Migraine Prevalence During Menopausal Transition

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Background.—The effect of menopausal transition on the frequency of migraine has never been the focus of a community-based study.

Methods.—A cross-sectional community-based survey was undertaken among Chinese women aged 40 to 54 years in Kinmen, Taiwan. Neurologists diagnosed migraine based on the 1988 International Headache Society classification criteria. Menstrual history including a past or current history of premenstrual syndrome was obtained. Serum levels of estradiol and follicle-stimulating hormone were measured.

Results.—The 1-year prevalence of migraine was 16.5% in the 1436 participants. Among the women who had not had hysterectomies and did not report symptoms of premenstrual syndrome, migraine prevalence did not vary according to menopausal status. In contrast, in women with self-reported premenstrual syndrome, menopausal status was a factor in migraine prevalence: the late perimenopausal group had the highest prevalence (31%) and the spontaneous menopausal group had the lowest (7%). Among all menopausal groups, women who had had hysterectomies reported the highest migraine prevalence (27%), with the highest occurring in those with premenstrual syndrome (44%). The presence of low estrogen (<50 pg/mL) and high follicle-stimulating hormone levels (>30 mIU/mL) was associated with lower migraine prevalence, even in the premenopausal and early perimenopausal women.

Conclusions.—Our data supported the clinical impression that migraine prevalence increases before menopause and declines after spontaneous menopause. However, in this study, this trend occurred only in women with increased vulnerability to hormonal change, such as those with premenstrual syndrome. The presence of low estrogen and high follicle-stimulating hormone levels predicted lower migraine prevalence, whereas a history of hysterectomy was related to higher prevalence.

Key words: estrogen, menopause, migraine, prevalence

Abbreviations: PMS premenstrual syndrome, E2 estradiol, FSH follicle-stimulating hormone, OR odds ratio, CI confidence interval

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women and found that many patients had migraine without aura. In that study, women with prior migraine generally improved with spontaneous menopause; in contrast, surgical menopause usually resulted in a worsening of migraine.

Many patients with migraine (26% to 60%) report increased migraine attacks during menses, and about 7% suffer from their attacks only during menses. The prevalence of menstrual migraine is dependent on how it is defined and diagnosed. Premenstrual syndrome (PMS) has also been variably defined. Menstrual migraine can be associated with PMS. They may both result from a cyclic control disturbance of pain perception and mood. Patients with severe PMS were noted to improve after the suppression of ovarian function by using a gonadotropin-releasing hormone agonist, and PMS recurred after ovarian steroid hormone replacement. Therefore, patients with migraine with PMS might also benefit from physiological menopause.

We investigated migraine prevalence in relation to different menopausal status during menopausal transition among women in Kinmen, Taiwan. In this cross-sectional study, we also analyzed the relevant predictors for the occurrence of migraine attacks during this important stage of the female life cycle. To our knowledge, no such community-based study of the change of migraine prevalence across the menopausal transition has been done previously.

**METHODS**

The present study is part of the Kinmen Women-Health Investigation (KIWI) that investigates changes in cognition and mental health and the occurrence of migraine in women during the menopausal transition. The Institutional Review Board of Taipei Veterans General Hospital approved the protocol of the study. The study design and methodology of KIWI have been published elsewhere.

Kinmen is a 176-km² island that is 154 miles (248 km) west of Taiwan and 25 miles (41 km) east of mainland China. The total population was 51060 in 1998. There are 4 townships in Kinmen with similar demographic compositions. Based on logistic convenience, we chose Kin-Hu and Kin-Cheng, 2 of the 4 townships, for the study. All women aged 40 to 54 years living in these 2 townships were contacted by mail or by trained personnel in an attempt to enroll the eligible subjects. The participants were encouraged to go to the local health office for evaluation.

**Personal Information.**—Demographic data, medical history, family history, and information on personal habits were obtained from the subjects through self-administered questionnaires, in the presence of well-trained interviewers.

The participants were also asked about their menstrual and reproductive history. A number of questions concerning premenstrual symptoms were included to screen for the presence or absence of PMS, either currently or previously. In this study, PMS was defined based on the Tenth Revision of the International Classification of Diseases (ICD-10) as a history of at least 1 of 7 specific physical or mood symptoms occurring in a cyclic fashion, that is, present during the last week before menses and absent in the week after menses. The 7 symptoms are minor psychological discomfort, bloating or weight gain, breast tenderness, muscular tension, aches and pains, poor concentration, and change in appetite.

**Menopause-Related Symptom Checklist.**—This was modified from the Kupperman index on the experience and frequency of symptoms in the previous 2 weeks. Two vasomotor symptoms, hot flashes and night sweating, were included.

**Headache Diagnosis.**—Each participant was interviewed, utilizing a semistructured headache questionnaire, and examined by a board-certified neurologist. The neurologists were experienced in headache diagnoses and the questionnaire has been used in previous studies with a good reliability among neurologists. The participants were queried about their headaches within the previous year including the frequency, severity, characteristics, location, duration, and accompanying symptoms.

The diagnoses of headache were made according to the International Headache Society (IHS) criteria by our neurologists, and included both migraine with aura and migraine without aura. To establish a diagnosis of IHS migraine without aura (code 1.1), 5 attacks were needed. Each attack must have lasted 4 to 72 hours and have had at least 2 of the following 4 pain characteristics: unilateral location, pulsating qual-
ity, moderate to severe intensity, and aggravation by routine physical activity. In addition, the attacks had to be associated with at least 1 of the following: either nausea or vomiting, or both photophobia and phonophobia. Migraine with aura (code 1.2) was diagnosed only if the subjects had had at least 2 auras compatible with the IHS criteria for migraine aura, that is, their aura had to meet the following criteria: a duration of more than 4 minutes and less than 60 minutes, and an interval between headache and aura of less than 60 minutes. It should be noted that whether or not their aura symptoms were due to “focal cerebral dysfunction” was not used as a criterion in this study. The subjects who suffered migraine both with and without aura were included in the “migraine with aura” diagnostic group. If the migraine attacks occurred more frequently 2 days before or during the menses, this was defined as menstrually related migraine.18

**Hormone Assay.**—All subjects had blood drawn for the measurement of estradiol (E2) and follicle-stimulating hormone (FSH) by commercial immunoassay (Boehringer Mannheim, Mannheim, Germany). The sensitivity of the E2 measurement was 10 pg/mL. In this study, we defined levels of E2 <50 pg/mL and FSH >30 mIU/mL as ovarian failure.

**Hospital Anxiety and Depression Scale.**—The Hospital Anxiety and Depression Scale (HADS) is composed of 14 questions, 7 related to anxiety and 7 related to depression. Scores range from 0 to 42.19 The Chinese version of the HADS exhibits good agreement with the English original.20 In this study, the HADS was used to measure psychological distress.

**Definition of Menopausal Status.**—Women were classified into 5 categories of menopausal status: premenopause, early perimenopause, late perimenopause, spontaneous menopause, and surgical menopause.21 The premenopausal period was defined as regular menstruation. Women were considered perimenopausal if their menstrual cycles had become irregular, defined as one of the following: (1) cycles lasting less than 23 days or more than 35 days, (2) cycles that varied by more than 5 days during the preceding 3 months (early perimenopause), or (3) menstrual bleeding that last occurred between 3 and 12 months prior to the study (late perimenopause).21 Women who had not menstruated within the previous 12 months were placed in the spontaneous menopause category. Women who had undergone hysterectomy or bilateral ovariectomy before spontaneous menopause were placed in the surgical menopause category.

**Statistical Methods.**—One-year prevalence of migraine is presented as the number of cases per 100 persons. Student t and chi-square tests were used for comparison when appropriate. The means and standard deviations of the various parameters were calculated for each menopausal category. The differences among means were compared by 1-way analysis of variance (ANOVA). The strength of the predictors for migraine prevalence during the menopausal transition was represented with an odds ratio (OR) with 95% confidence interval (CI) after multiple logistic regression analysis. A P value <.05 was considered as statistically significant.

### RESULTS

**Characteristics of the Study Population.**—According to the 1998 registration records, there were 2256 women aged 40 to 54 years in these 2 target townships.13 Of these registered women, 1622 women regularly resided in Kinmen according to our household census, comprising the eligible population of the present study. The others were actually living in Taiwan and rarely returned to Kinmen. Of the eligible population, 1436 women participated in this study with a response rate of 88.5%. The participants and nonparticipants did not differ in age (45.5 years; standard deviation [SD], 4.0 versus 45.8 years; SD, 4.2; P = .19). The mean completed education level of the participants was 6.3 years, and 90.2% of them were married.

Table 1 shows the characteristics of the study population in relation to their menopausal status. Most postmenopausal women (75.7%) were within the first 3 years of menopause, that is, early menopause. Their median age at menopause was 49 years. The clinical classifications of menopause status were compatible with age and hormonal status in their groups.21 Hot flashes and night sweating were not common in the participants, with the peak prevalence occurring in the late perimenopausal and surgical
menopausal groups. The surgical menopause group consisted of 104 women. Their clinical characteristics are shown in Table 2. All of them underwent hysterectomy with or without ovariectomy. None of the surgical menopausal women underwent bilateral ovariectomy without hysterectomy.

**Prevalence of Migraine.**—Of the 1436 participants, 985 (69%) reported having at least 1 headache in the previous year. Two hundred thirty-seven subjects (16.5%) were diagnosed with migraine by neurologists based on the IHS classification criteria. Of them, 198 were diagnosed to have migraine without aura (code 1.1) and 39, migraine with aura (code 1.2). Of the 39 subjects with migraine with aura, 29 subjects also had episodes of migraine without aura. The age-specific prevalence (Fig. 1), ranging from 8.5% to 21%, did not differ significantly among different age groups ($P = .6$).

In our subjects with migraine, 119 (50.2%) reported that their headaches were related to menses (menstrually related migraine). Seventeen subjects (7%) reported that their attacks occurred only during menstruation and at no other time.

**Migraine Prevalence in Relation to Menopausal Status.**—Figure 2 shows the prevalence of migraine among different menopausal groups. The prevalence was similar among the premenopausal and 2 peri-
menopausal groups. Compared with those who were in the premenopausal and perimenopausal groups (16.7%), the spontaneous menopausal women had lower migraine prevalence (10.5%; odds ratio [OR], 0.6; confidence interval [CI], 0.4 to 0.9; \( P = .03 \)).

**Premenstrual Syndrome.**—Forty-four percent of all participants reported having suffered from PMS (Table 1). The subjects with self-reported PMS had a higher prevalence of migraine (23.1%) than those without (11.3%) (OR, 2.4; CI, 1.8 to 3.2; \( P < .001 \)).

Among women with migraine, self-reported PMS was associated with a higher percentage of menstually related migraine (57.7%) than those without PMS (38.9%) (OR, 2.1; CI, 1.2 to 3.6; \( P < .01 \)).

We divided the subjects by the presence or absence of self-reported PMS and by menopausal stage (Fig. 2). In the women with PMS who had not undergone hysterectomy, the prevalence was highest in the late perimenopausal group (31%) and declined markedly in the spontaneous menopausal group (7%). In
contrast, in those without PMS, the prevalence of migraine was similar across the different menopausal groups, including the surgical menopausal group.

**Ovarian Failure.**—In women who had not undergone hysterectomy, the presence of ovarian failure (E2, <50 pg/mL and FSH, >30 mIU/mL) was associated with lower prevalence of migraine only in women with PMS but not in those without PMS (Table 3). In those women who had menstruated within the past 3 months (premenopausal or early perimenopausal groups), ovarian failure was also associated with a lower prevalence of migraine (9.0% versus 18.3%; OR, 0.4; CI, 0.2 to 0.9; \(P = .03\)).

**Current Use of Hormone Replacement Therapy.**—There was no difference in migraine prevalence between those who used HRT and those who did not, either in the surgical menopausal group or among the other participants.

**Surgical Menopause.**—The surgical menopausal women had the highest migraine prevalence (27%) among all the menopausal groups (Fig. 2). In those who reported having experienced PMS, surgical menopausal women had a much higher prevalence of migraine (44%) than spontaneous menopausal women (7%) (\(P < .0001\)). The difference did not exist in those without self-reported PMS (Table 3). We also analyzed the migraine prevalence in relation to the surgical procedures and the underlying causes for hysterectomy. Compared with the other 2 procedures, the prevalence of migraine was lowest in those with hysterectomy and bilateral ovariectomy, but not to a statistically significant level (hysterectomy only, 28.6%; hysterectomy with unilateral ovariectomy, 36.4%; hysterectomy with bilateral ovariectomy, 15.8%; \(P = .3\)). In addition, the prevalence of migraine did not differ in relation to their underlying disease categories for hysterectomy (data not shown).

**Vasomotor Symptoms.**—The subjects with either hot flashes (21.8% versus 15.8%; OR, 1.5; CI, 1.0 to 2.2; \(P = .044\)) or night sweating (27.9% versus 15.8%; OR, 2.1; CI, 1.3 to 3.4; \(P = .003\)) had a higher prevalence of migraine than those without these vasomotor symptoms. The presence of vasomotor symptoms (either hot flashes or night sweating) was also associated with the presence of self-reported PMS (42% versus 57%; OR, 1.9; CI, 1.4-2.5; \(P < .0001\)).

**Predictors of Prevalence of Migraine During Menopausal Transition.**—By using stepwise multiple logistic regression, we determined that the significant predictors for the migraine prevalence in our participants, after controlling for age and the HADS score, included self-reported PMS (OR, 2.1; CI, 1.6 to 2.8; \(P < .0001\)), a history of hysterectomy (OR, 1.9; CI, 1.2 to 3.1; \(P = .009\)), and spontaneous menopause (OR, 0.6; CI, 0.3 to 0.95; \(P = .03\)). In addition, the presence of vasomotor symptoms was not a significant predictor in this final model.

### Table 3.—Migraine Prevalence in Relation to Presence or Absence of Self-Reported Premenstrual Syndrome (PMS)*

<table>
<thead>
<tr>
<th></th>
<th>Self-reported PMS (+)</th>
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<th>Self-reported PMS (-)</th>
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<tbody>
<tr>
<td></td>
<td>Migraine Prevalence, %</td>
<td>OR (95% CI)</td>
<td>(P)</td>
<td>Migraine Prevalence, %</td>
<td>OR (95% CI)</td>
<td>(P)</td>
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<tr>
<td>Ovarian failure†</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>12</td>
<td>0.4 (0.2-0.7)</td>
<td>.002</td>
<td>11.4</td>
<td>0.97 (0.6-1.7)</td>
<td>.9</td>
</tr>
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<td>No</td>
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<td>—</td>
<td>—</td>
<td>11.6</td>
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<tr>
<td>Surgical</td>
<td>44</td>
<td>10.5 (3.5-31.1)</td>
<td>&lt;.0001</td>
<td>16.4</td>
<td>1.5 (0.6-3.5)</td>
<td>.35</td>
</tr>
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<td>—</td>
<td>—</td>
<td>11.6</td>
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</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval.

†In subjects without hysterectomy.
COMMENTS

Among our participants who were aged 40 to 55 years and experiencing menopausal transition, the prevalence of migraine was similar in premenopausal and perimenopausal women (16.7%) and lower in the spontaneous menopausal women (10.5%). It is of note that the pattern of change differed between the subjects with self-reported PMS and those without. That is, the prevalence was similar among all the different menopausal groups without PMS, but in the participants with PMS the prevalence slightly increased in the late perimenopausal group and markedly decreased in the spontaneous menopausal group in comparison with the premenopausal women.

Our findings supported a clinical notion that migraine prevalence increases during the perimenopausal state and decreases after physiological menopause. However, this was only demonstrated in the women with self-reported PMS. Therefore, this clinical impression may result from the Berkson bias, that is, more patients with PMS visit menopause or headache clinics.

The mechanisms of PMS are still controversial. It has been suggested that women with a history of PMS have increased sensitivity to changes in levels of reproductive hormones. A similar mechanism has also been implicated for menstrually related migraine because estrogen withdrawal is found to trigger migraine attacks in susceptible women, even when they are postmenopausal. In our study, about 60% of subjects with migraine with PMS had menstrually related migraine attacks, which was in line with a previous study. Therefore, patients with migraine with PMS are possibly more likely to experience a worsening of symptoms in the hormonally turbulent perimenopausal years and subsequently to improve after spontaneous menopause. A socially mediated model for PMS has also been suggested and psychological distress is important for its underlying mechanism. However, our final model showed that PMS was still a predictor for migraine prevalence after controlling for psychological distress.

Although menopause is associated with specific sex hormonal levels, hormone assay cannot be used by itself to determine menopausal status. The presence of low E2 and high FSH levels was associated with low migraine prevalence, even in the participants who had menstruated within the prior 3 months; ie, those in premenopause and early perimenopause. Menstrually related migraine was triggered by an abrupt decline in estrogen levels rather than by absolute levels. The laboratory indication of ovarian failure (E2, <50 pg/mL and FSH, >30mIU/mL) shows only that the estrogen levels are low and fluctuate little.

Hysterectomy as a risk factor for the occurrence of migraine during the menopausal transition was shown in this population-based study. The association was even stronger in the women with self-reported PMS who had undergone hysterectomy. These results support earlier clinic-based studies that show that surgical menopause might worsen migraine. However, our results could not exclude the possibility of the preexisting relationship among migraine, PMS, and hysterectomy. Hysterectomy was reported to cause early ovarian failure. Is it possible that hysterectomy might cause a more disturbed hormonal milieu and worsen headaches? Hormone replacement therapy should also be considered as a possibly related factor, although in our study the percentage of current users was only 24% in the women who had undergone hysterectomy.

Although not in the final model, vasomotor symptoms (hot flashes or night sweating) were related to migraine prevalence in our participants. The correlation among PMS, vasomotor symptoms, and migraine suggests that they all are related to vulnerability to the hormonal changes of menopause. Of note was the low prevalence of vasomotor symptoms in our participants, which is common among Asian women.

Methodology Issues.—Several points should be addressed concerning our methodology. (1) We adopted the definition of PMS based on the ICD-10, which was less strict and no prospective symptom scores were documented. Therefore, the scientific basis in our patients with PMS might not be as strong as those documented by prospective scoring methods; ie, premenstrual dysphoric disorder. It is also of note that retrospective diagnosis of PMS may be biased by recall error because subjects with mild PMS might amplify the degree to which symptoms varied during their menstrual cycles. We suggested that
self-reported PMS in this study might be conceived as increased vulnerability to the hormonal change. The prevalence of self-reported PMS in our study (44%) was similar to previous studies that used retrospective reporting. In addition, the association of PMS and migraine may, in part, result from the overlap of the diagnostic criteria between PMS and migraine.

(2) Any comparison with other studies regarding the worsening or improvement of migraine during the menopausal transition should be made carefully. The other published studies usually recruited clinic-based samples and the definitions of migraine worsening are not the same as the prevalence of migraine in our study, even though migraine is usually considered as a more severe type of headache.

(3) The validity of extrapolation of our results to the late menopausal women is indeterminate, because most of our postmenopausal women were within 3 years of menopause.

(4) Selective recall bias of the self-reported PMS in the spontaneous menopausal women should be considered since they had a significantly lower frequency of self-reported PMS (34%) than the other menopausal groups (42% to 48%).

(5) Finally, the results in this cross-sectional study cannot be completely regarded as defining the transitional process throughout different menopausal stages. A longitudinal follow-up of women starting at the perimenopausal period is warranted to demonstrate the pattern of change in migraine prevalence throughout the menopausal transition.

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REFERENCES