Cyclic Effects on Experimental Pain Response in Women with Temporomandibular Disorders

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Aims: *Since cyclic effects on experimental pain response in women with temporomandibular disorders (TMD) have not been adequately studied, the aim of this study was to assess variations in experimental pain response at 4 phases of the menstrual cycle.* ***Methods:*** *Eighteen normally cycling women with TMD, 25 women with TMD and taking oral contraceptives (OC), 25 normally cycling pain-free controls, and 26 pain-free controls taking OC underwent 3 experimental pain procedures at 4 phases during each of 3 menstrual cycles. These procedures included algometer palpations at fixed amounts of pressure and pressure pain thresholds at several body sites, and an ischemic arm pain task. Repeated measures analysis of variance was used to compare cycle phase, TMD group, and OC status differences in experimental pain response.* ***Results:*** *Significant phase-related differences were seen for palpation intensity measures (P values < .05). Normally cycling women with TMD showed higher palpation pain intensity at menses and midluteal phases, while women with TMD taking OC showed stable palpation pain intensity ratings at menses, ovulatory, and midluteal phases, with increased intensity at the late luteal phase. TMD subjects had greater palpation pain and ischemic pain intensity and lower pressure pain thresholds compared to controls.* ***Conclusion:*** *Phase-related differences in experimental pain response were not strong and were more often found for experimental stimuli with greater clinical relevance (ie, palpation pain) compared with an ischemic pain task.* J OROFAC PAIN 2005;19:133–143

Key words: experimental pain, menstrual cycle, temporomandibular disorders

Temporomandibular disorders (TMD) are a group of conditions characterized by pain or dysfunction in the temporomandibular joint (TMJ) and/or the muscles of mastication.[1] They occur with greater frequency in women and in particular, in women during their reproductive years.[2–4] The high predominance of females affected and seeking treatment[5] has led to consideration of the role of female reproductive hormones as an etiologic or contributory factor.

The authors' data[6] have shown that the intensity of TMD pain varies systematically across the menstrual cycle. Daily reports of facial pain intensity in women with TMD, whether using or not using oral contraceptives (OC), were found to rise toward the end of the menstrual cycle and peak during the first 3 days of menstruation. The timing of the increase in pain corresponds to a time of rapid estrogen fluctuation. In those not using OC, a secondary pain peak occurred around the time of ovulation, another time of rapid estrogen fluctuation. That secondary peak was not observed in women taking OC, who rarely ovulate.

When compared with pain-free controls, patients with TMD also demonstrated altered pain perception to experimentally induced pain stimuli. Subjects with TMD have been found to have lower pain thresholds and greater sensitivity to experimental pain, including thermal, pressure, and ischemic pain when compared to age- and gender-matched pain-free controls.[7] Numerous studies have examined changes in perceptual and behavioral responses to these same experimental pain stimuli across the menstrual cycle in healthy volunteers.[7–10] However, the studies do not present a consistent pattern of menstrual cycle effects.[11] For example, Hapidou and Rollman[12] compared pain sensitivity to palpation and pressure pain thresholds at fibromyalgia tender points in healthy, normally cycling women and those using OC. While there were no cycle effects on pressure pain thresholds in either group, phase differences were found for the number of tender points rated as painful to palpation. Normally cycling women had fewer tender points in the luteal as compared with the follicular phase, while women taking OC had no phase-related differences in number of tender points. In contrast, Drobek et al[13] compared pressure pain thresholds at temporalis and masseter muscle sites in healthy, normally cycling women and women using OC. Normally cycling women had higher masseter pressure pain thresholds in the menstrual phase when compared to the follicular phase but no significant difference at the temporalis site. Women using OC had no cyclic differences at the masseter site but higher pressure pain thresholds at the temporalis site during the menstrual phase when compared to the follicular phase.

An early review[14] concluded that the research demonstrated a consistent pattern of highest pain sensitivity during days 15 to 22 of the prototypical 28-day cycle. More recently, Riley et al[15] used meta-analytic methods to examine pain thresholds and tolerance times. They suggest that a clear pattern of menstrual cycle effects emerged for pressure stimulation, cold pressor pain, thermal heat stimulation, and ischemic muscle pain, with subjects demonstrating higher thresholds in the follicular phase (days 6 to 11) than in other phases.

When menstrual cycle effects on experimental pain were studied in samples with a chronic pain condition, results were somewhat different. Giamberardino et al[16] examined pain thresholds for electrocutaneous pulses applied to the skin at 2 sites of the abdomen within the uterine viscerotomes (abdomen-rectus abdominis, left and right) and at the deltoid and quadriceps muscles at 4 phases of 1 cycle. At all sites, the highest threshold values occurred during the luteal phase (days 17 to 22) when compared to all other phases. In contrast, Bajaj et al[17] found the lowest pressure pain thresholds in dysmenorrheic women during menses when compared to all other phases; no other phase-related differences were found. Only 1 study has examined menstrual cycle influences on experimental pain in subjects with TMD.[18] In a sample of 10 subjects with TMD, phase-related differences in pressure pain thresholds were not found.

Numerous methodological issues could account for the variations in findings. First, many of the studies had small sample sizes.[9,18,19] Second, many of the studies[20–23] did not determine when or even whether ovulation occurred. This is significant in that up to 20% of menstrual cycles can be anovulatory,[24] and if ovulation does not occur, the hormonal milieu in the second half of the cycle differs markedly from that which occurs in an ovulatory cycle. In those studies where ovulation was assessed, the method used most often was monitoring of basal body temperature, a method that is subject to considerable error.[25,26] Third, various specifications of specific menstrual cycle phases and their duration have been used in previous studies. This is a significant consideration in that the hormonal milieu changes considerably between and within phases of the menstrual cycle.[11] Finally, there is considerable variability in choice of pain tasks and pain assessment methods used across studies. Experimental pain stimuli differ along multiple dimensions, including time course (phasic versus tonic), site and depth of stimulation (cutaneous versus deep), site location (regional versus generalized), and potential response (perception versus behavioral withdrawal).

This study was designed to improve upon some of these methodologic shortcomings through the use of a sufficient sample size, confirmation of menstrual cycle phases through the use of both calendar methods and hormonal assays to confirm ovulation, and examination of responses over multiple menstrual cycles rather than a single cycle. Pain in regional (TMD) and generalized (fibromyalgia) sites were examined, as well as responses to ischemic pain in women with and without TMD who either had normal menstrual cycles or were users of OC. Specifically, the aim of the study was to assess variations in experimental pain sensitivity and response at 4 times of the menstrual cycle (menses, ovulatory, midluteal, and late luteal). Experimental pain response in normally cycling women with TMD, pain-free controls, and subjects with TMD taking OC were compared. The authors hypothesized that normally cycling

women with TMD would demonstrate greater cyclic changes in response to experimental pain at both masticatory and other bodily sites in comparison to women with TMD taking OC.

Materials and Methods

Subjects

Ninety-four women between the ages of 18 and 45 years participated in the study. Subjects were 18 normally cycling women with TMD who were not using OC and 25 women with TMD who used OC. Controls were 25 normally cycling women not using OC and 26 women who were using OC. OC used in both groups were required to be low-dose combination (estrogen plus progesterone) pills used in a cycle of 21 days of active medication followed by 7 days without active medication. Controls did not have pain in the temporomandibular region, severe headache, back pain, or other chronic pain problems. Subjects with TMD pain were volunteers responding to advertisements in the university community and patients identified through Oral Medicine Clinical Services at the University of Washington. Subjects with TMD were required to have had pain for the last 3 months and to meet Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)[27] for both myofascial pain (ie, Group Ia or Group Ib) and arthralgia or arthritis (Group IIIa or IIIb). That is, every TMD subject had both a masticatory muscle pain diagnosis and a TMJ pain diagnosis. This is the most common diagnostic presentation in the authors' clinic, representing about 35% of the TMD cases seen. Potential control subjects were also examined and were included as controls only if they did not meet criteria for any Group I or Group III diagnosis. Participants were excluded if they reported average menstrual pain in the last 3 months of greater than or equal to 4 on a 0-to-10 scale, a history of hypertension, or coagulation problems, or if they were taking any blood pressure–altering or opioidergic medications. Subjects were asked to refrain from taking any analgesic medications on study visit days.

Baseline Procedures

Subjects were contacted by telephone and the study was explained. Interested subjects were screened for inclusion and exclusion criteria and subjects meeting initial criteria were scheduled for a baseline appointment. At the baseline appointment, written informed consent was obtained and the subject was examined by a reliable, calibrated dental hygienist examiner using the examination procedures of the RDC/TMD[27] to confirm that the subject met inclusion criteria for myofascial pain and arthralgia/arthritis. Subjects completed a baseline questionnaire including information on demographics, TMD pain and related symptoms, history of other pain problems, depression, anxiety, and somatization.

After the baseline questionnaire was completed, the approximate current cycle phase (menses, ovulatory, midluteal, late luteal) for subjects was determined. For subjects not using OC, this was based on self-report of the date of the subject's last menses and average cycle length. For subjects taking OC, this was based on self-report of the date of the subject's last menses and the start date for their package of pills. Based on this approximation, normally cycling subjects thought to be in the ovulatory or luteal phases were asked to call the research coordinator on the first day of their next menses. Subjects not using OC found to be early in the follicular phase of the cycle were instructed to begin using an ovulation prediction kit (ClearPlan; Unipath Diagnostics) to test for luteinizing hormone (LH) in their urine on a specified date 5 to 21 days after the first day of their last menstruation (test start date was based on the subject's reported cycle length). When subjects either began menstruating or received a positive result from the ovulation testing, they called the research coordinator, who then assigned them to a cycle phase for the start date of experimental sessions.

The timing of the first experimental session was relatively equally distributed across the 4 phases and the 4 groups, with 27 subjects beginning at menses, 26 at their ovulatory phase, 21 at midluteal, and 20 at late luteal. For normally cycling women, the menses visit was scheduled within 3 days of the beginning of menstruation, the ovulation visit was scheduled within 2 days of receiving a positive ovulation test, the midluteal visit was scheduled 7 to 8 days after the positive test, and the late luteal visit was scheduled 12 to 14 days after the positive ovulation test. For women taking OC, the menses visit was scheduled between days 1 and 3, with day 1 being the first day of menstruation; the ovulation visit was scheduled between days 12 and 14; the midluteal visit was scheduled between days 19 and 21; and the late luteal visit was scheduled between days 26 and 28. All subsequent experimental sessions followed the same scheduling guidelines. One session was conducted at each of the 4 phases over 3 consecutive men-

strual cycles, for a total of 12 experimental sessions. Subjects were paid $20/session for the first cycle, $25/session for the second cycle and $30/session for the third cycle, plus a completion bonus of $50 (a total of $350 US).

Experimental Procedures

During the experimental sessions participants underwent 3 pain-inducing procedures in the following order:

1. **Palpation pain:** Standardized pressure was applied to diagnostically relevant anatomic sites, identified, and located as described in the specifications for the RDC/TMD Axis I examination[27] and the Manual Tender Point Survey (MTPS) for Fibromyalgia.[28] A Somedic Type II algometer was used to deliver pressure to sites on the head, face, neck, back, and arms. The pressure was applied using a probe diameter of 1 cm at a constant rate of pressure of 40 kPa/s. Site location and amount of pressure delivered corresponded to the recommendations from the RDC/TMD and the MTPS. The TMD sites and pressure delivered included bilateral posterior, middle, and anterior temporalis at 2 lb of pressure; the superior, middle, and inferior masseter at 2 lb of pressure; and the lateral pole of the TMJ at 1 lb of pressure. The fibromyalgia sites and pressure delivered included the occiput, trapezius, supraspinatus and lateral epicondyle sites at 8.8 pounds of pressure.
2. **Pressure pain thresholds:** Pain thresholds at RDC/TMD and MTPS sites were assessed using the Somedic algometer on 4 bilateral sites corresponding to the anterior temporalis, middle masseter, trapezius, and supraspinatus. Examiners delivered continuously increasing pressure at the rate of 40 kPa/s until the subject pushed a switch and said "stop" to indicate the point at which "pressure turned to pain."
3. **Ischemic pain:** Subjects then rested for 10 minutes before beginning the submaximal effort tourniquet procedure. The nondominant arm was raised for 20 seconds to promote venous drainage. The arm was then occluded with a cuff placed on the upper arm inflated to 230 mm Hg (Hokanson E20 Rapid Cuff Inflator with the AG101 Cuff Inflator Air Source) and lowered. The subject then performed 20 handgrip exercises at 30% of her maximum force of grip. The duration of each squeeze was 2 seconds, with an intersqueeze interval of 2 seconds. The tourniquet was maintained for a maximum of 20 minutes. Times to reach ischemic pain threshold and tolerance were recorded. Subjects then rated the intensity of their ischemic pain.

Interexaminer Reliability

There were a total of 7 examiners in the study. The examiners were trained at the start of the study and recalibrated 3 times during the study. Overall, the examiners had fair to good agreement on palpation pressure pain and pressure pain threshold measures. The percent agreement among examiners was usually 80% or higher, and there were no systematic differences among the examiners. The intraclass correlation coefficient (ICC) ranged from 0.48 to 0.74 for sites painful to palpation, from 0.42 to 0.81 for visual analog scale (VAS) ratings of palpation pressure pain, and from 0.53 to 0.76 for pain pressure thresholds. Low ICC values typically reflected a condition of low prevalence rather than a lack of examiner agreement.

Baseline Measures

In addition to demographic and health history information, subjects completed the RDC/TMD Axis II self-report measures.[27] These include the Graded Chronic Pain Scale[29] (GCPS) and measures of depression and somatization. The GCPS includes measures of characteristic pain intensity (CPI), pain-related interference, and number of disability days. The CPI is the average of 3 numeric (0-to-10) rating scales asking subjects to report on average, worst, and present facial pain levels. Pain interference is the average of 3 numeric (0-to-10) rating scales asking subjects to report on interference with daily, recreational/social/family, and work-related activities.

Somatization and depression were assessed using Symptom Check List 90 (SCL-90) items as described in the RDC/TMD.[27] Subjects indicated on a 0-to-4 scale the extent to which they had been distressed by specific symptoms in the past month.

Experimental Session Measures

Palpations. Examiners delivered a fixed amount of palpation pressure at a standardized rate. Subjects reported whether they experienced pain at that fixed amount of pressure and if so, rated their pain on a 0-to-100 VAS.

Pressure Pain Thresholds. Examiners delivered increasing pressure at a rate of 40 kPa/s. Subjects

reported the point at which they "felt the pressure turn to pain" by pressing a subject-controlled switch attached to the algometer and saying "stop."

Ischemic Pain. The point at which subjects first began to feel pain in their hand or forearm (ischemic pain threshold), the point at which participants could no longer tolerate ischemic pain (ischemic pain tolerance), and a 0-to-100 verbal rating of perceived ischemic pain intensity were measured in response to the tourniquet task.

Data Analysis

The groups were initially compared for similarity on demographics and other baseline measures. The experimental data gathered on each subject during 4 menstrual phases in 3 menstrual cycles was then summarized by determining each subject's average response for each cycle phase over all cycles. The influence of TMD pain, OC use, and cycle phase on experimental pain was examined by conducting 2 (TMD vs non-TMD) × 2 (OC vs non-OC) × 4 (menstrual cycle phases) repeated measures analysis of variance (ANOVA) procedures. The authors' hypotheses about the main effects of TMD pain, OC use, and menstrual cycle phase on subject responses to each experimental dependent pain measure—palpation pain, pressure pain thresholds, and ischemic pain—were tested, and any significant interactions among the independent measures were examined. Demographic and baseline data were tested using ANOVA procedures for continuous variables and exact chi-square tests for categorical variables.

Results

A total of 152 eligible subjects were given a baseline screening, and 129 (85%) agreed to participate in the study. Ninety-four subjects (73%) provided sufficient data to be included in the data analysis. The most common reasons for discontinuation of the study were related to the demanding nature of the experiments (eg, subjects indicated that they were too busy, lost interest in study, their commute was too far). Four subjects were dropped from the study because their menstrual cycles became irregular, and 3 subjects indicated they did not want to continue with the study because of the aversive nature of the ischemic pain task. Among the 94 subjects, there was some missing data due to failure to attend the experimental session during the designated phase of the cycle, such as when a cycle phase occurred over the weekend, particularly for the ovulatory and menses phases. Forty-seven (50%) subjects had data from 12 sessions, 26 (28%) from 11 sessions, 15 (16%) from 10 sessions, 2 (2%) from 9 sessions, 3 (3%) from 8 sessions, and 1 (1%) from 6 sessions (from 2 consecutive cycles). Preliminary analyses using mixed-effects regression modeling assessed whether there were differences by cycle (ie, 1, 2, or 3) or session number (ie, 1 to 12). No significant cycle or session effects were found. Hence, to simplify the analyses by using repeated measures ANOVA, observations from the same phase of the cycle were averaged by subject to accommodate the missing data.

Demographics

Table 1 shows the characteristics of the sample at baseline. Subjects with TMD not taking OC were older than subjects with TMD taking OC and pain-free control subjects taking OC. A higher proportion of pain-free controls taking OC were employed when compared to TMD subjects not taking OC. All subjects with TMD had higher levels of somatization and menstrual pain than pain-free controls, and subjects with TMD taking OC had higher levels of depression than pain-free controls. The levels of characteristic pain intensity, pain-related interference, pain duration, graded chronic pain somatization, depression, and average menstrual pain were similar between the TMD subjects with and without OC use.

Palpation Pain

Palpation pain intensity for TMD sites and fibromyalgia sites in response to standardized pressure is shown in Fig 1. Overall, the TMD pain groups reported higher intensity for both TMD (Fig 1a) and fibromyalgia (Fig 1b) sites ($P < .001$). Similarly, those with TMD pain reported more TMD and fibromyalgia sites as painful compared to controls ($P < .001$; Table 2). The differences between the subjects with TMD pain and the control group subjects were larger for the TMD sites than the fibromyalgia sites. In addition, the subjects using OC reported more fibromyalgia sites as painful than non-OC users ($P = .034$), although the difference between the 2 groups was not always consistent across the different phases of the menstrual cycle, as indicated by an OC use by phase interaction ($P = .023$).

Table 1 Demographic and Baseline Data for TMD Subjects and Controls

	TMD OC	TMD (no OC)	Controls OC	Controls (no OC)	P*
Mean (SD) age (y)	24 (3)	32 (8)	25 (4)	28 (7)	.0003†
Race (% white)	80	83	92	80	.59
Education (% with high school diploma or greater)	87	89	92	80	.37
Percent employed	84	67	92	88	.011‡
Marital status (%)					
Married	25	23	31	17	.62
Never married	67	59	65	71	
Other	8	18	4	12	
Household income (%)					
< $25,000/year	38	43	54	67	.35
$25,000–$49,999/year	37	36	35	12	
$50,000+/year	25	21	11	21	
Mean (SD) somatization	0.8 (0.5)	0.8 (0.5)	0.3 (0.3)	0.2 (0.2)	< .001§
Mean (SD) depression	0.9 (0.6)	0.8 (0.5)	0.4 (0.4)	0.4 (0.4)	.001‖
Mean (SD) average menstrual pain	2.9 (1.9)	2.9 (1.5)	1.5 (1.3)	2.6 (1.6)	.008¶
Mean (SD) CPI	5.1 (2.0)	4.9 (1.7)			.8
Mean (SD) pain-related interference	1.4 (1.6)	2.3 (2.2)			.12
Mean (SD) pain duration (y)	6 (4)	9 (9)			.71
Mean (SD) number of non-TMD pain conditions (0-5)	2.0 (1.2)	2.2 (1.2)			.74
Graded Chronic Pain (%)					
Grade 1	29	17			.46
Grade 2	0	5			
Grade 3	63	61			
Grade 4	8	17			

*One-way ANOVA for continuous variables; exact chi-square tests for categorical variables.
†TMD no OC subjects were older than TMD OC and control OC subjects.
‡More control OC subjects were employed than TMD (no OC) subjects ($P < .05$; Bonferroni adjusted P value).
§TMD subjects had greater somatization than non-TMD controls.
‖TMD OC subjects had greater depression than non-TMD controls.
¶TMD subjects had greater menstrual pain than OC controls ($P < .05$; Tukey studentized range test).

Table 2 Mean (SD) of TMD (0–14) and Fibromyalgia (0–8) Sites Painful to Palpation at Different Phases of the Menstrual Cycle

	Phase			
	Menses	Ovulatory	Midluteal	Late luteal
TMD sites				
TMD OC	5.1 (2.9)	5.3 (2.9)	5.4 (2.8)	5.5 (3.1)
TMD no OC	5.5 (3.5)	5.0 (3.7)	5.2 (3.8)	4.5 (3.6)
Control OC	1.2 (1.5)	1.1 (1.4)	0.9 (1.3)	0.9 (1.0)
Control no OC	1.3 (2.0)	1.2 (1.8)	1.1 (1.6)	1.3 (1.9)
Fibromyalgia sites				
TMD OC	7.0 (1.3)	7.1 (1.0)	6.9 (1.9)	7.4 (0.9)
TMD no OC	6.7 (1.5)	6.6 (1.1)	7.0 (1.4)	6.5 (1.5)
Control OC	6.1 (1.4)	6.1 (1.5)	6.1 (1.7)	6.0 (1.6)
Control no OC	5.1 (2.5)	4.9 (2.5)	5.4 (2.2)	4.6 (2.8)

Interestingly, there was a statistically significant 3-way interaction between TMD pain, OC use, and phase for both TMD and fibromyalgia palpation intensity ($P \leq .05$ for both interactions), which appears to be the result of an increase in palpation pain in the TMD OC group and a decrease in palpation pain in the TMD-no-OC group during the late luteal phase of the cycle. There was a consistent pattern for both variables, with normally cycling TMD subjects (ie, those not using OC) having lowest palpation pain intensity during the ovulatory and late luteal phases. Their OC-using counterparts had relatively stable reports of palpation pain intensity during the menses, ovulatory, and midluteal phases, with highest palpation pain intensity reported at the late luteal phase (Fig 1).

Pressure Pain Thresholds

To illustrate the patterns for the pressure pain thresholds in response to gradually increased, algometer-delivered pressure at standardized sites, the thresholds for the TMD masseter site and the fibromyalgia supraspinatus site are shown in Fig 2 (dominant-hand side shown for both sites). In general, TMD subjects had lower pressure thresholds than subjects without TMD for all TMD and fibromyalgia sites ($P < .006$). The pain-free con-

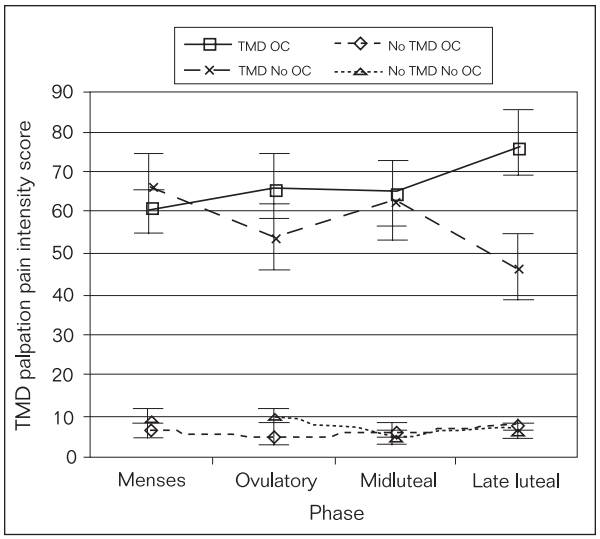

Fig 1a Palpation pain intensity at TMD sites.

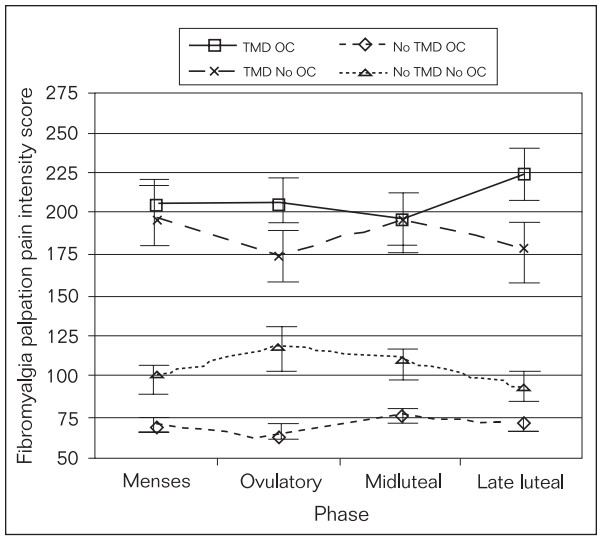

Fig 1b Palpation pain intensity at fibromyalgia sites.

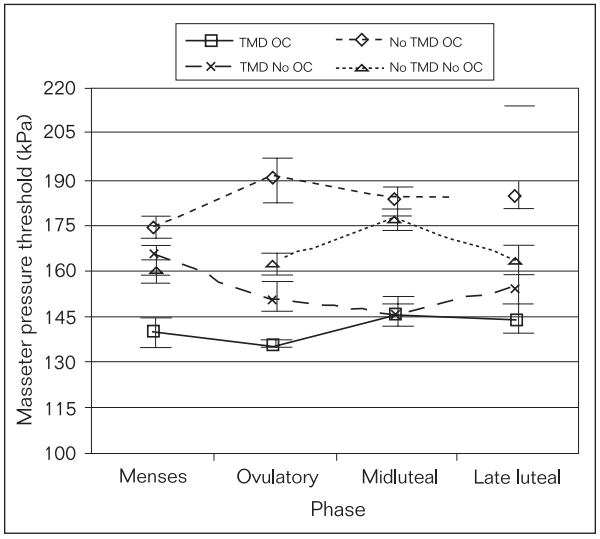

Fig 2a Pressure pain threshold at masseter sites.

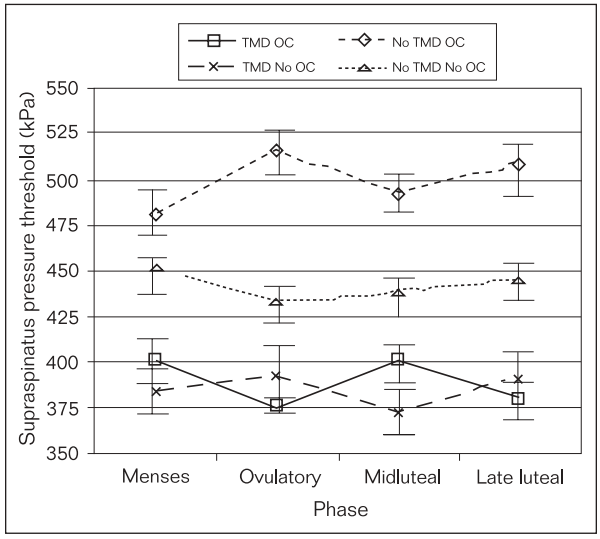

Fig 2b Pressure pain threshold at supraspinatus sites.

trols not using OC consistently had the highest pressure thresholds for all sites. The exceptions to the group differences were that differences between the groups tended to be smaller (or even absent) at menses for the TMD masseter site on the dominant-hand side (as shown in Fig 2a) and for both fibromyalgia sites on the non–dominant-hand side ($P < .05$, TMD pain by time interaction; data not shown).

Ischemic Pain

Ischemic pain tolerance times and intensity are shown in Fig 3. The 2 OC groups (with and without TMD pain) showed similar pain tolerance times, whereas among the normally cycling women, those with TMD pain had lower pain tolerance times than those without TMD pain, as indicated by an OC use by TMD pain interaction ($P = .033$; Fig 3a). A similar pattern was observed for the group differences for ischemic pain thresholds, but the differences were not statistically significant ($P > .05$; data not shown). In contrast, the normally cycling women with TMD had higher ischemic pain intensity than their OC-using counterparts ($P = .031$; Fig 3b). No differences were observed among the cycle phases for any of the groups ($P > .05$).

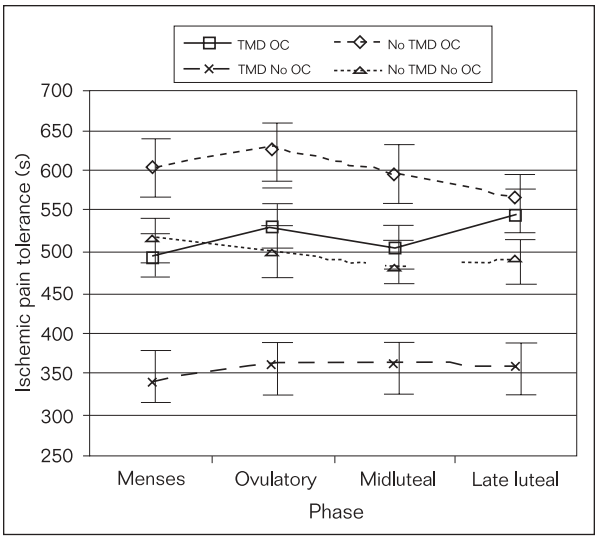

Fig 3a Ischemic pain tolerance.

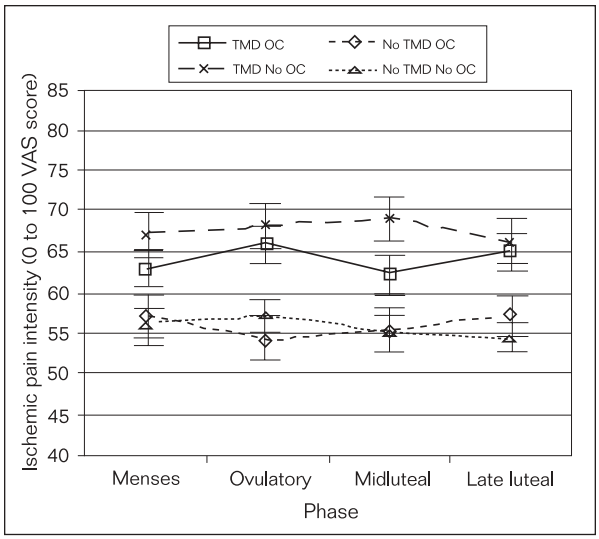

Fig 3b Ischemic pain intensity.

Discussion

The authors' previous research[6] suggests that daily facial pain reports vary across the menstrual cycle such that women with TMD pain, regardless of OC status, report increasing levels of facial pain at the end of the cycle (late luteal phase), with a peak at menses. For women with TMD not taking OC, a secondary peak has been observed at around the time of ovulation—that is, at a time of rapid estrogen fluctuation. This secondary peak was absent for women taking OC, who rarely ovulate.

The results of the present study of experimental noxious stimuli superimposed on the clinical chronic pain of TMD showed fewer definite patterns. With regard to experimental pain associated with palpation at clinically relevant sites, the findings of the present study suggest that intensity of pain in response to palpation varies across the phases of the menstrual cycle for women with TMD who are not using OC—that is, differences in the cyclic intensity of palpation pain reports were found in normally cycling women with TMD pain not taking OC in comparison to their TMD counterparts taking OC and in comparison to normally cycling pain-free controls. More specifically, for normally cycling women with TMD, palpation pain was highest in intensity at the menses and midluteal phases and lowest in intensity at the ovulatory and late luteal phases. This pattern differs from that in women with TMD taking OC, whose reports of palpation intensity remained relatively stable at the menses, ovulatory, and midluteal phases but increased in intensity at the late luteal phase.

While there was some variation across the menstrual cycle in palpation pain intensity, no menstrual phase-related differences in pressure pain thresholds were found. These findings are consistent with those reported by Hapidou and Rollman,[12] who found cyclic differences in numbers of tender points rated as painful but not in pressure pain thresholds in healthy volunteers. That palpation pain sensitivity differences but not pressure pain threshold differences were found is not surprising considering the numerous findings showing different response patterns in palpation sensitivity and pressure pain threshold.[12,30] Although both methods of experimental pain stimulation involve mechanical pressure, the underlying mechanisms and behavioral response characteristics for the 2 pain measures may differ considerably.[12] Ratings of pain in response to moderate amounts of pressure may relate more to sensory-perceptual pain response characteristics such as hypersensitivity, whereas pressure pain thresholds may relate more to behavioral response characteristics (ie, willingness to passively endure increasing pressure, hypervigilance to threatening stimuli).

In contrast to previous research,[8,10,13] no phase-related pressure pain thresholds or ischemic pain differences were found in either those with TMD pain or TMD pain-free controls. Methodologic differences in timing of the sessions in the present study may account for this inconsistency. Drobek et al[13] compared pressure pain thresholds at masseter and temporalis sites in healthy volunteers at the follicular phase (5 to 12 days after menses),

luteal phase (16 to 27 days after menses), and perimenstrual phase (1 day prior to 3 days after menses). Fillingim et al[8] compared ischemic pain response in 11 healthy women at the midfollicular phase (5 to 8 days after menses), ovulatory phase (within 24 hours of an LH surge) and mid- to late luteal phases (1 to 9 days prior to menses). Pfleeger et al[10] compared ischemic pain response in 11 healthy women at the follicular phase (4 to 9 days after menses) and the mid- to late luteal phases (5 to 10 days after ovulation). The timing of the sessions in the present study was designed to provide experimental pain data at phases of the menstrual cycle when reproductive hormones were at their peak and nadir. The variations in timing between these 4 studies highlights the need for greater methodologic consistency in this area of research.

The authors speculate that because use of OC reduces fluctuations in estrogen across the menstrual cycle, chronic TMD patients using exogenous hormones may show a beneficial effect when exposed to experimental pain stimuli, such as muscle palpation, because they experience neither the same intensity of estrogen depletion levels associated with normal late luteal and menses phases of the menstrual cycle nor the wide swings in estrogen associated with ovulation. While this finding may at first appear to contradict previous findings from our research group[5] showing that use of exogenous estrogen may increase the risk of TMD pain, there are several possible explanations that may reconcile the observed findings. Whereas this study examined responses to experimental pain stimuli, the initial study[5] examined the presence or absence of a clinical pain condition. Clinical pain may carry a heavier affective component than experimental pain. In addition, factors that predict pain onset do not necessarily predict pain intensity level for a clinical (or laboratory) pain once it has occurred. In light of other recent findings,[6] the authors believe that the effect of exogenous hormones on pain may be attributable to the fact that many exogenous hormone protocols involve stopping the use of estrogen for 1 week of the cycle. It is possible that it is change in estrogen levels (rather than the simple presence of estrogen) that increases the risk of TMD pain. It is also possible that the specific endogenous estrogens present in normally cycling women (primarily estradiol) versus the exogenous estrogens present in women using OC (primarily ethinyl estradiol) may have differing effects.

In the authors' prior study, a clear phase-related pattern in self-report of facial pain in both normally cycling women and those using OC was observed.[6] The present study found a different and less consistent pattern in the report of experimental pain. One possible reason is that phase-related effects are more apparent in response to more clinically relevant pain stimuli. Some phase differences in palpation pain were found at sites that are palpated as part of standard diagnostic examinations for TMD and fibromyalgia, but phase-related differences in response to the ischemic pain stimulus, which may have less clinical relevance in this population, were not found.

As already noted, the available scientific literature concerning menstrual cycle effects on responses to noxious stimuli presents an inconsistent picture: Some studies suggest no cycle effects[9,31,32]; others suggest highest pain threshold, tolerance, and/or lower tender point count during the luteal phase[16,12]; and still others suggest lower pain threshold and/or greater pain sensitivity in the luteal phase versus the follicular phase.[8,22] While most of these studies examined changes in perceptual and behavioral responses to experimental pain stimuli across the menstrual cycle in healthy volunteers (or in groups not screened for dysmenorrhea), some[14,16,17,20,22,31,33] examined such changes in women with dysmenorrhea (ie, abnormally painful menstrual periods). This may account for the inconsistent findings in this field. Women who reported average menstrual pain ≥ 4 on a 0-to-10 scale were excluded from all groups in this experiment. Women who were taking OC specifically to control dysmenorrhea were excluded from both OC groups.

In addition, inconsistencies in reported relationships between responses to noxious stimuli and phases of the menstrual cycle may have been caused by small sample sizes, failure to confirm ovulation with a hormone assay, testing at widely different time points within the same phase, or limiting experimental observations to 1 menstrual cycle. The present study was designed to address these potential sources of experimental error through use of larger sample sizes, confirmation of ovulation using hormone assays, running experimental sessions during precise windows of time at 4 phases of 3 cycles, and use of both mechanical pressure and ischemic pain stimuli. With these design features, few phase-related differences in experimental pain response between (or within groups of) chronic TMD patients and controls were found.

A secondary aim of the study was to compare experimental pain responses in those with TMD and pain-free controls independent of relationships to menstrual cycle phases. Consistent with previous

work,[7] the results of the present study showed that TMD pain groups, regardless of cycle phase and OC status, reported more palpation sites as painful to pressure and reported greater intensity of pain at regional (TMD) and widespread (fibromyalgia) sites. TMD pain groups reported higher ischemic pain intensity compared to pain-free controls, and among the normally cycling women, those with TMD pain had lower pain tolerance times than those without TMD pain. Taken together, these data support the contention that patients with TMD pain are more highly responsive to pain inside and outside of the craniofacial region and that the pathophysiological mechanisms associated with TMD may involve both peripheral afferents[34] and alterations in central nervous system processing of nociceptive information.[35]

The findings of the present study, along with previous findings,[6] have several implications for clinical assessment and management. There appears to be considerable cyclic variability in clinical TMD pain reports[6] and greater cyclic variability in responses to clinically relevant experimental stimuli (ie, palpation at muscle sites) compared to less clinically relevant stimuli (ie, ischemic pain response). As TMD is an episodic pain condition diagnosed by patient report of clinical pain and pain in response to palpation, attention to menstrual cycle effects when diagnosing the condition and tracking the effects of treatment may prove helpful. Further, patient education along with behavioral training regarding potential menstrual cycle effects may improve patient efficacy in predicting and managing episodic pain flare-ups. Finally, as is the case with headache and menstrual pain,[36] there appears to be a cyclic pattern of episodic pain flare-up in TMD. Recently, extending the use of active OC pills to eliminate monthly withdrawal bleeding has been shown to be effective in treating pain associated with endometriosis and menstrually related pain.[37] Coincidentally, extended or continuous OC protocols also appear to diminish the incidence of headache.[38,39] Although the mechanism for these effects is unclear, it is possible that such medication treatment regimens might prove efficacious in some TMD cases.

This study has several limitations. First, the design involved timing experimental sessions to precise 3-day windows during 4 phases of 3 menstrual cycles. This stringent design requirement led to inevitable loss of data in several instances, especially when the ovulatory and menses phases began on weekends. Further, in order to avoid having subjects with pre-existing cyclic pain conditions, potential subjects reporting symptoms consistent with dysmenorrhea were excluded from the study. It is possible that this exclusion led to a sample of subjects with lower overall levels of symptoms across the menstrual cycle than may be typical in a more heterogeneous TMD population. It is also evident that participation in this study was time-consuming, involved a significant amount of commitment to the study procedures, and significant flexibility in scheduling for subjects. It was decided to solicit women with facial pain from the university community rather than to recruit solely a treatment-seeking sample. Although all subjects met RDC/TMD criteria for both muscle and joint pain, 85% were recruited by advertisement and not from a clinic population. While the CPI levels in this sample are comparable with other findings,[6] the pain-related interference scores were quite low. The recruiting efforts may have led to sampling from a more psychosocially functional population than that typically seen in clinic samples.

To the authors' knowledge, this study is among the first such reports examining phase-related effects on experimental pain in women with TMD and pain-free controls. The study extended over 3 cycles and attempts to gather data were made at 4 carefully defined phases of each cycle. The present data have shown that although there are some phase-related differences in experimental pain response, the effects are not strong and are more often found in those experimental stimuli that have greater clinical relevance and more closely resemble the ambient pain associated with TMD.

Acknowledgments

This study was supported by National Institute of Dental & Craniofacial Resources (NIDCR) grants R01 DE12470, P30 DE09743, and R03 DE13438. The authors thank Ms Misa Perron-Burdick and Ms Mari Nosal for their scheduling and coordination of activities, Ms Marilynn Rothen and the staff of the Regional Clinical Dental Research Center for serving as examiners, Dr William Maixner for consultation on the ischemic pain task and apparatus, and the subjects for their time and dedication to the project.

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