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Bone Resorption Is Affected by Follicular Phase Length in Female Rotating Shift Workers

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Stressors as subtle as night work or shift work can lead to irregular menstrual cycles, and changes in reproductive hormone profiles can adversely affect bone health. This study was conducted to determine if stresses associated with the disruption of regular work schedule can induce alterations in ovarian function which, in turn, are associated with transient bone resorption. Urine samples from 12 rotating shift workers from a textile mill in Anqing, China, were collected in 1996–1998 during pairs of sequential menstrual cycles, of which one was longer than the other (28.4 vs. 37.4 days). Longer cycles were characterized by a prolonged follicular phase. Work schedules during the luteal-follicular phase transition (LFPT) preceding each of the two cycles were evaluated. All but one of the shorter cycles were associated with regular, forward phase work shift progression during the preceding LFPT. In contrast, five longer cycles were preceded by a work shift interrupted either by an irregular shift or a number of “off days.” Urinary follicle-stimulating hormone levels were reduced in the LFPT preceding longer cycles compared with those in the LFPT preceding shorter cycles. There was greater bone resorption in the follicular phase of longer cycles than in that of shorter cycles, as measured by urinary deoxypyridinoline. These data confirm reports that changes in work shift can lead to irregularity in menstrual cycle length. In addition, these data indicate that there may be an association between accelerated bone resorption in menstrual cycles and changes of regularity in work schedule during the preceding LFPT. Key words: bone resorption, deoxypyridinoline (DPD), follicular phase length, luteal-follicular phase transition (LFPT), shift work. Environ Health Perspect 111:618–622 (2003). doi:10.1289/ehp.5878 available via http://dx.doi.org/ [Online 9 December 2002]

Although the association between ovarian function and bone loss is well recognized, the minimal hormonal requirements for maintaining healthy bones are poorly defined. Exercise-induced amenorrhea (Beitins et al. 1991; Broocks et al. 1990; Bullen et al. 1985), prolactin-secreting tumors (Klibanski et al. 1980; Schlechte et al. 1983), and gonadotropin-releasing hormone (GnRH)-induced hypogonadism (Scharla et al. 1990; Surrey and Judd 1992) all result in bone loss in women. Female athletes have been shown to lose bone despite increased skeletal loading, a situation that places these women at increased risk for bone injuries (Cann et al. 1984). Older studies suggested that bone loss in healthy young women is related to abnormalities of progesterone production (Bullen et al. 1985; Prior 1990). However, recent reports have indicated that even modest exercise can result in alterations of ovarian function characterized by perturbations of the follicular phase but not the luteal phase of the menstrual cycle (De Souza et al. 1997; Waller et al. 1996; Winters et al. 1996). These subtle alterations of the follicular phase were associated with decreased bone integrity and an increased incidence of bone fractures (De Souza et al. 1997). Other data suggest that stress-related effects on bone health are associated with alterations in the rise of follicle-stimulating hormone (FSH) during the late luteal phase of the menstrual cycle, which in turn alter the follicular phase of the next cycle (De Souza et al. 1998).

The number of women in the workforce has grown over the past 20 years and continues to expand. Because a majority of working women are in their reproductive years, there is public concern about exposures in the workplace that could adversely affect menstrual function, fertility, or pregnancy. As a consequence of this concern, several studies have been designed to identify such hazards (Eskenazi et al. 1995; Gold et al. 1995a, 1995b; Lasley et al. 1995; Schenker et al. 1995). Despite clear evidence that subtle stressors such as changes in work schedule also may have adverse effects on reproductive health, there have been few studies on such nonchemical hazards, and there is little understanding of their mechanism(s) of action. Such stressors not only may have intrinsic adverse effects, but also they may exacerbate the effects of other workplace hazards. The presence of these stressors also can confound interpretation of the results of studies designed to evaluate other putative hazards.

Previous studies have indicated that stressors as subtle as night work or shift work can lead to irregular menstrual cycles (Miyauchi et al. 1992) through perturbations of the diurnal rhythms of reproductive hormones.

The present study was conducted to test the hypothesis that stresses associated with the disruption of the regular work schedule induce alterations in ovarian function which, in turn, are associated with transient bone resorption. Specifically, we assessed work shift status, ovarian hormone profiles, and bone metabolites during two consecutive menstrual cycles of female workers to determine if a delay of ovulation and lengthening of the follicular phase are induced by the changing of work-shift regularity, and if these alterations of the menstrual cycle are associated with increased bone resorption.

Materials and Methods

Subjects. Twenty-one healthy Chinese female workers on rotating work shifts in a textile mill in Anqing, China, were recruited into the study during 1996–1998. The Human Subjects Committees at the Harvard School of Public Health and the China Medical Institutes approved all study procedures, and informed consent was obtained from each participant (Cho et al. 2002; Ronnberg et al. 2000). Daily early morning urine samples were collected by the subjects during consecutive menstrual cycles. Paired sequential cycles were identified in which one of the pair was longer than the other. Of the 21 subjects enrolled, 9 subjects were excluded from the study because of noncompliance with the study protocol. Five subjects did not collect daily urine samples during the luteal-follicular phase transition (LFPT). Samples collected from the other 4 excluded subjects were too dilute to provide reliable information for follicular phase determination, as shown by low levels of creatinine in the sample (< 0.2 mg/mL). There was no association between the noncompliance of the subjects and their work shift schedules, and no other criteria were used to exclude subjects from the study.

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Of the 12 women (23–31 years of age) in the study, 11 were cotton-weaving workers and one was a laboratory technician. All 12 women worked rotating shifts during the study period, but the types of work shift were not known to the investigators until after the laboratory analyses were complete.

**Menstrual cycle definitions.** The menstrual cycle length was defined as the number of days from the onset of one period of menstrual bleeding to the day before the onset of the next period of menstrual bleeding. All cycles were determined to be ovulatory, as evidenced by a sustained rise of urinary pregnanediol-3-glucuronide (PdG) for 10 or more days immediately preceding the onset of menstruation. The midcycle urinary FSH peak was used as a biomarker to indicate the day of ovulation (Li et al. 2002) and for follicular phase length determination. The follicular phase length was defined as the number of days from the first day of menstruation up to and including the day of the FSH peak. The remaining days in the cycle were defined as the luteal phase. The LFPT was defined as the interval including days −8 to −1 of the preceding cycle, when day 1 is the first day of the menstrual bleeding in the study cycle. In other words, the LFPT was the last 8 days of the preceding cycle. Work schedules were evaluated during the LFPT preceding each of the two study cycles. FSH profiles were determined during the LFPT preceding the second of the two study cycles.

**Sample collection and storage.** The urine samples (3–5 mL) were self-collected, stored frozen without preservatives in the subjects’ home refrigerator freezers at −10°C, then transferred to the laboratory at the end of each menstrual cycle for storage at −35°C. All samples collected during the entire cycle were thawed and analyzed for estrone conjugates (E1C), PdG, FSH, and creatinine, and then were refrozen. When cycles were shown to be ovulatory and the follicular phase had been defined, the samples collected in the follicular phase were thawed for a second time and analyzed for deoxypyridinoline (DPD).

**Laboratory analyses.** Assays for urinary E1C, PdG, and the beta subunit of FSH were performed as previously described (Munro et al. 1991; Qiu et al. 1998). Urinary DPD was measured using the Pyrilinks-D kit (Metra Biosystems, Inc., Mountain View, CA). All assay results were indexed by the concentration of creatinine in the same urine sample. In the present data set, the interassay coefficients of variation for E1C, PdG, FSH, and DPD were 10.4, 10.4, 12.9, and 11.7%, respectively.

**Statistical analysis.** The hormone values of urinary E1C, FSH, and PdG, as well as urinary DPD values, were compared between longer cycles and shorter cycles by using 2-way analysis of variance with repeated measures. The area under the curve (AUC) of DPD was calculated by trapezoidal rule (Holder et al. 1999) and compared between longer cycles and shorter cycles by paired t-test. All data are presented as mean ± SEM. We considered $p < 0.05$ significant.

### Results

Seven subjects had a cycle pair in which a longer length cycle was followed by a shorter cycle, and five subjects had a shorter length cycle followed by a longer cycle (Table 1). The mean length (±SEM) of the longer cycles was $37.4 ± 1.3$ days, and the mean length of the shorter cycles was $28.8 ± 0.74$ days. The follicular phase length was significantly longer in the longer cycles compared with the shorter length cycles ($21.9 ± 1.2$ vs. $14.2 ± 0.56$ days; $p < 0.001$), but there was no difference in the lengths of the luteal phase.

### Table 1. Characteristics of menstrual cycles.

| Subject | First cycle | Second cycle |
|---------|-------------|--------------|
|         | Cycle length (days) | Follicular length (days) | Cycle length (days) | Follicular length (days) |
| 1       | 31          | 17           | 34          | 18           |
| 2       | 33          | 18           | 22          | 14           |
| 3       | 31          | 17           | 39          | 25           |
| 4       | 33          | 18           | 31          | 15           |
| 5       | 38          | 22           | 31          | 15           |
| 6       | 37          | 20           | 30          | 14           |
| 7       | 37          | 21           | 28          | 12           |
| 8       | 46          | 29           | 29          | 10           |
| 9       | 29          | 15           | 46          | 31           |
| 10      | 28          | 13           | 35          | 20           |
| 11      | 32          | 20           | 27          | 14           |
| 12      | 26          | 14           | 38          | 21           |

*Longer length cycle.

**Figure 1.** Daily urinary E1C concentrations (A) and FSH concentrations (B) indexed by creatinine concentrations of the same sample for 12 women that had pairs of sequential menstrual cycles in which one was of shorter length and the other was of longer length; both groups of cycles were aligned to the day of the midcycle FSH peak (day 0). (A) There was no statistical difference between E1C values on any day when the shorter and longer cycles were aligned in this manner ($p > 0.05$). (B) There was no statistical difference between FSH values on any day when the shorter length and longer cycles were aligned in this manner ($p > 0.05$).
phases between the two cycle types (14.6 ± 0.75 and 15.5 ± 0.36 days; *p* > 0.05).

Urinary hormone metabolite profiles were characterized by a gradual rise and abrupt fall of E1C (Figure 1A), with a single, prominent preovulatory FSH peak on approximately day 14 (shorter length cycles) or day 22 (longer cycles) after the onset of menstruation. When the midcycle FSH peak was defined as day 0, the E1C profiles from day −5 to day 0 were not different between the two groups of cycles (*p* > 0.05) (Figure 1A). Neither the FSH peak concentrations (2.95 ± 0.85 vs. 3.14 ± 0.91 ng/mg Cr, *p* > 0.05) (Figure 1B) nor the PdG profiles (data not shown) were statistically different between the two cycle types. The only difference between the hormone profiles in the shorter length cycles and longer cycles was that the urinary E1C and FSH peaks were delayed in the longer cycles (Figure 1A). In addition, FSH levels were significantly lower during the interval from day −7 to day −3 of the LFPT preceding longer cycles compared with FSH levels in the same interval prior to shorter length cycles and longer cycles except for those associated with the delay of ovulation.

Work schedules were available for all 12 of the cycles preceding the shorter length study cycles and for 10 of the cycles preceding the 12 longer study cycles. A regular, forward progression of work shifts (day–day–swing–graveyard–off day–off day) (Table 2). Work schedules were available for all 12 of the cycles preceding the shorter length study cycles and for 10 of the cycles preceding the 12 longer study cycles. A regular, forward progression of work shifts (day–day–swing–graveyard–off day–off day) with no more than two consecutive shifts was found preceding all but one of the 12 shorter length cycles (first cycle of subject 1). In contrast, only 5 of the 10 longer cycles were associated with this normal progression, and 4 of the 5 remaining longer cycles (second cycle of subjects 3, 9, 10, and 12) were preceded by extra off days, which broke the regularity of the work schedules. The LFPT preceding the remaining longer menstrual cycle (first cycle of subject 8) was characterized by an extended period of work (swing–swing–swing–graveyard–day) (Table 2).

Discussion

Previous reports indicate that even subtle stressors, such as night work or shift work, can increase the incidence of irregular menstrual cycles in healthy young women (Miyauchi et al. 1992). In the present study, rotating shift workers had some shorter length menstrual cycles (27–31 days) as well as some longer cycles (33–46 days). The hormone profiles of these cycles show that the variations in cycle length resulted primarily from differences in the length of the follicular phase of the cycle rather than the length of the luteal phase. Our findings suggest that the disruption of the regularity of rotating shift work is associated with longer menstrual cycles characterized by a delay in the day of ovulation and a lengthening of the follicular phase. We also found evidence of increased bone resorption in the follicular phases of these longer cycles. In this study, we were able to identify pairs of sequential menstrual cycles that included cycles of different lengths. Our ability to study consecutive cycles of the same woman decreases the possibility that changes in nutrition, general health, or lifestyle would contribute to changes in hormone secretion or bone accrual. In fact, all of the endocrine parameters that we measured were similar in the longer and shorter length cycles except for those associated with the delay of ovulation.

Our previous study of young women who exercised regularly demonstrated that perturbations of FSH secretion during the LFPT are associated with a delay of ovulation in the subsequent cycle and a prolongation of its follicular phase (De Souza et al. 1998). Thus, it appears that this transition period from the luteal phase of one cycle to the follicular phase of the next cycle is particularly sensitive to effects of environmental stressors. The present

**Figure 2.** Daily urinary FSH profiles during the LFPT preceding shorter cycles and longer cycles. Day 1 is the first day of the next menstrual bleeding. FSH levels were significantly lower during the interval from day −7 to day −3 of the LFPT preceding longer cycles compared with those in the same interval prior to shorter length cycles (*p* < 0.05).

![Figure 2](image2.png)

**Figure 3.** Urinary DPD concentrations indexed by creatinine during the follicular phase of the shorter cycles and longer cycles aligned as shown in Figure 1A. Trend lines show that DPD concentrations gradually increased during the late follicular phases of longer cycles, whereas DPD concentrations gradually decreased during the same interval of shorter cycles.

![Figure 3](image3.png)
report suggests that changes in the regularity of work shift can have adverse effects on menstrual function when they take place at this time. The frequency of off days during the LFPT may have similar effects, but further investigation of confounding factors is needed before any conclusions can be drawn. The observed differences in FSH profiles during the transition periods preceding shorter and longer cycles may provide an important clue to the underlying mechanism. The apparent inhibition of FSH secretion during this time is consistent with a previous study of women who exercised regularly in which a decreased FSH secretion during the LFPT was 90% predictive of a prolonged follicular phase and delay of ovulation in the following menstrual cycle (De Souza et al. 1998).

Table 2. Work schedule during the LFPT prior to each cycle.

| Subject | Days prior to first cycle | Days prior to second cycle |
|---------|--------------------------|---------------------------|
| 1       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 2       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 3       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 4       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 5       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 6       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 7       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 8       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 9       | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 10      | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 11      | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |
| 12      | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD | DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD DD |

Abbreviations: D, day (8:00 hr–14:00 hr); OD, off day; S, swing (14:00 hr–22:00 hr); G, graveyard (22:00 hr–06:00 hr); NA, information not available.


day 1 is the first day of the next menstrual cycle. 

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