unclear in this group. For these reasons, the International Society for Clinical Densitometry recommends against the use of T-scores to categorize BMD measurements in premenopausal women. Instead, Z-scores, which compare women to an age matched reference population, are recommended. Young women with BMDZ-scores below − 2.0 should be categorized as having BMD that is "below expected range for age" and those with Z-scores above − 2.0 should be categorized as having BMD that is "with-in the expected range for age."[10] Diagnostic categories of "osteoporosis" and "osteopenia" based on T-scores should not be applied to premenopausal women. An exception to these recommendations occurs in perimenopausal women, in whom the use of T-scores and T-score cut-offs is appropriate.

Special Issues Related to Interpretation of Low BMD Measurements in Premenopausal Women

1. Although the majority of bone mass acquisition occurs during adolescence, BMD may continue to increase slightly between ages 20 and 30.[11] Thus, very young women with slightly low BMD measurements may have not yet achieved peak bone mass.
2. There are expected changes in bone mass associated with both pregnancy and lactation. At the lumbar spine, longitudinal studies document losses of 3% to 5% over a pregnancy and 3% to 10% over a 6-month period of lactation,[12] with recovery of bone mass expected over 6 to 12 months, thereafter. Therefore, when interpreting a low BMD measurement in a premenopausal woman, the clinician must take into account the timing of recent pregnancy and lactation, as well as timing of peak bone mass.

Pregnancy-associated and Lactation-associated Osteoporosis

In some women, premenopausal osteoporosis may first present with low-trauma fracture(s), usually at trabecular sites, during the last trimester of pregnancy, or during lactation. [13,14] Given the physiologic bone mass changes described above, pregnancy and lactation may represent particularly vulnerable times for the premenopausal woman's skeleton, particularly if she has low BMD when she becomes pregnant. However, premenopausal fractures, including those associated with pregnancy and lactation, remain quite rare, suggesting that additional factors contribute to bone fragility in those women who present

with fractures during this time. Women with low-trauma fractures sustained during pregnancy and/or lactation require the same thorough evaluation for secondary causes (Table 1) as young women with fractures who are not associated with reproductive events. Women with low-trauma fractures associated with pregnancy or lactation, in whom low BMD persists 6 to 12 months after stopping lactation and in whom no cause is found after extensive evaluation, can be said to have idiopathic osteoporosis (IOP).

Secondary Causes of Osteoporosis in Premenopausal Women

Secondary causes of osteoporosis are listed in Table 1 and fall into several broad categories: estrogen deficiency, inflammatory diseases, collagen disorders, gastrointestinal diseases, and glucocorticoids and other medication exposures. Many diseases of childhood and young adult-hood (eg, gastrointestinal diseases, inflammatory diseases) lead to osteoporosis through multifactorial mechanisms involving the combined effects of malnutrition, systemic inflammation, estrogen deficiency/delayed puberty, and medication effects. The laboratory evaluation (Table 2) should be aimed at identifying secondary causes such as hyperthyroidism, hyperparathyroidism, Cushing's syndrome, early menopause, renal or liver disease, celiac disease, malabsorption, and idiopathic hypercalciuria. The main goal of the evaluation of a premenopausal woman with low-trauma fractures or low BMD is to identify any past or currently active secondary cause and to institute specific treatment for that cause if possible.

IOP

In some cases of low-trauma fracture in premenopausal women, no known secondary cause can be found after extensive evaluation. These women are said to have IOP. In most studies of IOP, the mean age at diagnosis is approximately 35 years.

On the basis of current guidelines, the term IOP applies only to those with a history of low-trauma fractures and not to those with low BMD and no history of fractures. That being said, several studies of IOP in women (andmen) have included both those with fractures and those with low BMD alone. On the basis of such studies, IOP is predominantly reported in whites, and family history of osteoporosis is common.[15–17]

Available evidence suggests that IOP is a heterogenous disorder, in which abnormalities in skeletal microstructure and strength may be due to diverse pathogenetic mechanisms. Some studies have documented lower follicular phase estradiol concentrations,[18] whereas others have not.[19,20] In addition, some studies have documented higher calcium excretion[19] or frank hypercalciuria in a subset.[20] In our prospective study of premenopausal women with IOP, we found there were significant microarchitectural differences in affected women: thinner cortices; fewer, thinner, more widely spaced and heterogenously distributed trabeculae; and lower mechanical competence. Women with IOP compared with normal controls did not differ in evaluation of bone remodeling as assessed by serum bone turnover markers or dynamic histomorphometry. However, women with IOP who had low bone turnover exhibited the most marked deficitis in microarchitecture and stiffness.[21]

Management Issues

GENERAL MEASURES

For all patients, one should recommend a set of general measures that benefit bone health: adequate weight-bearing exercise (defined as movement against gravity while upright),[22,23] nutrition, and lifestyle modifications (smoking cessation, avoidance of excess alcohol).

In the authors' opinion, pharmacological therapy is rarely justified for premenopausal women with isolated low BMD and no history of fractures, in whom there is no identifiable secondary cause, particularly if the Z score is>− 3.0. Low BMD in such young woman may be due to genetic low peak bone mass or past insults to the growing or adult skeleton (nutritional deficiency, medications, estrogen deficiency) that are no longer operative. Such young women usually have low short-term risk of fracture. Moreover, Peris et al[24] recently reported slight BMD improvement and no further fractures in 16 women with unexplained osteoporosis managed with only calcium (total intake of 1500 mg/d), vitamin D (400 to 800 IU/daily), and exercise. Bone density should be remeasured after 1 or 2 years to confirm that it is stable and identify patients with ongoing bone loss.

In women with low BMD or low-trauma fractures and a known secondary cause, the underlying cause should be addressed, if possible. Women with estrogen deficiency should receive estrogen (unless contraindicated), those with celiac disease should begin a gluten-free diet, those with primary hyperparathyroidism may benefit from parathyroidectomy, and those with idiopathic/ primary hypercalciuria may benefit from thiazide diuretics. Estrogen replacement in premenopausal women who are estrogen deficient may have beneficial effects on bone mass,[25–27] although oral reproductive hormone replacement has been shown to be ineffective in most studies examining bone mass in anorexia nervosa, a more complex condition.[27–29]

In some women, it is not possible to address or alleviate the secondary cause directly. Premenopausal women requiring long-term glucocorticoids and those with other active underlying causes of bone loss may require pharmacological therapy to prevent excessive bone loss or fractures. Treatment options include antiresorptive drugs, such as estrogen, bisphosphonates and denosumab, or anabolic agents such as teriparatide. Selective estrogen receptor modulators, such as raloxifene, should not be used to treat bone loss in menstruating women as they block estrogen action on bone and lead to further bone loss.[30]

BISPHOSPHONATES

Bisphosphonates have been shown to prevent bone loss in premenopausal women with various conditions.[13,31,32] However, large randomized trials are scarce and the US Food and Drug Administration has approved oral bisphosphonates only for premenopausal women on glucocorticoids (see below). Because bisphosphonates accumulate and persist in the maternal skeleton, cross the placenta, accumulate in the fetal skeleton,[33] and cause toxic effects in pregnant rats,[34] they should be used with caution in women who may become pregnant. Although several reports document normal pregnancies and fetal outcomes in women receiving bisphosphonates,[13,35–37] the potential for fetal abnormalities should be considered when prescribing bisphosphonates for a premenopausal woman.

Because there are so few data on the long-term efficacy and safety of bisphosphonates in young women, the decision to initiate treatment must be made on a case-by-case basis with consideration of individual fracture risk and with a plan for the shortest possible duration of use. In general, bisphosphonates should be reserved for those with fragility fractures or ongoing bone loss.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Bisphosphonates are approved for prevention and treatment of glucocorticoid-induced osteoporosis. However, relatively few premenopausal women participated in the relevant large registration trials for bisphosphonates in glucocorticoid-induced osteoporosis and none of the premenopausal women in those trials experienced a fracture.[38–40] Guidelines from the American College of Rheumatology suggest that bisphosphonates should be considered for prevention and treatment of glucocorticoid- induced osteoporosis in premenopausal women taking at least 7.5mg of prednisone or equivalent per day for ≥3 months.[41] There were no consensus recommendations for premenopausal women on lower doses of prednisone nor on <3 months of glucocorticoids.[41] Because of potential harm to the fetus in women who may become pregnant, they also urge great caution in the use of bisphosphonates in premenopausal women.[41] As an alternative to bisphosphonates, one can consider treatment of glucocorticoid-induced osteoporosis with estrogen as these patients may have suppressed gonadotropin release and estrogen deficiency that may manifest as oligomenorrhea or amenorrhea.[42]

Bisphosphonate Use for Other Secondary Causes of Osteoporosis

Bisphosphonates have been studied for various conditions including osteogenesis imperfecta, anorexia nervosa, and pregnancy-associated/lactation-associated osteoporosis.[13,31,43] Given the potential risks of long-termuse of these medications, many women may receive greater overall benefit from measures that address the underlying cause of their bone loss. However, those with multiple or recurrent fractures, or ongoing bone loss, may benefit from medical treatment.

Human Parathyroid Hormone [PTH(1-34)]

There are even fewer data on the effects of teriparatide or PTH(1-34) in premenopausal women, but this medication has been studied in women with medication-induced amenorrhea, women with IOP, women with pregnancy-associated or lactation- associated fractures,[44] and those on glucocorticoids. In young women treated with the gonadotropin-releasing hormone analog nafarelin for endometriosis, spine BMD declined by 4.9%, whereas those treated with PTH(1-34) 40 μg daily together with nafarelin had an increase of 2.1% (P<0.001).[45] It is not clear whether these results would apply to premenopausal women with normal gonadal status. A recent study comparing teriparatide and alendronate for glucocorticoid-induced osteoporosis included some premenopausal women. Overall, teriparatide was associated with significantly greater increases in lumbar spine and total hip BMD and resulted in significantly fewer incident vertebral fractures compared with alendronate. [46] The BMD responses were similar in premenopausal women as in men and postmenopausal women, but no fractures occurred in either premenopausal group. In an

observational study of teriparatide 20 μg daily in 21 premenopausal women with IOP, BMD increased by 9.8% at the lumbar spine and 2.9% at the total hip (both $P<0.05$) after 18 months of treatment. [47] However, among this unique cohort, a small subset with very low baseline bone turnover had little or no increase in BMD on this medication.[47] Because the long-term effects of teriparatide in young women are not known, use of this medication should be reserved for those at highest risk for fracture or those who are experiencing recurrent fractures. In young women younger than 25 years of age, documentation of fused epiphyses is recommended before consideration of teriparatide treatment, as this medication is contraindicated during growth.

Summary and Conclusions

Premenopausal woman with low-trauma fracture(s) or low BMD (Z score ≤ − 2.0) should undergo a thorough evaluation for secondary causes of osteoporosis and bone loss. In most cases, secondary causes can be found, the most common being glucocorticoid excess, anorexia nervosa, premenopausal estrogen deficiency, and celiac disease. Where possible, identification and treatment of the underlying cause should be the focus of management. Although pharmacologic therapy is rarely justified in premenopausal women, those with an ongoing cause of bone loss and those who have had or continue to have low-trauma fractures may require pharmacological intervention, such as bisphosphonates or teriparatide. Few high-quality clinical trials exist to provide guidance, and there are no data that such intervention actually reduces the risk of future fractures.

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TABLE 1

Secondary Causes of Osteoporosis in Premenopausal Women

Any disease that affects skeletal development or bone mass acquisition during puberty and adolescence
Connective tissue diseases
Osteogenesis imperfecta
Marfan syndrome
Ehlers Danlos syndrome
Premenopausal amenorrhea/estrogen deficiency
Pituitary diseases and hypothalamic amenorrhea
Medications leading to suppression of ovulation and amenorrhea
GnRH agonists (when used to suppress ovulation)
Depot medroxyprogesterone acetate (DMPA)
Chemotherapy leading to amenorrhea
Anorexia nervosa (this condition is associated with complex bone effects that are also related to nutritional deficiencies and other hormonal abnormalities)
Other endocrinopathies and abnormalities of calcium metabolism
Cushing’s syndrome
Hyperthyroidism
Primary hyperparathyroidism
Idiopathic hypercalciuria
Gastrointestinal/nutritional
Vitamin D, calcium, and/or other nutrient deficiency
Gastrointestinal malabsorption
Celiac disease
Inflammatory bowel disease
Cystic fibrosis
Postoperative states
Inflammatory conditions
Rheumatoid arthritis
SLE
Other inflammatory conditions
Other conditions:
Renal disease
Liver disease (particularly cholestatic liver disease)
Excessive alcohol consumption
HIV infection and/or medications
Gaucher’s disease
Mastocytosis
Hereditary hemochromatosis
Thalassemia major
Diabetes (type 1 and 2)
Medications (not all have been studied in premenopausal populations)
Glucocorticoids

Calcineurin inhibitors (eg, cyclosporine)
Antiepileptic drugs (particularly cytochrome P450 inducers such as phenytoin, carbamazepine)
Chemotherapeutic drugs (particularly high dose methotrexate)
Medications associated with estrogen deficiency/suppression of ovulation (see above)
Heparin (effects of low molecular weight heparins are not clear)
Antidepressants [particularly selective serotonin reuptake inhibitors (SSRIs)]
Proton pump inhibitors
Excess vitamin A intake
Thiazoledinediones
Conditions with potential effects:
Depression
Elevated homocysteine levels

GnRH indicates gonadotropin-releasing hormone; SLE, systemic lupus erythematosus.

TABLE 2

Laboratory Evaluation

Initial laboratory evaluation
Complete blood count
Electrolytes, renal function
Serum calcium, phosphate
Serum albumin, transaminases, total alkaline phosphatase
Serum TSH
Serum 25-hydroxyvitamin D
24 h urine for calcium and creatinine
Additional laboratory evaluation
Estradiol, LH, FSH, prolactin
PTH
1,25-dihydroxyvitamin D
24 h urine for free cortisol
Iron/TIBC, Ferritin
Celiac screen
Serum/urine protein electrophoresis
ESR or CRP
Bone turnover markers
Transiliac crest bone biopsy

CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; PTH, parathyroid hormone; TIBC, total ironbinding capacity; TSH, thyroid stimulating hormone.