Bone Loss in Young Women With Karyotypically Normal Spontaneous Premature Ovarian Failure

JAMES N. ANASTI, MD, SOPHIA N. KALANTARIDOU, MD, LORENE M. KIMZEW, RN, RUBI A. DEFENSOR, RN, AND LAWRENCE M. NELSON, MD

Objective: To evaluate the effects of karyotypically normal spontaneous premature ovarian failure on femoral neck bone mineral density.

Methods: Eighty-nine women with karyotypically normal spontaneous premature ovarian failure who desired fertility were evaluated at a tertiary care academic center and underwent hip and spinal bone density measurements by conventional dual-photon absorptiometry. Seventy-seven of the women (87%) had sought medical advice previously and had taken a variety of estrogen and progestin replacement regimens at least intermittently. The median (range) age was 32 (20–39) years, and the median (range) time since diagnosis was 1.5 (0.5–11) years. Findings were compared with a reference group of 218 regularly menstruating women of similar age.

Results: Sixty of the 89 women with premature ovarian failure (67%, 95% confidence interval 57, 77) had a femoral neck bone mineral density more than 1 standard deviation (SD) below the mean of the reference group (P < .001, χ² with Yates correction). Even in women in whom the bone mineral density measurement was made within just 1.5 years of the diagnosis, nearly one-half (47%) had a femoral neck bone mineral density more than 1 SD below the mean of the reference group (P < .01).

Conclusion: Two-thirds of young women with karyotypically normal spontaneous premature ovarian failure have a femoral neck bone mineral density more than 1 SD below the mean of a reference group. These young women need early education regarding strategies to maintain their bone mass and ongoing medical evaluation to maintain compliance with these strategies. (Obstet Gynecol 1998;91:12–5.)

Ideally, hormone replacement strategies for young women with premature ovarian failure should maintain bone mass as well as the normal ovary maintains bone mass in regularly menstruating women. Women with normal ovarian function achieve peak femoral bone mineral density in their early 20s. Sex steroids play an important role in maintaining bone mass, and cessation of ovarian function results in significant bone loss. By age 40, 1% of women spontaneously develop premature ovarian failure, a condition that causes amenorrhea, elevated gonadotropins, hypogonadism, and hypoandrogenemia.

Young women can experience ovarian failure by several mechanisms, including karyotypic abnormalities, radiation or chemotherapy, and surgical castration. Previous studies have shown that women with premature ovarian failure due to these diverse causes have reduced bone mass, but specific information regarding the bone density and the associated subsequent risk of hip fracture in women with karyotypically normal spontaneous premature ovarian failure has not been examined. To evaluate the effects of spontaneous premature ovarian failure on bone mineral density, we investigated the hip and spinal bone mineral densities of 89 women with karyotypically normal spontaneous premature ovarian failure. The findings were compared with those from a reference group of women of similar age with normal ovarian function.

Materials and Methods

From December 1988 to January 1993, we recruited women with premature ovarian failure who desired fertility by means of letters to physicians and notices in medical journals. To qualify for referral under a protocol approved by the Institutional Review Board of the National Institute of Child Health and Human Development, women had to be younger than 40 years of age, have at least 4 months of amenorrhea, and have two
serum FSH levels greater than 40 mIU/mL (at least 1 month apart). Women with iatrogenic causes of premature ovarian failure or chromosomal abnormalities were excluded from the study. All women who contacted us and fulfilled recruitment criteria participated.

Evaluation at the National Institutes of Health Clinical Center included a history and physical examination, a high-resolution karyotype, hip and spinal bone density measurements, and tests for the diagnosis of autoimmune endocrine disorders associated with premature ovarian failure (described in detail elsewhere). Because the study started in 1988, bone mineral density of the hip (femur neck, Ward’s triangle, and femur trochanter) and the spine (L2–4) were measured by conventional dual-photon absorptiometry with a commercially available unit (DP3 Lunar Corporation, Madison, WI). The unit was calibrated properly according to the three-chamber standard provided with the instrument. The precision error (% coefficient of variation) was 3% for the femur and 2% for the spine. We completed the study using the same unit in order to obtain comparable results throughout the study period.

Reference data from 218 regularly menstruating women were available from the manufacturer of the absorptiometry machine. All women in this reference group were white and were free of any current or previous chronic diseases (including renal disease, hepatic disease, amenorrhea, hyperparathyroidism, hyperthyroidism, and malabsorption) or medications (including corticosteroids and chronic anticonvulsant use) known to affect bone metabolism. Details of these measurement methods and quality control procedures, as well as results from this cohort of subjects, have been published previously.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Data were compared using a goodness of fit test with $\chi^2$ (Yates correction). Statistical analysis was performed using Sigma Stat (Jandel Scientific, San Rafael, CA), and $P < .05$ was considered significant. Confidence intervals (CIs) of an observed frequency were calculated using the binomial distribution.

Results

During the study period, we examined 89 women with karyotypically normal spontaneous premature ovarian failure. Seventy-nine women were white; four Asian; three Hispanic; two black; and one native American. The median (range) time since diagnosis was 1.5 (0.5–11) years. The median (range) age of patients with premature ovarian failure was 32 (20–39) years and of women in the reference group 31 (20–39) years. The mean (± standard deviation [SD]) BMI of the patients was 23.2 ± 4.7 kg/m² and of the reference group was 22.5 ± 4.0 kg/m². Seventy-seven of the patients (87%) had sought medical advice previously regarding fertility or amenorrhea and had received a variety of regimens of estrogen and progesterin replacement therapies at least intermittently.

Sixty of the 89 women with premature ovarian failure (67%; 95% CI 57, 77) had femoral neck bone mineral densities exceeding 1 SD below the mean of the reference group of women ($P < .001$, Table 1). Seventeen (19%) had femoral neck bone mineral densities exceeding 2 SD below the mean of the reference group, and two had femoral neck bone mineral densities exceeding 3 SD below the mean of the reference group. Similar results were obtained at Ward’s triangle and the trochanter (data not shown). Spinal (L2–4) bone mineral density measurements also are demonstrated in Table 1.

In the subset of 45 women who had their bone densities measured within 1.5 years of the diagnosis, 21 (47%; 95% CI 32, 62) had femoral neck bone mineral density exceeding 1 SD below the mean of the reference group ($P < .01$).

Discussion

Hip fractures are the most serious complication of low bone density; more than 250,000 occur annually in the United States. In a study of 8134 women 65 years of age or older, Cummins et al demonstrated that hip bone density is a valuable predictor of hip fracture risk. Indeed, it was shown that a femoral neck bone mineral density more than 1 SD below the mean of age-matched controls predicts a 2.6-fold increased risk of hip fracture in these women. We found that 66% of women with karyotypically normal spontaneous premature ovarian failure had femoral neck bone mineral density more than 1 SD below the mean of similar-age women with

<table>
<thead>
<tr>
<th>Table 1. Distribution of Bone Mineral Density Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women (%)</td>
</tr>
<tr>
<td>Skeletal site</td>
</tr>
<tr>
<td>Femur neck</td>
</tr>
<tr>
<td>Women with premature ovarian failure (n = 89)</td>
</tr>
<tr>
<td>Reference women (n = 218)</td>
</tr>
<tr>
<td>Spine (L2–4)</td>
</tr>
<tr>
<td>Women with premature ovarian failure (n = 89)</td>
</tr>
<tr>
<td>Reference women (n = 218)</td>
</tr>
</tbody>
</table>

SD = standard deviation.
Data are presented as n (%).
* $P < .001$ compared with reference women.
normal ovarian function. Our findings, together with those of Cummings et al.\textsuperscript{13} suggest that 66% of women with karyotypically normal spontaneous premature ovarian failure may be at increased risk for hip fracture.

We measured bone mineral density in 50% of our patients within 1.5 years of the diagnosis of premature ovarian failure. Almost one-half (47%) of these young women had femoral neck bone mineral densities exceeding 1 SD below the mean, even this soon after the diagnosis. Thus, substantial bone loss can occur rapidly in these women. Possibly, some of the loss might have even occurred as ovarian function was declining before the development of failure. In contrast to ovarian failure that develops abruptly as a result of surgical castration, chemotherapy, or radiation, estrogen deficiency may occur insidiously in women with karyotypically normal spontaneous premature ovarian failure. Indeed, menstrual irregularities occur often in the years preceding premature ovarian failure (prodromal premature ovarian failure), and menstrual irregularities have been associated with significant bone loss.\textsuperscript{14} This might explain why 66% of this pure group of young women with karyotypically normal spontaneous premature ovarian failure had a hip bone density associated with an increased risk for hip fracture. Our findings suggest that prodromal premature ovarian failure should be included in the differential diagnosis in women with menstrual irregularities, and in fact, to protect bone, there may be a need to diagnose and manage prodromal premature ovarian failure as early as possible.\textsuperscript{4}

Current hormone replacement strategies were developed for women who experience natural menopause at an average age of 50. The postmenopausal estrogen/progestin interventions trial\textsuperscript{15} showed that estrogen/progestin replacement therapy can maintain bone mass in postmenopausal women 45–64 years of age. However, these strategies may be inadequate for young women with premature ovarian failure. Indeed, the recognized bone-sparing dose of 0.625 mg of conjugated estrogen\textsuperscript{16} failed to prevent vertebral bone loss in premenopausal women made estrogen-deficient by gonadotropin-releasing hormone agonist therapy.\textsuperscript{17}

Young women with karyotypically normal spontaneous premature ovarian failure face decades of exposure to hormone replacement therapy. Although our patients had previously sought medical advice and had taken estrogen and progesterin replacement therapy at least intermittently, they had significantly reduced bone mineral density compared with similar-age women with normal ovarian function. It is clear that these young women need ongoing medical evaluation and education regarding the need for hormone replacement, physical activity (weight-bearing exercise), and adequate calcium intake. Furthermore, strategies to improve compliance are needed. Fear of breast cancer was frequently a reason for compliance failure. The concerns regarding estrogen therapy in postmenopausal women may not be directly applicable to young women with premature ovarian failure.\textsuperscript{4} Postmenopausal women are prolonging their exposure to estrogen effect beyond the normal age range. In contrast, women with premature ovarian failure take estrogen to replace what their ovary should be making normally.

Hormone replacement for these young women, some of whom develop ovarian failure even before they reach peak adult bone mass, should ideally mimic normal ovarian function as closely as possible. The normal premenopausal ovary produces estrogen, progesterone, and androgen. A prospective study\textsuperscript{18} has shown that low serum androgen levels are associated with greater bone loss in all women (premenopausal, perimenopausal, and postmenopausal). Furthermore, in postmenopausal women, androgen replacement along with estrogen has been shown to increase spinal bone mineral density significantly more than estrogen alone.\textsuperscript{19,20} Women with premature ovarian failure have lower androgen levels compared with normal ovulatory women.\textsuperscript{3} This raises the possibility that androgen replacement along with estrogen may be necessary to maintain bone mass in these young women.

This study is an exploratory analysis to evaluate the current reality regarding bone mass and hormone replacement in young women with premature ovarian failure. We used reference data for this purpose. These findings should be confirmed by a prospective study that includes controls. We are developing a prospective study to attempt to define an ideal hormone replacement strategy to maintain bone in these young women. One arm of the study will evaluate the addition of androgen.

In conclusion, our study shows that 66% of women with karyotypically normal spontaneous premature ovarian failure have femoral neck bone mineral densities more than 1 SD below the mean of a reference group of normal women. Within 1.5 years of the diagnosis 47% of these young women have a femoral neck bone mineral density exceeding 1 SD below the mean. These young women need early education regarding strategies to maintain their bone mass and ongoing medical evaluation to maintain compliance with these strategies.

References


Address reprint requests to:
Lawrence M. Nelson, MD
Section on Women's Health
National Institute of Child Health and Human Development
National Institutes of Health
Building 10, Room 10N262
Bethesda, MD 20892-1862
E-mail: nelsonl@cc1.nichd.nih.gov

Received July 2, 1997.
Accepted October 10, 1997.