Vasomotor symptoms in infertile premenopausal women: a hitherto unappreciated risk for low bone mineral density

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Objective: To identify the prevalence of vasomotor symptoms (VMS) in a population of premenopausal infertile women and to determine whether VMS is associated with enhanced bone turnover and low bone mineral density (BMD).
Design: Cross-sectional study.
Setting: Academic infertility practice.
Patient(s): Eighty-two premenopausal infertile, but otherwise healthy, women attending for routine infertility care.
Intervention(s): Bone mineral density testing, general health and Profile of Mood States questionnaires, and serum samples (cycle d 1–3).
Main Outcome Measure(s): Vasomotor symptoms, specifically hot flashes (HF) and night sweats (NS); BMD z score, BMD categorized as low ($Z \leq -1.0$) or normal ($Z > -1.0$); ovarian reserve assessment (biochemical and ovarian dimensions on transvaginal ultrasound); and serum markers of bone turnover (collagen *N*-terminal telo-peptide, tartrate-resistant acid phosphatase, and bone-specific alkaline phosphatase) and ovarian reserve (FSH, E_2, and inhibin B). Multivariable regression analyses determined the associations between VMS, BMD, and bone turnover (individual markers and composite turnover score).
Result(s): The prevalence of VMS was 12% in this relatively young population (mean [± SD] age [years], 34.53 ± 4.32). Symptomatic women were statistically significantly more likely to report sleep disturbances and to exhibit evidence of low BMD, as well as to exhibit enhanced bone turnover and poorer ovarian reserve parameters. Multivariable logistic regression analyses confirmed the statistical significance of both HF and NS as independent correlates to low BMD after adjusting for age, body mass index, smoking status, menstrual regularity, and ovarian reserve status. Multivariable linear regression analyses demonstrated that NS, but not HF, predicted higher bone turnover at a statistically significant level after adjusting for age, smoking, menstrual regularity, and ovarian reserve.
Conclusion(s): We demonstrate, in a premenopausal population of infertile women, evidence of morbid accompaniments to VMS, including sleep disturbances and evidence of low BMD. Our data further suggest a state of enhanced bone turnover in association with VMS, specifically in those experiencing NS. Declining ovarian reserve may be the common pathophysiological mechanism underlying VMS and low BMD in the symptomatic population and merits further investigation. (Fertil Steril® 2008;90:1626–34. ©2008 by American Society for Reproductive Medicine.)

Key Words: Vasomotor symptoms, night sweats, hot flash, bone mineral density, premenopause, bone turnover, NTX, TRAP, BAP

Vasomotor symptoms (VMS), that is, hot flashes (HF) and night sweats (NS), although a hallmark of perimenopause (1–3), are not uncommonly encountered in the premenopausal period (4–6). Elevations in serum levels of FSH, a hallmark of reproductive aging, predate these clinical stigmata of perimenopause (7). Both elevations in the pituitary gonadotropins and declining serum E_2 levels are suggested to play a pathogenic role in the occurrence of VMS (8, 9).

Skeletal health is intimately related to and influenced by gonadal function (10, 11). Bone mineral density (BMD) and bone metabolism or turnover have been shown to be independent predictors of risk for fracture (12–14). Limited data accrued in the perimenopausal and postmenopausal populations suggest an association between VMS and reduced BMD (15–18). The occurrence and the frequency of VMS have been shown to associate with low BMD as well as with

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a rapid deterioration in BMD parameters in postmenopausal as well as perimenopausal women (15–17). These data are limited, however, as much by a retrospective and recall nature of the symptomatology as by the relatively aging populations that have been studied thus far. Data supporting an association between low BMD and VMS in the premenopausal years are strikingly sparse (19).

In the era of assisted reproduction, elevations in early follicular phase FSH and decline in inhibin B levels have emerged as reliable markers of declining ovarian reserve (20). Although testing for ovarian reserve constitutes an integral component of infertility workup, it is yet uncommonly used beyond this context, at least in the premenopausal years. Thus, infertile, yet healthy, premenopausal women constitute an optimal population for studying the relationship between VMS, ovarian reserve, and BMD status. Emerging literature suggests an association between elevations in FSH levels and bone loss (21), highlighting a potential pathogenic mechanism for bone loss in the setting of declining ovarian reserve and further suggesting a relevance for ovarian reserve testing and implications, for assessment not just of reproductive potential but also of skeletal health.

This study explores the hypothesis that premenopausal and infertile women experiencing VMS will demonstrate evidence of both low BMD and poor ovarian reserve parameters and will demonstrate biochemical evidence of enhanced bone turnover (i.e., elevated levels of markers of bone resorption and formation) compared with those without these symptoms.

MATERIALS AND METHODS

Premenopausal women with infertility who attended an academic practice in the early follicular phase of their menstrual cycle (d 1–3) were offered participation in a cross-sectional study. Inclusion criteria were age of <42 years and generally good health, defined as the absence of known systemic diseases contraindicating pregnancy and/or known to adversely influence skeletal health (i.e., systemic lupus erythematosus, diabetes mellitus, Crohn's disease, renal failure, or untreated or overtreated thyroid disease). Eighty-nine women were enrolled over a 3-year period (April 2004 to April 2007). Institutional review board approval was obtained, and written consent was provided by the participants. Bone mineral density assessments were performed in 82 of 89 participants. In the initial 10 women, BMD was assessed by dual x-ray absorptiometry of the lumbar spine and hip (Lunar Prodigy; GE, Madison, WI). Secondary to recruitment constraints that were attributable to the logistics of participant transportation to an off-site bone-density center, subsequent enrollees underwent BMD assessment with a peripheral quantitative calcaneal ultrasound device (n = 72, Lunar Achilles Insight; GE) with a known repeat-measurement precision of <2% (22). The respective devices were calibrated per manufacturer guidelines by using the provided phantoms before each measurement. Anthropometric parameters assessed included height (cm) and weight (kg), and body mass index (BMI) was calculated [weight in kg/(height in m)^2].

Serum samples were collected and stored at −80°C until assessment of serum levels of markers of interest. Biomarkers of ovarian reserve that were assessed included FSH (mIU/mL, DELFIA, Pharmacia, Gaithersburg, MD; DELFIA intra-assay coefficient of variance [CV], 3.2% and interassay CV, 8.7%), E_2 (pg/mL, DELFIA; sensitivity, 10 pg/mL; intra-assay CV, 4.2%; and interassay CV, 9.0%), and inhibin B (pg/mL; Oxford Bio-Innovations, Upper Heyford, Oxfordshire, United Kingdom; sensitivity, <15 pg/mL; intra-assay and interassay CV, <7%). As per the guidelines followed in clinical practice, the maximal historical FSH level for each patient was considered to reflect the ovarian reserve status. In a subset of patients, markers of bone turnover were assessed, including a formation marker, bone-specific alkaline phosphatase (BAP, μg/L; ELISA, IDS, Inc., Fountain Hills, AZ; sensitivity, 1.0 ng/mL; intra-assay CV, <10%; interassay CV, <10% in 65/82), and the resorption markers tartrate-resistant acid phosphatase (TRAP, U/L; ELISA, IDS, Inc.; sensitivity, <0.5 U/L; intra-assay CV, <9%; interassay CV, <10% in 64/82) and collagen *N*-terminal telo-peptide (NTX, nM of bone collagen equivalents; ELISA, Wampole Laboratories, Raritan, NJ; standard range, 3.2 to 40.0 nM per bone collagen equivalents; intra-assay CV, 7.3%; interassay CV, 6.9% in 50/82), using commercial kits.

The participants were provided with a questionnaire addressing medical, social, family, and personal histories. Specific questions were phrased to inquire about occurrence of VMS, including "are you bothered by night sweats (Yes/No)" and "are you bothered by hot flashes (Yes/No)". Additional questions were asked to specify the frequency of occurrence of VMS as follows: less than once a day, one to two times per day, three to four times per day, and equal to or more than five times per day. Specific questions inquired about age at menarche, regularity of menstrual cycles (yes or no), and current smoking status (yes or no). Two specified questions enquired about "regular exercise" (yes or no) and "regular weight bearing exercise" (yes or no), and a single question asked whether the participant was experiencing disturbed sleep (yes or no).

An assessment of dysphoric mood parameters was performed by using the Profile of Mood States questionnaire (23, 24). Briefly, a 60-item validated tool requesting responses ranging from "0—very little" to "5—extremely" evaluates the participant responses across six dimensions of mood. Five of these represent "negative mood states," namely *tension, anger, depression, fatigue*, and *confusion*. The sixth is a positive mood, *vigor*. The questionnaires were scored by a single investigator (K.B.) who was blinded to the participant's vasomotor symptomatology. A total dysphoric mood score is calculated on the basis of the sum of negative mood scores, minus the vigor scores. Higher total mood scores thus reflect a greater degree of dysphoria.

Bone density z scores were regarded as the BMD parameter of interest, given the premenopausal study population (25). Bone mineral density was categorized as low (LBMD), if z score was ≤−1.0 (≤1 SD below the age-