

NEUROLOGY

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Neurology 2006;67;2154-2158; originally published online Sep 13, 2006;
DOI: 10.1212/01.wnl.0000233888.18228.19

This information is current as of November 27, 2009

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<http://www.neurology.org/cgi/content/full/67/12/2154>

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Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen

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Abstract—Objective: To investigate the association between urinary hormone levels and migraine, with particular reference to rising and falling levels of estrogen across the menstrual cycle in women with menstrual and menstrually related migraine. **Methods:** Women with regular menstrual cycles, who were not using hormonal contraception or treatments and who experienced between one and four migraine attacks per month, one of which regularly occurred on or between days 1 ± 2 of menstruation, were studied for three cycles. Women used a fertility monitor to identify ovulation, conducting a test each day as requested by the monitor, using a sample of early morning urine. Urine samples were collected daily for assay of estrone-3-glucuronide, pregnanediol 3-glucuronide, follicle-stimulating hormone, and luteinizing hormone. All women kept a daily migraine diary and continued their usual treatment for migraine. **Results:** Of 40 women recruited, data from 38 women were available for analysis. Compared with the expected number of attacks, there was a significantly higher number of migraine attacks during the late luteal/early follicular phase of falling estrogen and lower number of attacks during rising phases of estrogen. **Conclusion:** These findings confirm a relationship between migraine and changing levels of estrogen, supporting the hypothesis of perimenstrual but not postovulatory estrogen “withdrawal” migraine. In addition, rising levels of estrogen appear to offer some protection against migraine.

NEUROLOGY 2006;67:2154–2158

During the female reproductive years, migraine is up to three times more common in women than in men of similar age.¹ This sex difference is generally considered to be due to the additional hormonal trigger in women. In specialist clinics and in population-based studies, 50% of women report an association between migraine and menstruation.^{2,3} The peak time for migraine is on or between 2 days before the start of menstruation and the first 3 days of bleeding.⁴⁻⁸

Identification of the underlying mechanisms of menstrual migraine could enable more effective treatment strategies to be developed. However, despite clinical evidence for the effect of hormonal events, the pathophysiology remains poorly understood.

The main hormones considered have been progesterone and estrogen. Levels of both these hormones fall in the late luteal phase of the menstrual cycle, preceding the increase in menstrual attacks of migraine.

Evidence for the importance of progesterone in migraine is conflicting.⁹⁻¹² A greater body of evidence suggests that migraine is associated at least in some women, with the “withdrawal” of exogenous and endogenous estrogen.¹³⁻¹⁹

However, results from studies assessing serum or urinary hormones levels and headache risk are based on limited data. Further, headache risk has been analyzed according to standard menstrual, follicular, and luteal phases of the menstrual cycles rather than specifically analyzing risk during rising and falling hormone phases.²⁰ We here present the results of a longitudinal study that examined the association between migraine and daily urinary hormone levels, with particular reference to rising and falling levels of estrogen across the menstrual cycle, in women with pure menstrual or menstrually related migraine.

Methods. Women were selected from those who attend the City of London Migraine Clinic and identified from a review of their

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This article was previously published in electronic format as an Expedited E-Pub on September 13, 2006, at www.neurology.org

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Supported by a grant from Unipath Limited.

Disclosure: E.A.M. has received consulting fees from Unipath Limited. E.A.M. and A.F. have received funding from Unipath to attend an international meeting. The City of London Migraine Clinic has received research funds from Unipath Limited. Clearblue Easy Fertility Monitors were supplied by Unipath Limited.

Received January 13, 2006. Accepted in final form April 27, 2006.

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diary cards, as all women are requested to regularly complete daily diary cards as part of their routine management. They were eligible for inclusion into the study if they had pure menstrual migraine or menstrually related migraine and they had regular menstrual cycles (21 to 35 days). The intention was to observe hormone levels and migraine occurrence during three consecutive cycles.

Only women for whom at least three consecutive diary cards were available were included. Pure menstrual migraine was defined as migraine attacks on or between day 1 of menstruation \pm 2 days (i.e., on or between days -2 to $+3$ of the cycle, assuming day 1 is the first day of menstruation and that there is no day 0) in at least two of three cycles with no migraine at other times of the cycle.²¹ Menstrually related migraine was defined as up to four attacks of migraine per month, of which one must occur on or between day 1 of menstruation \pm 2 days in at least two of three cycles.

Women were not eligible if headaches (including migraine headaches) occurred more often than 3 days a week on average, that is, more than 12 days per month; analgesics or acute headache medications were used regularly on more than 3 days a week; they were pregnant or intended to become pregnant during the study period (women used nonhormonal contraception) or were breastfeeding; had evidence of impaired liver or kidney function; had evidence of polycystic ovarian syndrome (unless they had regular menstrual periods); used hormonal contraception, hormone replacement therapy, or other hormonal treatment within 6 months prior to the start of the study or at any time during the study period; used treatments that might affect the menstrual cycle such as a diet high in soy or use of soy/isoflavane supplements; be taking tetracycline (which affects luteinizing hormone [LH] assay) or had any medical or psychiatric condition that might have been affected adversely by use of estrogen supplements or that would preclude participation in the study.

All women gave informed consent and were reviewed monthly, either by telephone or by a clinic visit. The local ethics committee approved all study documents.

Women were provided with a diary card for each month on which the following information was recorded for each migraine attack as it occurred: date and time of onset of symptoms; peak severity (mild, moderate, or severe); duration of attack (to nearest day); associated symptoms (nausea, photophobia, and phonophobia); aura, if present; medication (name, dose, time taken). All diary card data were input into an Excel database by one individual and reviewed by one of the authors to ensure consistency of interpretation. If there was doubt about the nature of any headache episode, the patient was contacted for clarification.

Daily early morning urine (EMU) samples were collected on each morning of the study, in universal vials containing sodium azide (0.1%) as a preservative. During the collection period, women sent their samples to the laboratory weekly where specimens were aliquoted and stored at 4 °C until analyses were carried out. Urine samples were analyzed for estrone-3-glucuronide (E_1G) and pregnanediol 3-glucuronide (PdG), urinary metabolites of estradiol and progesterone, together with LH and follicle-stimulating hormone (FSH) using an AutoDelfia (Perkin Elmer Life Sciences, Cambridge, UK). LH was used to confirm ovulation, whereas FSH allowed classification of menopause status.²² Urinary E_1G reflects the changes of plasma estradiol (E_2).²³ EMU samples were convenient and the excretion pattern of E_1G in EMU is similar to the pattern obtained for 24-hour urine samples.²⁴ Because of this, concentrations can be expressed in mass/volume instead of mass steroid/creatinine ratio.²⁵ Further, creatinine adjustment is not essential for the study of menstrual cycle urinary hormones based on daily sampling.²⁶ Data were shifted back 1 day for comparison with the diary card data, as morning collection of E_1G and PdG reflects serum hormone levels 12 to 24 hours earlier.²⁷

Rather than dividing the menstrual cycles into the standard three follicular, ovulatory, and luteal phases, each menstrual cycle was divided into phases of rising and falling estrogen. Hence, there were two phases of rising estrogen (the first during the early follicular phase; the second during the early luteal phase) and two phases of estrogen "withdrawal" (the first occurring during early luteal phase; the second during late luteal phase) identified as follows: phase 1: follicular phase rising estrogen from the follicular E_1G nadir to the ovulatory peak; phase 2: postovulatory falling

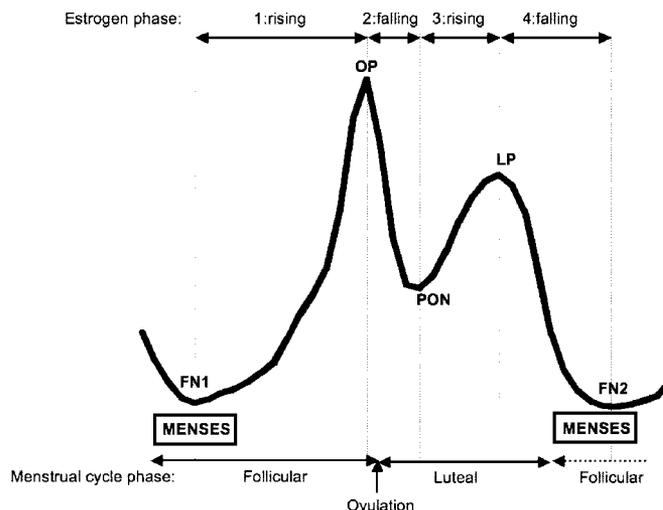


Figure 1. Example of rising and falling phases of estrone-3-glucuronide (E_1G) across one menstrual cycle. Phase 1: follicular phase rising estrogen from the follicular E_1G nadir (FN1) to the ovulatory peak (OP); phase 2: postovulatory falling estrogen from the ovulatory peak (OP) to the postovulatory nadir (PON); phase 3: luteal phase rising estrogen from the postovulatory nadir (PON) to the luteal E_1G peak (LP); phase 4: late luteal/early follicular falling estrogen from the luteal E_1G peak to the E_1G nadir of the next cycle (FN2).

estrogen from the ovulatory peak to the postovulatory nadir; phase 3: luteal phase rising estrogen from the postovulatory nadir to the luteal E_1G peak; phase 4: late luteal/early follicular falling estrogen from the luteal E_1G peak to the E_1G nadir of the next cycle.

These are shown in figure 1. For each cycle the total number of migraine attacks in each phase was determined. The expected number, assuming random occurrence, was calculated as the total number times the ratio of the phase length to the cycle length. The expected and observed numbers in each phase were then cumulated over all cycles.

The E_1G slopes and E_1G concentrations on the first day of each migraine attacks and the preceding 5 days were analyzed to assess whether migraine was related to rate of change E_1G or if a critical threshold existed.

We also examined the association between migraine occurrence and menstruation. A migraine attack was counted as consecutive days of migraine. An interval of 48 hours freedom from symptoms defined discrete attacks.²⁸ A migraine day was each day on which the woman reported migraine. For each woman, the risk of having a migraine during the pre- or postmenstruation period (day 1 \pm 2) was compared with the risk of migraine at all other times of her cycle, and the relative risk calculated. The relative risks (RRs) were then combined across all women using a method that allows for small occurrences and provides a p value and 95% CI.²⁹

Results. Forty women were recruited into the study. Two were excluded from the data analysis: One experienced cycles longer than the maximum cycle length acceptable for inclusion; another with prestudy diaries confirming migraine with menstruation did not experience menstrual attacks during the study period. Final analyses were undertaken on data from 38 women.

Mean age was 43 (range 29 to 50) years; 87% were over age 35 and 29% were over age 45. All women had migraine without aura; one also had attacks of migraine with aura, but all her menstrual attacks were without aura. Most

Table Observed and expected frequency of migraine during different phases of the menstrual cycle

	Observed no. of migraine attacks	Expected no. of migraine attacks	χ^2
Phase 1: follicular phase rising estrogen	52	64.4	2.39
Phase 2: postovulatory falling estrogen	40	42.4	0.13
Phase 3: luteal phase rising estrogen	23	33.5	3.29
Phase 4: late luteal/early follicular falling estrogen	90	64.7	9.87
Total	—	—	15.68

Overall $p < 0.0013$ for observed vs expected.

women had menstrually related migraine; one woman had pure menstrual migraine.

Nine women (24%) used analgesics alone for symptomatic treatment; 21 (55%) used analgesics and triptans; 6 (16%) used triptans alone; 2 (5%) used ergots. Nine women (24%) were taking daily nonhormonal prophylaxis: three amitriptyline; three beta-blockers; one pizotifen; one amitriptyline and atenolol; one fluoxetine and pizotifen. There were no differences in demographic data or migraine frequency between these women and women who were not using prophylaxis.

There was a total of 476 migraine days during the study. Women experienced a mean of 1.86 migraine attacks per cycle and 3.98 migraine days per cycle. Migraine was more likely to occur on day 1 ± 2 vs all other times of the cycle (RR 1.45 [95% CI 1.17 to 1.79], $p < 0.001$). Furthermore, these attacks were more likely to be moderate or severe (RR 1.35 [95% CI 1.03 to 1.74], $p = 0.03$) and associated with nausea (RR 1.46 [95% CI 1.04 to 2.00], $p = 0.03$) or vomiting (RR 2.56 [95% CI 1.05 to 5.78], $p = 0.04$).

Migraine incidence was lower during phases of rising estrogen and higher during phases of falling estrogen (table). The differences between phases were significant ($p < 0.0013$). Phase 4 (late luteal/early follicular falling estrogen) had the highest incidence of migraine vs the expected incidence. In contrast, phases of rising estrogen (phase 1: follicular phase rising estrogen; phase 3: luteal phase rising estrogen) had the lowest incidence of migraine compared with the expected incidence. There was no significant difference between expected and observed number of migraine attacks at the time of ovulatory falling estrogen (phase 2).

Figure 2 shows the pooled incidence of migraine correlated with urinary E_1G and PdG on each cycle day of 120 cycles from 38 women. The incidence of migraine began to rise 3 days before menstruation (day -3), associated with falling levels of E_1G . Peak incidence was on the first full day of bleeding (day +1) and the preceding day (day -1). The median cycle day of the E_1G nadir was day +2. As E_1G began to rise, the incidence of migraine declined.

The mean peak luteal phase E_1G was 32.8 ng/mL. With respect to a critical “threshold,” analysis of pooled data did not reveal any relationship between the concentration of E_1G on the day on which migraine occurred in the late luteal phase or any of the 5 preceding days. Neither was there any apparent relationship between the rate of change of E_1G on the day on which migraine occurred in the late luteal phase or on any of the 5 preceding days.

Discussion. This study assesses migraine during phases of rising and falling levels of estrogen across

the menstrual cycle. Our results confirm previous studies showing that migraine is significantly more likely to occur in association with falling estrogen in the late luteal/early follicular phase of the menstrual cycle. This supports the hypothesis of estrogen “withdrawal” triggering migraine. A new finding, which has not been assessed in earlier studies, is that migraine was significantly less likely during phases of rising estrogen. There was no significant association between migraine and ovulation. As only luteal estrogen “withdrawal” but not ovulatory estrogen “withdrawal” was associated with migraine, we agree with the suggestion that a period of sustained high estrogen priming is a necessary precursor.¹⁵⁻¹⁷

The age of the study population is of note (mean age is 43 years). The clinical impression is that the menstrual trigger for migraine affects women entering the perimenopause more than younger age groups. Although we have no control population, this is supported by results of other studies of women who were similarly not using hormonal contraception. In one study the mean age of women in the menstrually related group was 37 years, whereas the mean age of women who had migraine unrelated to menstruation was 29 years.¹⁹

Our failure to identify a critical “threshold” for estrogen associated with migraine in the late luteal phase is in line with the theory that falling levels are

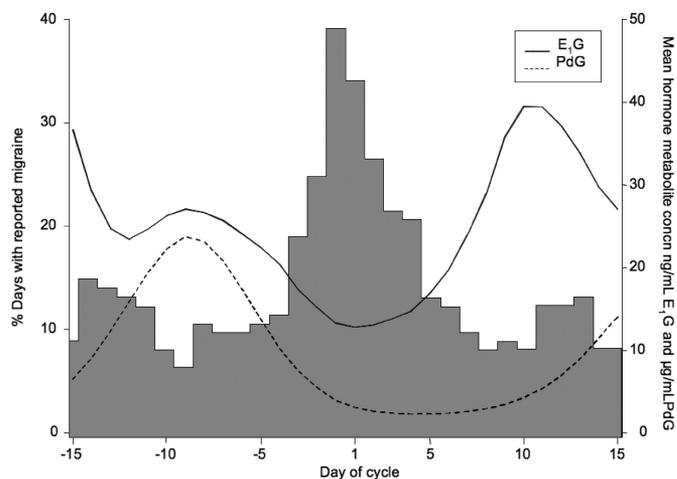


Figure 2. Incidence of migraine, urinary estrone-3-glucuronide (E_1G) and pregnanediol-3-glucuronide (PdG) levels on each day of the menstrual cycle in 120 cycles from 38 women.

more important than an absolute level.¹⁵ Neither was there evidence of an association between the rate of change of estrogen "withdrawal" and migraine. Other researchers have also failed to find a correlation with critical threshold or rate of change.²⁰ However, they may still be important at an individual level, although it would be necessary to have more individual cycle data to analyze this. Further, urinary E₁G levels may not be sensitive enough to establish a difference.

If estrogen "withdrawal" is an important mechanism, why does it not trigger migraine in all women? In our study, the mean peak luteal phase urinary E₁G level of 32.8 ng/mL is worth noting as it is significantly higher than the expected mean urinary peak luteal phase E₁G levels of 14.9 ng/mL for normal fertile cycling women reported in population studies matched by menopause status.²² Other researchers noted raised serum concentrations of both estrogen and progesterone in women with migraine, most striking in the late luteal phase.¹⁹ But high luteal phase estrogen may just reflect the age of the population, as the perimenopause can be associated with high estrogen levels.³⁰ High baseline estrogen would result in a greater luteal drop, which might account for the increased prevalence of menstrual attacks of migraine at this time of life.

Biologic predisposition may also be important. A study of postmenopausal women found that despite similar serum estradiol levels, only postmenopausal women with a premenopausal history of migraine associated with menstruation developed migraine as estrogen levels declined following a single depot estradiol injection.¹⁸ In contrast, women with no premenopausal migraine did not develop migraine. This would be interesting to study in more depth in future research, particularly in light of a recent study of women with migraine and chronic daily headache, the results of which suggest that headaches are influenced by hormone fluctuations even in women without an apparent association with menstruation.³¹

Is the effect of estrogen "withdrawal" primary or secondary? It is recognized that both estrogen and progesterone have a clinically relevant effect on vascular tone.³² Regulation of the menstrual cycle is complex, with ovarian steroids playing a limited role in the overall control. It is likely that the chemical alteration more directly responsible for migraine is the effect of the changing hormonal environment on other biochemical and metabolic pathways, rather than a direct effect of sex hormones. Serotonin-producing neurons are sensitive to the presence or absence of ovarian hormones.³³ Fluctuating levels of estrogen and progesterone in the luteal phase of the menstrual cycle affect levels of brain serotonin and abnormalities of the serotonin system in menstrual migraine have been reviewed.³⁴ Close interrelationships between estrogens and the brain neurotransmitters have also been confirmed, including the catecholamines, norepinephrine, dopamine, and the endorphins.

The strengths of this study are the careful diagnosis of migraine for each attack, the larger number of women, and daily hormone levels assessed over several consecutive cycles.

We did not analyze migraine relative to rising and falling phases of progesterone. Although no obvious association with migraine was apparent in our study, it cannot be discounted. However, our finding of the importance of estrogen is supported by previous research showing that withdrawal of estrogen is associated with migraine in the absence of progesterone. In a study of two postmenopausal women with a past history of menstrual migraine who had been free of migraine since the menopause, migraine followed estrogen withdrawal following depot estradiol despite plasma progesterone concentrations never exceeding 1 ng/mL.¹² Similarly, when 28 postmenopausal women were challenged with estrogen, the drop in serum estrogen precipitated migraine in the absence of progesterone, and a period of estrogen priming was a necessary prerequisite.¹⁸

Acknowledgment

The authors thank John Coley, Lorraine Butlin, and Amanda Colbert.

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