Does the Ovarian Cycle Influence the Pressure-Pain Threshold of the Masticatory Muscles in Symptom-Free Women?

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Aims: *To test the hypothesis that the ovarian cycle influences the pressure-pain threshold of the masticatory muscles.* **Methods:** *Eighteen healthy women with a regular menstrual cycle (28 ± 2 days), ranging in age from 18 to 35 years, participated in the study. For each subject, pressure-pain thresholds (PPTs) of the masseter and temporalis muscles were assessed at 4 muscular sites by means of an electronic algometer. Measurements were taken at 4 separate sessions across the menstrual cycle corresponding to the following phases: menstrual, follicular, periovulatory, and luteal. Menstrual cycle phases were determined by a pelvic ultrasonographic screening. The study was carried out in a single-blind design, and the initial session was randomly determined for each individual. Data collected were analyzed by repeated-measures analysis of variance.* **Results:** *The findings suggest that the PPTs of several masticatory muscles (2 of 4) are influenced by the ovarian cycle, but to a minor extent ($P < 0.05$), and the influence is of limited clinical relevance.* **Conclusion:** *In healthy subjects, there is a link between mechanical sensitivity of the masticatory muscles and fluctuation of the ovarian hormones. The relationship between PPTs of the masticatory muscles and the ovarian cycle should be also investigated in patients with temporomandibular disorders and/or orofacial pain conditions.*
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A strong female predominance has been observed in patients with temporomandibular disorders (TMD) and other orofacial pain conditions[1]; more specifically, women are found to report more headache, temporomandibular joint (TMJ) clicking, TMJ tenderness, and muscle tenderness than men.[2–4] The reasons for the higher prevalence of TMD in women are largely unknown. Hormonal and constitutional factors, along with psychosocial differences between the sexes, have been claimed as possible etiologic factors.[1,2]

The intake of endogenous female reproductive hormones has been found to increase the risk of TMD pain in postmenopausal women, but a clear hormone-related risk has not been identified with a particular subtype of TMD.[5] It is also of note that the fluctuation in reproductive hormones may affect pain levels of TMD patients; indeed, the pain levels in patients using oral contraceptives appear less variable than those of patients not under contraceptive therapy.[6] Since pain symptoms in many disorders are reported to vary with the stages of the menstrual cycle, a connection between hormones and persistent pain of muscular origin has

been hypothesized. In support of this view, there is some evidence that female pain sensitivity varies according to the phase of the ovulatory cycle.[7–9] Using a variety of experimental pain stimuli, including heat, shock aversion, and electrical stimuli, studies have shown a variation in pain threshold and/or pain tolerance over the menstrual stages in symptom-free, normally ovulating women.[7–10] On the other hand, women taking birth control pills do not exhibit significant variation in pain perception across menstrual stages.[7] This could be ascribed to the fact that in medication-free women the levels of estrogen and progesterone vary in rhythmic patterns across the menstrual cycle, whereas in women taking oral contraceptives the effects of these hormones are found to be more stable.

Pressure algometry is often employed for the measurement of orofacial pain.[11,12] The assessment of pressure-pain threshold (PPT) has been shown to be valid and reliable in patients with a variety of musculoskeletal pain syndromes[11–14] and in asymptomatic subjects.[15–17] Decreased PPTs of the involved muscles have been found in headache sufferers[13,14,18] and in both myogenous and arthrogenous TMD patients.[11,12,19] Interestingly, these chronic pain patients show an increased pain sensitivity also at some extracephalic sites,[18,20] which may result from disruption of nociceptive modulation within the central nervous system.[21,22]

To the authors' knowledge, the relationship between the ovarian cycle and PPTs of the masticatory muscles has not yet been evaluated. Therefore, the present study aimed to evaluate the PPTs of the jaw muscles in healthy women during different menstrual cycle phases. The hypothesis was that the PPTs in the masseter and anterior temporalis muscles are influenced by the ovarian cycle.

Materials and Methods

Subjects

Twenty-four normal menstruating women volunteered to take part after giving informed consent. They were staff members or students at the Dental School at the University of Naples "Federico II." The mean age (± SD) of the subjects was 25.1 ± 3.6 years (range, 21 to 31 years). Health and demographic information was obtained through a questionnaire administered at the beginning of the study. The following information was collected: age in years; age at menarche; days of menstrual flow; occurrence of headache, low back pain, and menstrual pain/cramps; and intake of drugs. The severity of menstrual pain symptoms was scored on 4-point ordinal scales as follows: 0 = no pain at all; 1 = slight pain; 2 = moderate pain; and 3 = severe pain. Women reporting moderate or severe pain symptoms (score 2 to 3) were excluded from the study. Furthermore, to be included in the study, the subjects were required to have a regular menstrual cycle (28 ± 2 days). The following conditions were considered as additional exclusion criteria: TMD and/or orofacial pain diagnosed according to the Research Diagnostic Criteria,[23] intake of oral contraceptives, wearing of intrauterine contraceptive devices, consumption of nonsteroidal anti-inflammatory agents or any other medication within the last month prior to participation, and migraine and/or neurologic disorders. The existence of episodic tension-type headache (less than twice a month) was not considered an exclusion criterion. Eighteen of the 24 subjects fulfilled these criteria and formed the experimental group.

Experimental Protocol

The study took place over 4 sessions in each subject, with 1-week intervals between sessions. Assessments were taken at the following phases of the menstrual cycle: the 1st day of menstruation; the 7th day ± 2 days, during the follicular phase; the 14th day ± 2 days, during ovulation; and the 21st day ± 2 days, during the luteal phase. A pelvic ultrasonographic screening was performed to single out the follicular, the ovulatory, and the luteal phases. Ultrasonography was preferred to common blood tests because it is noninvasive. The echographic approach gives immediate evidence on the cycle phase by monitoring normal follicular growth and ovulation.[24–27] To minimize order effects, the phase at which the first testing began was determined with a balanced randomization across subjects, whereas subsequent assessments were performed consecutively: 4 subjects (22%) began in the menstrual phase, 4 subjects (22%) in the follicular phase, 5 subjects (28%) during ovulation, and 5 subjects (28%) in the luteal phase. All subjects were informed about the whole procedure and measurements in advance. The study was performed in a single-blind design, since the examiner was not aware of the subject's cycle phase; furthermore, subjects were not informed about the expectation of the study. All experimental sessions lasted about half an hour and took place in the morning. In each session, the following parameters were assessed in a sequential

order: visual analog scales (VAS) for pelvic pain and headache and PPTs of the masseter and anterior temporalis muscles.

Visual Analog Scales. Pelvic pain and headache were rated on 100-mm horizontal VAS after careful instruction of the volunteers. These scales are widely used for measuring pain and have been described as being sensitive and reliable.[28] The left endpoint of the scale indicated "no pain/headache at all" and the right endpoint corresponded to "worst pain/headache I can now imagine."

Pressure-Pain Thresholds. The PPT was determined as the point at which a pressure stimulus applied to the skin changed from a sensation of pressure to pain.[15] The algometer (Somedic AB), the procedure, and the muscular sites have been described in detail elsewhere.[29] Briefly, algometric measurements were performed with a probe of 1 cm^2 and a rate of pressure increase of approximately 20 kPa/sec.[14] Before the procedure began, the subjects were carefully instructed about the significance of PPTs and a few test measurements were performed on their hand. The subjects sat in a dental chair, and they were asked to relax in the mandibular rest position during the recordings. Pressure-pain thresholds were assessed at 2 sites located on the right masseter and 2 sites on the right anterior temporalis. For the masseter muscle the following sites were chosen: M1 was located over the bulkiest part of the muscle, as determined by palpation during voluntary contraction; and M2 was located 1.5 cm superior to M1, along the main direction of the muscle fibers. For the temporalis muscle the following sites were selected: T1 was located on the line between the upper orbital margin and the upper point of the outer ear, 2 cm behind the anterior border of the muscle (this border was determined from palpation during forceful voluntary contraction); and T2 was located 2 cm superior to T1, along the main direction of the muscle fibers. The sites were measured in the order M1, M2, T1, T2, with approximately 5-second intervals between sites. Four PPT measurements were made at each recording site, with a 2-minute rest interval between trials. Since the first PPT assessment has been shown as being highly variable,[14,16,30] it was discarded, and each PPT was defined by the mean of the successive 3 trials.

To ensure precise relocation of these sites in each session, a transparent pliable plastic template was aligned to the ear, the labial margin, and the eye, and the location of the sites was marked.

Statistical Analysis

The data collected were first analyzed with the Kolmogorov-Smirnov test. Since this test failed to show normality for VAS scores, subsequent analysis of these data was performed with non-parametric Friedman's analysis of variance (ANOVA). Since the hypothesis that the PPT was normally distributed could not be rejected, subsequent analysis of PPTs was performed with repeated-measures ANOVA. Where appropriate, post hoc analysis was performed by means of Newman-Keul's multiple comparison test. A power analysis was carried out from preliminary PPT measurements obtained from the anterior temporalis muscle. The estimated standard deviation was 50 kPa, alpha error was set at 0.05, beta error was set at 0.2, and the difference between means was not to be overlooked at 10%. This last value was considered clinically significant because it is slightly higher than methodologic errors for PPT.[31] The data were analyzed with a commercial statistical software package (Prism 2.01 GraphPad Software). Statistical significance was accepted at $P < 0.05$. The results are presented as the mean and the standard error of the mean.

Results

The PPT measurements obtained during different ovarian cycle phases are shown in Fig 1. Repeated-measures ANOVA revealed that the PPT values measured at sites M1 and T2 were significantly influenced by the 4 menstrual cycle phases investigated (ANOVA; $F = 3.1$ and $F = 3.5$, respectively, $P < 0.05$). Post hoc analysis revealed that PPT values at M1 recorded during the periovulatory phase were significantly different from those recorded during the menstrual, the follicular, and the luteal phases (Newman-Keul's test; $P < 0.05$). The PPT values at T2 were significantly different during the periovulatory phase versus during the luteal phase (Newman-Keul's test; $P < 0.05$).

The VAS scores for pelvic pain and headache are shown in Fig 2. Pelvic pain, as assessed on VAS, was significantly higher during the first day of menstruation (Friedman's test; $F = 15.5$; $P = 0.001$). Conversely, headache VAS scores did not differ significantly across the phases of the menstrual cycle (Friedman's test; $P > 0.05$).

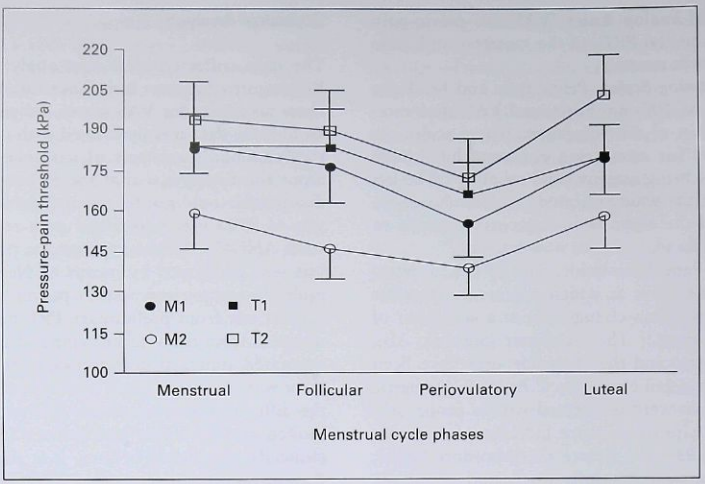

Fig 1 Effects of the ovarian cycle on pressure-pain thresholds of the masticatory muscles. Dots and vertical bars indicate the mean and standard error of the mean. Statistical significance (ANOVA: $P < 0.05$) was obtained for sites M1 and T2. Post hoc analysis revealed that PPT values at M1 were significantly different between the following phases: periovulatory-menstrual, periovulatory-follicular, and periovulatory-luteal (Newman-Keul's test: $P < 0.05$). Mean PPT values at site T2 were significantly different between the periovulatory and the luteal phase (Newman-Keul's test: $P < 0.05$). M1 and M2 = sites on the right masseter; T1 and T2 = sites on the right anterior temporalis.

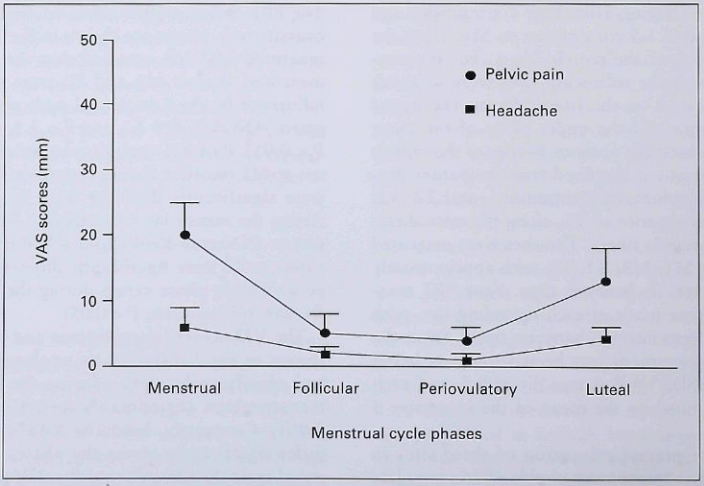

Fig 2 Visual analog scale scores (mean and standard error) for pelvic pain and headache during the ovarian cycle. Pelvic pain scores were significantly different between ovarian cycle phases (Friedman's test; $P < 0.01$); headache scores did not change significantly (Friedman's test, $P > 0.05$).

Discussion

On the basis of the results of this study, the hypothesis that the PPTs of healthy masticatory muscles are influenced by the phases of the ovarian cycle could not be rejected. Indeed, the PPT values obtained from 18 normally menstruating women were found to vary significantly during the 4 cycle phases investigated, being lowest during ovulation. However, significant phase-related differences in PPTs occurred at only 2 muscle sites (M1 and T2). At sites M2 and T1 it was observed that the mean PPT values tended to be lower during the ovulatory phase, and P values approached statistical significance ($0.05 < P < 0.12$); hence, a trend similar to that of M1 and T2 was also evident for M2 and T1. One weak point of the present study is represented by the limited number of subjects investigated. Indeed, the results of the power analysis revealed that, to reach a statistical power of 80%, the study should have included over 50 subjects; therefore, the lack of statistical significance at some muscle sites may be ascribed to the limited power of the study, which can be considered a preliminary report.

A variation in pain thresholds during the menstrual cycle has already been reported.[8–10] Nevertheless, the pattern of this variation is often inconsistent between different studies.[8–10] Our observation of a lower mechanical pain threshold in the human jaw muscles during ovulation (ie, periovulatory phase) appears to be in agreement with the findings of Goolkasian,[9] who evaluated variations of thermal pain thresholds that were assessed at the forearm across different menstrual stages. On the other hand, our findings do not agree with those of Tedford et al,[8] who demonstrated an increase in pain thresholds, as assessed by aversion to electric shock at finger sites, during the periovulatory phase. Procacci et al[32] found low threshold values for radiant heat during the luteal phase. Other investigators[33] found that pain thresholds remained stable throughout the menstrual cycle in both normally menstruating women and users of oral contraceptives. Discrepancies among findings may be related to the different types of stimulation (ie, thermal, electrical, mechanical) or to the different stimulus sites and the different tissues stimulated. Furthermore, the diverse criteria used by investigators to determine ovarian cycle phases across time may also contribute to the variability of results. In this respect, it should be emphasized that several ovarian hormones (ie, estrogens, progesterone, follicle-stimulating hormone, and luteinizing hormone) fluctuate markedly during menstrual phases, particularly in the days around ovulation.[34,35] When these fluctuations are taken into account, the determination of menstrual phases based on temporal criteria alone may not be considered accurate. A greater accuracy may be obtained by direct measurements of hormonal serum levels across the ovarian cycle. In the current study, menstrual cycle phases were determined by means of scheduled timing, supported by pelvic ultrasonographic screening. Ultrasonographic images allow follicular size and the thickness of the endometrium to be estimated with relatively good accuracy and can help to document ovulation.[24–27] Furthermore, it has been shown that follicular diameter and the plasma level of estradiol, as assessed by ultrasonography, are highly correlated ($r = 0.968$).[24]

It has been shown recently[10] that pain thresholds to electrical stimulation of skin, subcutaneous tissue, and muscle tissue are all influenced by menstrual phase, segmental site, and tissue depth. Pain thresholds to electric stimulation were found to be lower during the periovulatory phase for skin, and lower during the perimenstrual phase (ie, the luteal phase of the present study) for muscle and subcutaneous tissues. The different responses of superficial and deeper tissues have been related to variation in sympathetic nervous activity during the menstrual cycle.[10] It has been shown that pressure-pain sensation in the human masseter derives predominantly from the muscle itself and not from the cutaneous tissue.[36] Nevertheless, other findings suggest that quantitative assessments of PPTs of the human jaw muscles reflect the sensitivity of both myofascial tissues and skin.[37,38] In the present study, the influence of the skin overlying the masticatory muscles on PPT measurements has not been assessed; therefore, we cannot draw conclusions about the relative contribution of superficial and deep tissues in determining sensitivity to mechanical stimulation. It would be advisable to further investigate this issue in future studies.

Several hypotheses have been suggested to explain menstrual influences on sensitivity to noxious stimuli. Ovarian hormones may interact with central opioid peptide systems[39] and with inflammatory mediators.[40,41] Furthermore, there is some evidence that the release of nitric oxide in the muscle can be mediated by estrogens and can be involved in the central and peripheral processing of pain.[42] It has also been suggested that gonadotropic hormones may interact with nerve growth factor and its receptors.[43,44] This neurotrophin is thought to play a role in some persistent pains, including masticatory myalgia.[45]

Variation of pain thresholds across the menstrual cycle has also been linked to dysmenorrhea status,[10] but the criteria for diagnosis of dysmenorrhea are inconsistent among different studies. In the present study, only women who reported slight or absent menstrual pain symptoms (ie, scores 0 and 1) were selected. Despite this restriction, analysis of VAS scores revealed that pelvic pain was significantly influenced by the ovarian cycle and was highest during menstruation. However, it should be noted that VAS scores obtained during the menstrual phase were generally low, and only 1 of the 18 subjects investigated exceeded the cutoff value (30 mm on the VAS) previously suggested.[10]

In our previous study,[29] PPTs of patients affected with myofascial pain of the jaw muscles were compared with those of symptom-free control subjects. A significant difference in PPTs between myogenous TMD patients and matched controls has been found. Indeed, the relative differences of PPTs between the 2 groups amounted to about 40 to 50%. In the present study, relative variations of PPTs across the menstrual cycle amounted to about 10 to 12%. These differences were only slightly higher than the errors of measurement of PPTs.[31] Despite their statistical significance, such small variations of PPTs across phases of the menstrual cycle suggest that the fluctuations of ovarian hormones have limited clinical relevance in the occurrence of muscle tenderness and/or pain. This is further supported by the observation that VAS ratings for sporadic headaches reported by the subjects did not differ significantly among the 4 cycle phases investigated.

Fluctuations in pain thresholds during the ovarian cycle are likely to be more relevant in subjects with TMD. Some preliminary findings[46] support a relationship between PPTs in the masticatory muscles and reproductive hormone levels in myofascial pain patients. This relationship should be more extensively investigated in patients with TMD and other orofacial pain conditions.

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