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Menstrual cycle modulation of tender points

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Abstract

Changes in pain sensitivity throughout the menstrual cycle were assessed in 36 normally menstruating women and 30 users of oral contraceptives. Pain sensitivity was measured with palpation of rheumatological tender points and with pressure dolorimetry. The number of tender points identified by palpation was greater in the follicular (postmenstrual) phase of the cycle as compared to the luteal (intermenstrual) phase in normally cycling women but not in users of oral contraceptives. These findings are related to previously described physiological and psychological features of the menstrual cycle, with particular emphasis on the role of hormonal events in modulating pain perception, particularly in musculoskeletal disorders such as fibromyalgia. © 1998 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Menstrual cycle; Hormones; Tender points; Pain threshold; Dolorimetry

1. Introduction

Assessment of women's responsiveness to pain across the menstrual cycle provides evidence as to whether normal cyclic fluctuations in the levels of gonadal hormones are associated with systematic variations in pain sensitivity. Such variations, if demonstrated, would suggest that the menstrual cycle is a modulating factor of pain.

Phase-related fluctuations in experimentally-induced pain have been demonstrated in several studies. Although there are some methodological differences in these reports (pain induction techniques and responses measured), the alterations in pain sensitivity in normally menstruating women often seem to follow changes in gonadal hormone levels. More specifically, higher thresholds are generally obtained in the follicular (preovulatory) phase and lower thresholds are obtained in the luteal (postovulatory) phase.

Procacci et al. (1974) found low threshold values for radiant heat during the luteal phase with a subsequent steady rise which reached peak toward the end of menstruation. Using signal detection methods with radiant heat, Goolkasian (1980, 1983) noted enhanced discriminability during the luteal phase but no phase differences in the willingness to report pain. Hapidou and deCatanzaro (1988), employing the cold pressor task, found a significantly lower pain threshold during the luteal as compared to the follicular phase. Fillingim et al. (1997) discovered that the pain threshold and tolerance times for ischemic pain on the arm were significantly greater during the follicular phase than the ovulatory or luteal phases (replicated by Pfleeger et al., 1997), but there were no phase-related effects on thermal pain threshold. However, using an aversion-to-electric-shock technique, Tedford et al. (1977) obtained cyclical effects in the opposite direction from these investigators, with minimum sensitivity in the luteal phase (maximum sensitivity occurred during menstruation). Likewise, Giamberardino et al. (1997), who measured pain thresholds for electrocutaneous pulses applied to the skin at the abdomen and limbs, found that the highest threshold values always occurred during the luteal phase.

These studies involved noxious stimuli which are utilized frequently in the laboratory but occur rarely in day-to-day experience. Few (Harman-Boehm et al., 1993) have investigated the possible influence of menstrual cycle phase on

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fluctuations in more natural or usual pain experiences. Smolensky and D'Alonzo (1993), in a review of medical chronobiology, presented evidence which suggested that the symptoms of a number of chronic diseases, including rheumatoid and osteoarthritis, show circadian and, in premenopausal women, monthly cycles.

Endogenous pain in the musculoskeletal system occurs frequently in the general population and, particularly when chronic, leads to considerable personal distress and disability (Magni, 1993). One of the most common (Wolfe et al., 1995b) and pernicious forms of the muscular pain syndromes is fibromyalgia, a chronic rheumatological disorder characterized by widespread aches and pains, multiple localized tender points, fatigue, and nonrestorative sleep (Wolfe, 1989; Wolfe et al., 1990).

Fibromyalgia patients are often unaware of the specificity of their tender points (Smythe, 1986). They tend to be markedly more sensitive to experimentally-induced pain as compared with age-matched rheumatoid arthritis patients and controls (Scudds et al., 1987; Tunks et al., 1988; Lautenbacher et al., 1994). Moreover, numerous studies suggest a diffuse change in pain modulation in fibromyalgia (Quimby et al., 1988; Tunks et al., 1988; Yunus, 1992; Arroyo and Cohen, 1993; Granges and Littlejohn, 1993; Rollman and Lautenbacher, 1993; Gibson et al., 1994; Lautenbacher et al., 1994; Yunus, 1994; McDermid et al., 1996).

The overwhelming majority of fibromyalgia patients are women (Wolfe et al., 1995a). Women are also found to have a higher count of tender points and lower dolorimeter pain thresholds than men (Croft et al., 1994; Wolfe et al., 1995a). This, coupled with the frequent onset of the disorder at early middle age, suggests some links with gynecological events such as changes in menstrual status (Hapidou and Rollman, 1991). Although an association with the menstrual cycle is reported anecdotally by individual women, there have been few systematic studies to investigate possible associations between musculoskeletal pain and ovarian function.

Dao et al. (1997) noted that reproductive hormones may play a role in temporomandibular disorders. They found, in a pilot study, that women with myofascial pain of the masticatory muscles who were not oral contraceptive users showed considerably more variance in pain estimates than those who used the pill. For the non-users, peaks of pain were observed at the menstrual and premenstrual phases of the menstrual cycle.

Menstrual cycle effects have also been reported to occur with migraine headaches (Edelson, 1985; Holm et al., 1996; Fettes, 1997; Lokken et al., 1997). Migraine affects twice as many women as men, with the gender difference becoming apparent in adolescence (Fettes, 1997). In up to 70% of female migraineurs, headaches are closely related to the menstrual cycle (generally occurring during the premenstrual and menstrual phase). A hormonal link has been implicated to account for this relationship, but the exact relationships have not been identified (Beckman et al., 1992; Kornstein and Parker, 1997).

A number of recent reports have examined possible links between ovarian function and rheumatoid arthritis (RA) and other autoimmune diseases (Bijlsma and Van den Brink, 1992). Valentino et al. (1993) found that progesterone and androgen plasma levels were significantly lower in RA patients than in controls during the luteal phase, while corticosterone plasma levels were significantly higher for patients during the follicular and luteal phases. Da Silva and Hall (1992) concluded that sex and sex hormones are independent risk factors in rheumatoid disease, with a peak onset at menopause in women and later in life in men. For younger women, arthritic symptoms abate during preg-nancy. Flaisler et al. (1995) indicated that women of childbearing age with RA had a decreased likelihood of ovulation, a factor which may account for their reduced fertility.

Both the experimental and clinical data suggest that the menstrual cycle may modulate pain, but there is a surprising lack of consensus regarding which phase is associated with greater or lesser degrees of discomfort. In order to assess responsiveness to a clinically-relevant pain in individuals free from chronic pain, we sought to establish the relationship between pain at the fibromyalgic tender points and menstrual cycle phase in a group of female university students. The group was divided into normally menstruating women and ones using oral contraceptives, as it was expected that any fluctuations in pain sensitivity seen during the unregulated menstrual cycle would not be found in oral contraceptive users (Goolkasian, 1980; Dao et al., 1997).

2. Method

2.1. Subjects

Ninety student volunteers from an Introductory Psychology subject pool, naive to the purposes of the study, agreed to participate in a study involving four testing sessions. Thirty-six women with normal and regular menstrual cycles and 30 women on oral contraceptives provided data coinciding with four phases of the menstrual cycle. The remaining 24 subjects were excluded from the main data analysis, which utilized menstrual phase as the variable of interest, because they either had irregular, short ($<$28 days) or long ($>$31 days) menstrual cycles.

Prior to scheduling test sessions, each woman, as part of a health and demographic information questionnaire, reported the date of her most recent menses and the length of her cycle. This allowed for preliminary estimation of each subject's average cycle length (number of days from the onset of menstruation up to, but not including, the day of onset of the next menstrual period). Upon completion of testing, subjects reported the date of onset of their last menses, thus permitting retrospective confirmation of phase assignment.

Date of the most recent menses was used, retrospectively, to calculate the phase during which the experimental session actually occurred. For example, the luteal phase included a period of 8–14 days prior to last menses or days 15–21 following the onset of the previous menses in a 28-day cycle. The follicular phase included a period of 8–14 days following the onset of the previous menses. Subjects with cycles longer than 28 days (up to 31 days) were assigned the 1–3 extra days in their follicular phase, following common practice, as this phase is reported to be more variable in length than the luteal phase (Vollman, 1977).

Sessions were counterbalanced in terms of menstrual phase and scheduled approximately one week apart. One fourth of the subjects were registered to begin in the menstrual (days 1–7) phase, one fourth during the postmenstrual or follicular phase (days 8–14), one fourth during the intermenstrual or early luteal phase (days 15–21) and one fourth during the premenstrual or late luteal phase (days 22–28).

2.2. Apparatus

The first author served as the examiner for all participants. Manual palpation was achieved by applying the right thumb with a standard pressure of approximately 1 kg. The examiner was trained by a rheumatologist specializing in the management of fibromyalgia and it was determined that her 'calibrated thumb' matched that of other experienced examiners. Periodic checks of exerted pressure were obtained by taking readings after intended 1 kg. applications against the footplate of a dolorimeter. For pain threshold determinations, a variable pressure dolorimeter (Pain Diagnostics and Thermography, Great Neck, NY), whose head was 1.2 cm in diameter, was used to apply pressure on the designated testing points (range 0–17 kg).

2.3. Measures

Health and demographic data, tender point count and sensitivity, and visual analogue scale (VAS) ratings of current muscle stiffness, generalized aches and pains, anxiety, tension, worry, depression, fatigue and sleep problems were obtained. The VAS scales utilized a 10 cm line anchored by the terms 'none' and 'maximum imaginable'.

Health and demographic information was obtained through a questionnaire administered at the beginning and the end of the study. Menstrual cycle information was embedded in a series of several items such as age, height, weight, frequency of exercise, symptoms, pains, medication use, etc., so that subjects were not made specifically aware that testing was related to their menstrual cycle.

The following 13 points were assessed bilaterally by thumb palpation in order to determine a count of tender points. The nine marked with an asterisk were examined in greater detail with the pressure dolorimeter, applied to the right side, in order to determine pain thresholds (Fig. 1).

Points 1, 2, 3, 4, 6, 8, and 10 are included in the list of Diagnostic Criteria for Fibromyalgia Syndrome established by the Multicenter Criteria Committee (Wolfe et al., 1990). Points 5, 7, and 9 are among those also considered to be tender in clinical studies (Yunus et al., 1989; Tunks et al., 1995). Points 11–13 have been used as control points.

1. Occiput (Occ.): at the subcortical muscle insertion areas*
2. Low cervical (L.c.)
3. Trapezius (Tr.): at the midpoint of the upper border*
4. Supraspinatus (Su.): at origins above the scapular spine near the medial border
5. Paraspinous (Pa.): bilateral, 3 cm lateral to midline at level of midscapula*
6. Second rib (S.r.): at the second costochondral junctions on upper surfaces*
7. Lateral pectoral (L.p.): at the level of the fourth rib at the anterior axillary line
8. Lateral epicondyle (L.e.): 2 cm distal to the epicondyles within muscle tensing when long finger is extended*
9. Medial epicondyle (M.e.)
10. Medial knee (M.k.): at the medial fat pad overlying medial collateral ligament distal to the joint line*
11. Forearm (For.): mid-volar aspects of forearm*
12. Thumbnail (Thu.): thumb placed on the table*
13. Mid-foot (M.f.): at mid point of dorsal third metatarsal*

2.4. Procedure

Each testing session consisted of palpation of all 26 points as well as dolorimeter assessment of nine unilateral

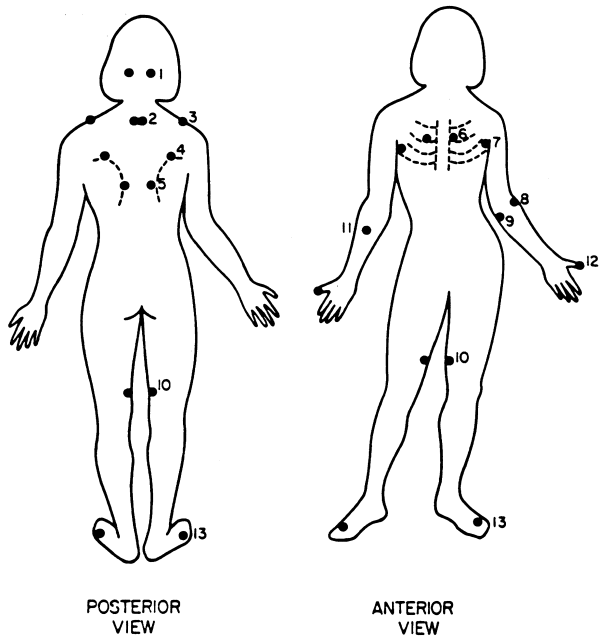

Fig. 1. Body map showing test sites. Tenderness to manual palpation was examined at all sites. Pain threshold on the right side of the body was determined with a dolorimeter at sites 1,3,5,6,8,10,11,12, and 13.

points. Subjects also completed the visual analog scales. The order of tender point examination and VAS completion was counterbalanced to counteract order effects, since some VAS scales also assessed pain (aches and pains, muscle stiffness). Test sessions lasted approximately 15 min each. The first and last sessions lasted somewhat longer because subjects had to complete the health and demographic questionnaire.

3. Results

3.1. Demographic information

Table 1 presents descriptive statistics for the health and demographic data, averaged separately for users and non-users of oral contraceptives. The percentage of women using oral contraceptives agreed with that of other studies for that age group (Warner and Bancroft, 1988). No differences were found between the two groups in any of these variables. Table 2 presents severity ratings for the different types of common pain complaints reported by the two groups of subjects. Ratings were as follows: 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain). The two groups differed only in their rating of joint pain, with the oral contraceptive users reporting more joint pain ($F(1, 64) = 5.74$, $P < 0.02$).

After excluding women who did not meet the criteria for menstrual cycle length, the following counterbalancing was achieved: Twenty-one subjects (32%) began in the menstrual, 17 (26%) in the follicular, 12 (18%) in the luteal and 16 (24%) in the premenstrual phase.

Table 1

Health and demographic variables in normally menstruating women and users of oral contraceptives (OC)

	Normally menstruating women	OC users
Age in years		
Mean	21.19	20.90
SE	0.63	0.55
Age at menarche		
Mean	13.11	13.15
SE	0.18	0.19
Height (in cm)		
Mean	163.83	162.20
SE	1.18	1.35
Weight (in kg)		
Mean	58.01	59.83
SE	1.62	1.27
Years at university		
Mean	1.67	1.53
SE	0.21	0.18
Times/week of exercise		
Mean	1.92	2.03
SE	0.24	0.27
Cycle length (in days)		
Mean	29.29	28.00
SE	0.16	0.00
Days of menstrual flow		
Mean	5.16	4.90
SE	0.22	0.20
Reported no. of Symptoms[a]		
Mean	1.03	0.90
SE	0.24	0.18
Reported no. of types of pain[b]		
Mean	2.14	2.43
SE	0.17	0.25

[a]chills, fever, colds, fainting, dizziness, chest pains, shortness of breath, leg cramps, nose bleeds, easy bruisability.
[b]headache, low back pain, menstrual pain/cramps, joint pain, other.

Table 2

Severity ratings of various types of pain as reported on the health and demographic questionnaire (rating scale 0–3) by normally menstruating women and users of oral contraceptives (OC)

	Normally menstruating women	OC users
Headache		
Mean	1.19	1.20
SE	0.16	0.18
Low back pain		
Mean	0.53	0.83
SE	0.14	0.16
Menstrual pain/cramps		
Mean	1.31	1.53
SE	0.15	0.20
Joint pain		
Mean	0.14	0.50
SE	0.06	0.14
Other pain		
Mean	0.17	0.10
SE	0.09	0.07

3.2. Tender points

Thirteen bilateral points were palpated with the thumb with a standard pressure of approximately 1 kg while the subject was asked to report if the pressure was or was not painful. Raw data were the total number of points reported as painful upon palpation. This was a highly variable measure, with individual session scores ranging from 0 to 15 (out of a possible maximum of 26). The sites of the three most frequent tender points, as a function of contraceptive status and menstrual phase, are shown in Table 3. The similarities across conditions are striking; the trapezius and knee were reported as painful upon palpation by the greatest numbers of subjects in both contraceptive-status groups.

There was an a priori hypothesis of differences in the number of tender points during the four phases of the cycle in normally menstruating women. The repeated-measures analysis of variance (ANOVA) for this group of 36 women yielded a significant phase effect, $F(3, 105) = 3.84$, $P < 0.01$. As shown in Fig. 2, the mean (SE) number of tender points was 2.19 (0.41) for the menstrual phase, 2.86 (0.54) for the follicular phase, 1.64 (0.40) for the luteal

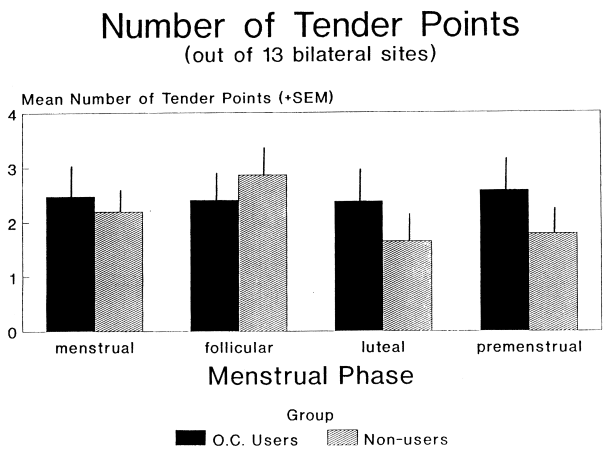

Fig. 2. Number of tender points to manual palpation as a function of menstrual phase in normally menstruating women and users of oral contraceptives.

phase, and 1.78 (0.40) for the premenstrual phase. A Tukey's test showed a difference between the follicular and the luteal phases. As expected, no phase differences occurred for the oral contraceptive users, whose means for the same phases were 2.47 (0.64), 2.40 (0.51), 2.37 (0.67), and 2.57 (0.64), respectively. Also, when number of tender points was entered into a repeated measures two (group) by four (phase) ANOVA (unweighted means solution), no significant main effects or interactions were revealed.

Fifteen subjects (nine with normal cycles and six pill users) did not report any tender points in any of the sessions. A repeated-measures ANOVA, which excluded these subjects, yielded the same phase effect, $F(3, 78) = 3.95$, $P < 0.01$, for normally menstruating women, thus showing that the variability in the data did not affect the magnitude of the phase effect. Again, a Tukey's test indicated that the number of tender points was highest for the follicular phase and lowest for the luteal. Also, for the group using oral contraceptives, a phase effect was absent.

3.3. Pain threshold

Pain threshold was obtained at nine unilateral points by determining the amount of pressure required for the subject to report pain when each site was stimulated by a pressure dolorimeter. As shown in Fig. 3, no significant differences in pain threshold were found for either the control or the tender points across menstrual cycle phases in the two groups.

Consequently, pain thresholds were determined for data collapsed across groups and menstrual phases. Fig. 4 presents the magnitude of dolorimeter pressure needed to produce pain at each of the nine points (six active and three control sites), averaged across the four phases of the cycle.

Table 4 shows the sites which ranked first, second and third in sensitivity to dolorimeter pressure for the two groups across the menstrual cycle. There was enormous consistency across subjects in the pain threshold for each point. The occiput was almost always the most sensitive region followed by the second rib, lateral epicondyle, and knee. This was true both for normally cycling women and oral contraceptive users.

The six most sensitive points (occiput, trapezius, paraspinous, second rib, lateral epicondyle, and medial knee) are deemed to be classical rheumatological tender points and the three least sensitive ones (forearm, thumbnail, and mid-foot) are generally considered by rheumatologists as control sites. Even for this normal group of young women, there was a highly significant difference between the two groups of points, $F(1, 62) = 131.02$, $P < 0.0001$, with sensitivity being markedly higher for the rheumatological sites.

Table 3
Most frequent tender points found by palpation across the menstrual cycle on both sides of the body

Normally cycling women (n = 36)							
Menstrual		Follicular		Luteal		Premenstrual	
R	L	R	L	R	L	R	L
M.k.(28) Tr(22) Su(17)	Tr(33) M.k.(25) Su(19)	Tr(33) M.k.(28) Su(22)	Tr(36) M.k.(28) S.r. and L.e.(17)	Tr(28) M.k.(25) Pa and L.e.(8)	Tr(25) M.k.(25) Pa and S.r. and L.e. (11)	Tr(25) M.k.(17) P.a. and L.e (11)	Tr(28) M.k.(19) P.a. and L.e. (11)
OC users (n = 30)							
Tr(33) L.e. and M.k.(17) Su and Pa and L.p.(10)	Tr(33) M.k.(17) Pa (10)	Tr(50) M.k.(27) Su and S.r. and L.e. (10)	Tr(43) M.k.(23) Pa and S.r.(10)	Tr(33) M.k.(17) Su and Pa and S.r.(13)	Tr(23) M.k.(17) S.r.(13)	Tr(37) M.k.(17) Su and L.e.(13)	Tr(43) Su and M.k. (20) Pa(13)

Note: Abbreviations, in each instance, refer to sites noted below. Numbers in parentheses show the percentage of subjects who reported that point as painful upon palpation.
Sites (numbers refer to sites shown in Fig. 1). 1, Occiput (Occ); 2, Low cervical (L.c.); 3, Trapezius (Tr); 4, Supraspinatus (Su); 5, Paraspinous (Pa); 6, Second rib (S.r.); 7, Lateral pectoral (L.p.); 8, Lateral epicondyle (L.e.); 9, Medial epicondyle (M.e.); 10, Medial Knee (M.k.); 11, Forearm (For); 12, Thumbnail (Thu); 13, Midfoot (M.f.); R, right; L, left.

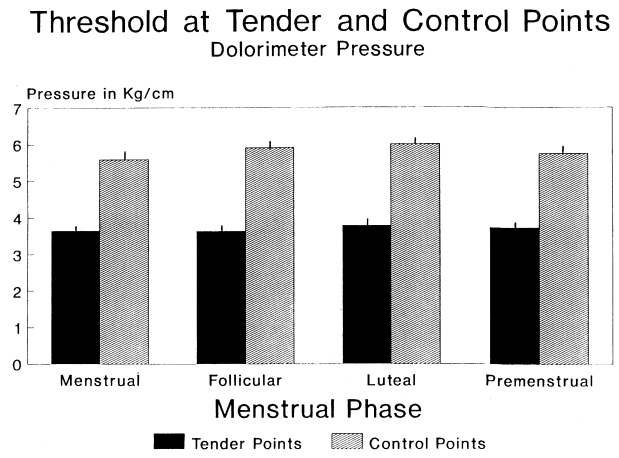

Fig. 3. Dolorimeter threshold at tender and control sites as a function of menstrual phase. Since there were no differences between normally menstruating women and users of oral contraceptives, data for the two groups were combined.

No menstrual cycle phase differences were found for any of the VAS measures of self-assessed health and mood state. Because no such differences were found, VAS data were averaged across the four phases and the results are shown in Table 5.

3.4. Correlations

Sensitivity to palpation and pressure are shown, respectively, by increased number of tender points and lower threshold. One would expect individuals with many tender areas to also have low pressure pain threshold. Significant negative correlations were found between tender point count and dolorimetry across the menstrual cycle. The higher the number of tender points in each phase, the lower the average pain threshold. From 9 to 20% of the variance in each measure was accounted for by the other across the four phases. The correlations, as a function of menstrual cycle phase, were as follows, menstrual: $r = -43$, $P < 0.001$; follicular: $r = -45$, $P < 0.001$; luteal: $r = -34$, $P < 0.005$; premenstrual: $r = -30$, $P < 0.01$.

Table 4
Points with lowest dolorimetry threshold as a function of menstrual phase

Normally cycling women ($n = 36$)			
Menstrual	Follicular	Luteal	Premenstrual
1 (100)	1 (97)	1 (92)	1 (94)
6 (53)	6 (67)	6 (53)	6 (50)
8 (25)	8 (22)	8 (28)	8 (28)
Oral contraceptive users ($n = 30$)			
Menstrual	Follicular	Luteal	Premenstrual
1 (87)	1 (93)	1 (87)	1 (90)
6 (60)	6 (70)	6 (60)	6 (67)
8 (33)	8 (20)	8 (20)	8 (27)

Note: First numbers, in each instance, refer to sites noted below. Numbers in parentheses shows the percentage of subjects who had the lowest threshold to dolorimeter pressure at that point.
1, Occiput; 6,: Second rib; 8, Lateral epicondyle.

4. Discussion

4.1. The menstrual cycle affects tender point count but not pain threshold

Phase differences were found for the number of testing points reported as painful upon palpation. Normally cycling women had fewer tender points in the luteal as compared with the follicular phase, whereas oral contraceptive users obtained the same number of tender points across the menstrual cycle. This last finding is consistent with those of previous studies in that only normally menstruating women show changes in pain responsiveness (Goolkasian, 1980; Goolkasian, 1983; Hapidou and deCatanzaro, 1988; Dao et al., 1997) and well-being (Warner and Bancroft, 1988) across the menstrual cycle. If our finding that tender point counts vary with menstrual cycle status is confirmed, clinicians assessing female patients for myofascial pain or fibromyalgia (particularly those who are not taking oral contraceptives) should determine the phase of the menstrual cycle at the time of each examination and take hormonal modulation of pain and mood (Morse and Dennerstein, 1988) factors into account when evaluating their scores.

While tender point count varied with menstrual phase, pain threshold, as measured with the dolorimeter over fibromyalgic tender and control points, remained stable throughout the menstrual cycle in both normally menstruating women and oral contraceptive users. Others have also reported striking differences between the findings obtained by palpation and by pressure dolorimetry (Rasmussen et al., 1990; Samborski et al., 1991; Cott et al., 1992). The critical distinction between what appear, at first glance, to be

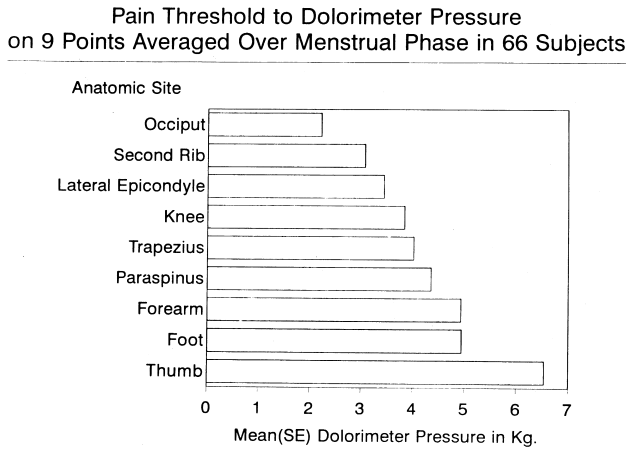

Fig. 4. Dolorimeter threshold at nine test sites, averaged across menstrual phase in all subjects.

Table 5

Average VAS ratings collapsed across four phases of the menstrual cycle for normally-menstruating women and oral contraceptive users

	Muscle stiffness	Aches and pains	Anxiety problems	Tension	Worry	Depression	Fatigue	Sleep
Normally menstruating women								
Mean	24.83	21.51	25.56	25.19	30.02	16.17	31.42	21.96
SE	3.34	2.80	2.89	2.87	3.26	2.45	3.54	3.17
Oral contraceptive users								
Mean	28.87	22.75	27.54	28.29	36.40	18.08	35.85	24.32
SE	3.13	2.89	2.76	3.59	3.66	3.19	3.62	3.53

similar methods may be related to a number of possible factors.

Firstly, the data depend upon different measures and different (although overlapping) populations. Tender point scores are determined by the number of individuals reporting pain upon palpation at 13 bilateral sites and, therefore, are based on only some subjects (27 out of 36 normally-cycling women and 24 out of 30 oral contraceptive users, in this study). The dolorimetry scores reflect the pressures necessary to induce pain, at nine of those sites, in all participants.

Secondly, the underlying mechanisms for the two determinations may be quite different. Tender points in muscles may reflect an initial peripheral pathophysiology (Simons, 1986; Mense, 1993; Ursin et al., 1993; Bennett and Jacobsen, 1994). Pain thresholds, summed across sites, may be indicative of a perceptual hyper-responsiveness attributable to higher order mechanisms (Rollman, 1989; Bennett, 1993; Rollman and Lautenbacher, 1993; McDermid et al., 1996).

Thirdly, tender points may be influenced by such factors as fatigue, depression, and sleep disturbances (Croft et al., 1994) and level of daily stress (Urrows et al., 1994) in ways that are not seen when pain thresholds are determined, with considerably greater force, at non-tender sites.

Fourth, palpation and dolorimetry may be selectively influenced by variables such as the different pressure exerted by the thumb and the dolorimeter as well as the different surface area of the two contactors (White et al., 1993; Solga and Muller, 1996). The rubber tip of the dolorimeter has a different shape, a different surface area, and different compliance to compression than that of the thumb.

Finally, there may be something special, in terms of affect or cognition, about discovering that relatively light pressure, which is innocuous in most instances, causes pain when applied to certain loci. Wolfe (1994) observed, 'There is a measure of global pain and distress that comes through in the tender point examination that is missing in dolorimetry. Dolorimetry is a very useful technique, but has major limitations in diagnosis'.

Our findings, along with those of other investigators (Wolfe and Cathey, 1985; Jensen et al., 1993; Wolfe et al., 1995a), suggest that these distinctions have important methodological implications for the design and evaluation of studies involving tender points. Since the choice of technique may markedly influence the potential conclusions, investigators should likely employ both palpation and dolorimetry.

4.2. Tender points increase during the follicular phase

Interestingly, in our study, the greatest responsiveness to a potentially noxious stimulus (number of points painful upon palpation with 1 kg pressure) occurred during the follicular phase and the least during the luteal. The second of these findings replicates those of Tedford et al. (1977) and Giamberardino et al. (1997), both of whom applied electric shock to the skin, but the results were in the opposite direction from the effects obtained by Hapidou and deCatanzaro (1988) with cold pressor pain, Fillingim et al. (1997) with ischemia, and Procacci et al. (1974) with radiant heat. Further research is needed to determine whether pain induced by thermal stimulation or muscle anoxia is influenced differently by menstrual cycle status than pain induced by primary stimulation of muscle or nerve. Likewise, there is still a need to see whether the level of clinical pain shows corresponding cycle-related changes in chronic pain patients (and, if so, whether their response to experimental pain changes in a parallel manner).

Not all studies of somatosensory function have shown menstrual cycle effects. Helstrom and Lundberg (1992), assessing vibratory thresholds in the hands, feet, and genital region of healthy women and those with gynecological disorders, found no effect of menstrual phase on any of their threshold measures. Likewise, Veith et al. (1984), using electric shock and the cold pressor task, Amodei and Nelson-Gray (1989), using a constant pressure device on the finger and muscle ischemia, and Miro and Raich (1992), using the cold pressor test, failed to find an effect of menstrual phase on pain threshold. In each of these cases, the data from all of their subjects were included in the analyses. As noted above, tender point scores focus on the most sensitive observers.

Discrepancies between studies of menstrual cycle modulation of pain may also be due to different procedures for phase calculations. There is little ambiguity about determining menstrual phase for our subjects. Test dates were indi-

vidually adapted to each woman's cycle length. The time window for high estrogen and progesterone levels during the luteal phase is sufficiently long (8–9 days) (Asso, 1983; Schnatz, 1985) that misestimation would be unlikely. Although the follicular estrogen peak is rather sharp, estrogen levels rise during this phase over a period of 5–7 days. Thus, while not all women may have been tested at their follicular peak, nearly all would have been tested during a period of rising estrogen concentrations.

4.3. Effects of body site on pain threshold and tenderness

Our data clearly show, using both methods of inducing pain, that responsiveness is not uniform across the body. There are major differences between, say, the occiput or the second rib and the thumb or the foot. In this study, we found that the responsiveness of diverse body areas to palpation and to pressure dolorimetry was markedly different. Pain thresholds determined by dolorimetry varied by a ratio of more than 3 to 1 between the least and most sensitive site.

Weinstein (1968), among others, has shown considerable variations across the body surface, in measures such as absolute threshold or two-point limen. Less is known about tender points for normal individuals. Simms et al. (1988) studied tolerance thresholds, using a dolorimeter, at 75 right-sided anatomic locations in ten fibromyalgia patients and ten normal control subjects. Scores for their patients varied by nearly fourfold across sites, while those for their controls varied by about twofold, although they set an upper limit.

The pain thresholds for the sites which we examined by dolorimetry varied from about 2 kg to over 6 kg. Six of the nine testing points are ones that are particularly sensitive in patients suffering from fibromyalgia. Our data indicate that they are also highly sensitive in a normal population. When the examination points are rank ordered by pain threshold, these six points all come before the three fibromyalgia 'control points'. The overall mean of the control points is 50% higher than that of the traditional 'tender points'.

While it is still uncertain what pathophysiological processes underlie the large differences in pain threshold between fibromyalgia patients and normal subjects, it is evident that 'tender points' are common in both populations. It is also clear that in our normal population there is a relationship between tender points and total myalgic score, the sum of the individual pain thresholds. Thus, individuals tend to be consistent in their degree of responsiveness to muscle-induced discomfort, although the correlations are far from perfect.

In the general population, individuals with great sensitivity may demonstrate subclinical levels of fibromyalgia. Forseth and Gran (1993) found a sizable number of women who had multiple tender points and other symptoms regarded as typical of fibromyalgia, but who failed to meet the ACR 1990 criteria (Wolfe et al., 1990). For them, there was no other evident disorder which could account for their complaints and clinical findings.

A striking finding in our study is that the tender points identified as the most sensitive with palpation were not the same ones that yielded the lowest threshold values. Whereas the greatest sensitivity to manual palpation exerted by the thumb was shown in the trapezius muscle and the knee pad, and, to a lesser extent, the supraspinatous, the second rib, and the lateral epicondyle, dolorimetry revealed that the occiput, second rib, and lateral epicondyle showed the highest sensitivity. The knee and trapezius then followed.

In our study, the data differ particularly with respect to the occiput, which is not often a tender point to thumb palpation but which almost inevitably has the lowest threshold to dolorimetry. Simms et al. (1988) had a similar outcome. This spot on the back of the head-neck region seems to find a soft, wide, yielding thumb as being comfortable but responds very differently to a small, hard dolorimeter tip.

4.4. Endogenous pain and mood were unaffected by menstrual phase

A multitude of studies on the menstrual cycle have found phase differences in a variety of physical and psychological states and symptoms. This study revealed no phase differences in the VAS measures of pain or mood. This may be due to several reasons. First, the subjects in this study were not selected on the basis of menstrual or premenstrual complaints, as is the case with many previous investigations. This was advertised as a study of muscle tenderness and mood with no reference made to the menstrual cycle. The only requirement for inclusion in the data analysis was regularity in menses so that menstrual phase could be properly assigned. Second, this was a prospective study. A lot of the evidence of changes in psychological state according to cycle phase stems from retrospective studies which have been shown to measure expectations rather than actual change, as well as to be affected by memory problems (Parlee, 1974; Ruble, 1977). Third, the purposes of the study were not made known to the subjects, as such knowledge might bias their responses. Fourth, our subjects were young women of university age; older subjects, particularly those suffering from musculoskeletal problems, may show quite different effects.

4.5. Biological factors modulating pain during the menstrual cycle

The relationship between menstrual phase and number of tender points which we have shown in normal control subjects suggests that endocrine activity can modulate tenderness and, possibly, the level of endogenous pain. Stratz et al. (1993) found a significant correlation between number of tender points and serotonin levels in fibromyalgia patients and a significantly lower level of plasma serotonin in the patients, compared to controls. D'Andrea et al. (1995) found

menstrual cycle-related fluctuations in platelet serotonin levels (which show an inverse correlation with serum levels), with maximum value in the follicular phase. Blum et al. (1992) found the same. Others have also shown menstrual cycle modulation of post-synaptic serotonergic responsivity (Halbreich and Tworek, 1993), plasma and urinary norepinephrine as well as plasma serotonin (Leibenluft et al., 1994), and plasma serotonin (Hindberg and Naesh, 1992).

Cyclic variations in serotonin levels may modulate tender points. Serotonin deficiencies are common in fibromyalgia (Klein et al., 1992; Russell et al., 1992; Yunus et al., 1992). Our findings, together with the biochemical evidence, indicate that clinical examinations for musculoskeletal pain ought to consider menstrual status and they strengthen the possibility that neurotransmitter and endocrine disturbances play a crucial role in the initiation or maintenance of syndromes such as fibromyalgia and myofascial pain.

Dolorimeter threshold, which was based upon data from all subjects, was not dependent upon menstrual cycle, whereas tender point count, based upon data from those who responded to relatively gentle palpation, was significantly influenced. Given the variability of tender point count, these results also suggest the hypothesis that those young women who show increased pain responsiveness now are at greater risk of developing fibromyalgia in future years.

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