



A meta-analytic review of pain perception across the menstrual cycle

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Abstract

The purpose of this article is to review the sixteen published studies that examine associations between the perception of experimentally induced pain across menstrual cycle phases of healthy females. We also performed a meta-analysis to quantitatively analyze the data and attempt to draw conclusions. The results suggest that there are relatively consistent patterns in the sensitivity to painful stimulation. These patterns are similar across stimulus modality with the exception of electrical stimulation. The magnitude of the effect was approximately 0.40 across all stimulation. For pressure stimulation, cold pressor pain, thermal heat stimulation, and ischemic muscle pain, a clear pattern emerges with the follicular phase demonstrating higher thresholds than later phases. When the effect size was pooled across studies (excluding electrical) comparisons involving the follicular phase were small to moderate (perioovulatory phase, $d_{thr} = 0.34$; luteal phase, $d_{thr} = 0.37$; premenstrual phase, $d_{thr} = 0.48$). The pattern of effects was similar for tolerance measures. Electrical stimulation was different than the other stimulus modalities, showing the highest thresholds for the luteal phase. When the effect size was pooled across studies for electrical stimulation, effect sizes were small to moderate (menstrual ($d_{thr} = -0.37$), follicular ($d_{thr} = -0.30$) perioovulatory ($d_{thr} = -0.61$), and premenstrual ($d_{thr} = 0.35$) phases. This paper raises several important questions, which are yet to be answered. How much and in what way does this menstrual cycle effect bias studies of female subjects participating in clinical trials? Furthermore, how should studies of clinical pain samples control for menstrual related differences in pain ratings and do they exist in clinical pain syndromes? What this paper does suggest is that the menstrual cycle effect on human pain perception is too large to ignore. © 1999 International Association for the Study of Pain. Published by Elsevier Science B.V.

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1. Introduction

Sex differences in pain perception have recently received considerable attention in the scientific community. Differences in pain perception among men and women have been demonstrated in the experimental (see Riley et al., 1998 for meta-analysis) and epidemiological (see Unruh, 1996 for review) literature. Variables including biological, psychological, and cultural differences, divergent social role expectations, situational factors, and an individual's past history have been hypothesized as possible explanatory factors for these differences (Berkley, 1997). Biological sex differ-

ences, such as gonadal hormones, may provide a partial explanation for the reported sex differences in the perception of painful stimulation.

For many years, clinical research has focused more on males than females, in part because of the potential variability introduced by fluctuations in hormones associated with menstruation (Holdcroft, 1997). Research has shown fluctuations in physical and psychological symptomatology during a woman's monthly menstrual cycle (Bardwick, 1976; Johannes et al., 1995; Wetherby, 1995). Physical symptoms such as headache, blood pressure, and bloating and emotional symptoms such as depression and anxiety have all been shown to fluctuate throughout the menstrual cycle (Pfleeger et al., 1997). Further, findings from animal research (Frye et al., 1993; Kayser et al., 1996; Sapsed-Byrne et al., 1996) suggest that pain sensitivity changes across the menstrual cycle. However, among humans the

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nature of menstrual cycle effects on pain responses remains unclear.

A recent epidemiological study conducted by LeResche et al. (1997) found that the odds on having temporomandibular disorder pain were increased by about 20% and 30%, respectively, in young women who used oral hormone contraceptives and postmenopausal women who used estrogen (or estrogen and progestin) replacement therapies. For the postmenopausal women, these odds increased with increased doses of estrogen. Research has also shown a relationship among syndromes linking symptom changes with other pain-related syndromes with both reproductive events and alterations of sex hormones, including fibromyalgia (Ostensen et al., 1997), rheumatoid arthritis (Da Silva and Hall, 1992), and irritable bowel syndrome (Heitkemper et al., 1993). Taken together, this suggests that gonadal hormones play a role in clinical pain perception.

Research has also shown a woman's menstrual cycle to influence her perception of experimentally induced pain. A recent literature search found 16 studies that examined the relationship between menstrual cycle and experimentally induced pain. These studies were all conducted in a laboratory setting, using controlled stimulation to induce pain and various measurement procedures. As with many studies of pain perception, the use of small sample sizes has influenced results when interpreted in terms of statistical significance (Riley et al., 1998).

Methodologically, these studies are quite diverse, making interpretation across studies difficult. The majority of studies have used pain threshold and tolerance as response measures, however, several have used two-point threshold and signal detection methodology to assess pain perception. A variety of stimulation modalities have been used to induce pain, including muscle ischemia, electrical current, thermal heat, cold pressor, and pressure stimulation.

Research laboratories also lack standardized operational definitions and methods for identifying menstrual cycle phase (Amodei and Nelson-Grey, 1989). In most women in the middle reproductive years, menstruation recurs every 25–35 days, with a median cycle length of 28 days. The interval from the onset of menses to ovulation (follicular phase) is the most variable in duration and accounts for the range of cycle lengths observed in ovulating women. The interval from ovulation to the onset of menstrual bleeding (luteal phase) is relatively constant and averages 1412 days in most women. The greatest variability in cycle length is found in the first few years after menarche and the years immediately preceding menopause (Hunt and Newcomer, 1984; Greenspan and Strewler, 1997). Researchers have used several terms for the various cycle phases (i.e. premenstrual, menstrual, postmenstrual, intermenstrual, ovulatory, follicular, and luteal), each consisting of a different range (span) of days. Another important issue is the method for tracking cycle phase. Some researchers have relied on

the calendar method for operationalizing menstrual cycle phase whereas others attempted to use physiological events (e.g. hormone level) to identify cycle phase.

The purpose of this article is to review published studies reporting experimental pain perception across menstrual cycle phases of healthy women. Studies are presented in chronological order by publication date. In an attempt to reduce the confusion of terms used to describe menstrual cycle phase, we report phase by days, numbered based on a 28-day cycle, with day one representing onset of menses. We will follow with a meta-analysis of the data reported in these studies and attempt to draw conclusions.

2. Review of studies

Herren's 1933 study appears to be the first to examine the effect of a woman's menstrual cycle on her perception of experimentally induced pain. In five normally menstruating women, Herren examined the effect of menstrual cycle on pressure pain sensitivity. He measured pressure pain applied to the forearm using a two-point threshold method. Data was collected during three phases of the cycle, premenstrual (5 days prior to the onset of menses), intermenstrual (within 3 days following the cessation of menses), and postmenstrual (on the day 2 weeks following the onset of the last menses) for 11 complete menstrual cycles. Results showed women to have considerably lower thresholds during the premenstrual phase.

Procacci et al. (1974) report data from a series of investigations employing a radiant heat stimulation to measure cutaneous pricking pain thresholds across the menstrual cycle. Pain thresholds in eight normally menstruating women (aged 15–20 years) were recorded daily or every 3 days for 1 month. Operational definitions of menstrual cycle phase were not available. Results were descriptive in nature and revealed pain thresholds to vary cyclically, reaching lowest thresholds approximately 22 days after menstrual onset and a peak at menstruation. These researchers hypothesized that the pain threshold changes were the expression of a 'central rhythmic activity, presumably diencephalic' and common to both sexes and characterized by the menstrual cycle in females.

Robinson and Short (1977) examined changes in breast sensitivity at puberty, during the menstrual cycle, and at parturition. Sensitivity to pressure pain and touch was measured in three areas of the breast in six nulliparous women, aged 20–22 years, for eight menstrual cycles. Analyses revealed that seven of the eight menstrual cycles studied showed a significant rhythm in pain thresholds, but comparison of cycles within and between subjects showed few common features. In all but two cases peaks of sensitivity coincided with the menstrual or premenstrual period. Other peaks, however, appeared randomly throughout the cycle. The authors concluded that women's breasts appeared to undergo rhythmic changes during the menstrual cycle,

with maximal sensitivity just after mid-cycle and again at menstruation.

Electrical shock thresholds were examined by Tedford et al. (1977) in introductory level psychology students. Twelve normally menstruating women were tested three times a week for approximately 5 weeks with data blocked into four phases; menstrual (days 1–7), postmenstrual (days 8–14), ovulatory (days 15–21), and premenstrual (days 21–28). Analyses revealed women with normal menstrual periods showed significant differences in pain thresholds, with maximum sensitivity found one week following menstruation and the point of least sensitivity occurring during ovulation. The authors offer several explanations for the mechanism resulting in this change, including social conditioning predisposing females to expect pain during the menstrual period and physiological mechanisms including cyclic fluctuations in the gonadal hormones. A potential problem with this study is that the electrical shock employed was designed as a distraction task secondary to a perceptual vigilance task and may have served as a distraction from the pain.

Goolkasian (1980) was the first to employ signal detection methodology in this line of research. This procedure measures both a subject's discriminability and response criterion. Her study measured the cutaneous perception of radiant heat stimulation in 12 normally menstruating women. She defined the menstrual cycle phases as menstrual (days 1–7), postmenstrual (days 8–14), ovulatory (days 15–21), and premenstrual (days 22–28). Results indicated women experienced a heightened sensitivity to pain during ovulation. Discrimination scores were found to increase significantly during ovulation, however, such a change across phase was not found for the response criterion for pain. Goolkasian (1983) replicated the results of her 1980 study, finding a significant increase in pain discriminability during ovulation compared with the pre- and postmenstrual phases. There was no difference between discriminability in the ovulation and menstrual phases. Again, cyclic effects were not apparent in the analysis of the response criteria.

Aberger et al. (1983) investigated pain sensitivity throughout the menstrual cycle in addition to coping strategies among female undergraduate psychology students. Measures of pain threshold and tolerance were assessed during a muscle ischemia task. Menstrual cycle phases were staged as pre-menstrual, menstrual or post-menstrual phase based on a single question from a health questionnaire. Aberger et al. did not define what days operationalized each phase or provide data by phase, consequently their results are difficult to compare with other studies. They reported significantly greater threshold and tolerance times for subjects in the premenstrual phase relative to subjects in what they described as the menstrual or post-menstrual phases.

Veith et al. (1984) assessed pain thresholds and anxiety levels in response to electric shock and a cold pressor task across the menstrual cycle. Their subjects were nine nor-

mally cycling female volunteers with a mean age of 26. They were tested during five phases of their menstrual cycle defined as menstrual (days 2–4), follicular (days 8–10), ovulatory (as determined from a basal body temperature chart), luteal (day 6–8 from ovulation), and premenstrual (days 11–13 from ovulation). Venipunctures were also performed and the plasma of normally menstruating women was assayed for, endorphin. Analyses revealed that the variance but not the mean levels of endorphin levels significantly differed across the menstrual cycle, with the greatest amount of variance found during the ovulatory phase and the least during the luteal phase. There was no significant difference in pain threshold across menstrual cycle phases for either pain stimulation procedure.

Kuczmeirczyk and Adams (1986) examined autonomic arousal and pain sensitivity in a sample of 10 healthy women, aged 20–43 years, across three phases of the menstrual cycle. The phases were identified as menstrual (days 1–4), intermenstrual (days 7–22) and premenstrual (days 24–28). Pressure stimulation was used to experimentally induce pain and measures of pain threshold and pain tolerance were assessed. Analyses revealed no main effect of phase for behavioral measures of threshold and tolerance. The authors acknowledge that the small number of subjects and resultant low statistical power limited interpretation of their findings.

Rao et al. (1987) tested for pain threshold differences across the menstrual cycle of healthy female subjects using a novel mechanical stimulus. Their methodology consisted of inflating a sphygmomanometer over a serrated bottle cap placed on the flexor surface of the forearm. They used inflation pressure at onset of pricking pain as the dependent measure to test for threshold variability during three time periods in the female subjects' menstrual cycle (days 0–5, 15–18, and 25–30). Data were collected across three months, unfortunately they did not state how cycle phases were determined. Additionally, the use of a 30-day cycle is unusual. The results indicated a group of college age female students and a group of working females with ages ranging from 30–40 reported statistically higher thresholds in the 15–18 day period compared to the other two periods.

Amodei and Nelson-Grey (1989) examined pain sensitivity of twelve undergraduate females using three different experimental pain protocols across the menstrual cycle. The authors reported the mean age for the sample was 18, but did not indicate the range. Repeated measures were obtained across three phases of the menstrual cycle defined as premenstrual (days 24–28), menstrual (days 1–4), and intermenstrual (any one of days 12 through 16) using the calendar method. During each of the three laboratory sessions, pain threshold and pain tolerance were assessed in the women's pain responses to muscle ischemia and a pain stimulator (low and high pressure pain). Analyses reported no significant main effects or interactions for the two behavioral dependent measures.

Hapidou and De Catanzaro (1988) studied sensitivity to cold pressor pain during the menstrual cycle. Pain responses as measured by threshold, tolerance, and a VAS rating to the cold pressor task were examined in 43 normally menstruating undergraduate students with a mean age of 21. The study design was between subjects, with 20 subjects tested during the follicular phase (days 8–14) and 20 tested during the luteal phase (days 15–21) of the menstrual cycle. Hapidou employed the calendar method to determine cycle phase, using menstrual cycle information provided before and after the completion of the experimental session. Exact dates of most recent menses were used to calculate the phase during which the experimental session actually occurred. Results revealed a significantly higher pain threshold during the follicular phase as compared to the luteal phase. Pain tolerance showed a similar but non-significant trend. Consistent with pain threshold measures, VAS ratings were significantly higher in the luteal than the follicular phase. The between-subject design employed in this study (as opposed to within-subjects designs used in all other studies reviewed here) offers less experimental control and consequently, provides a less powerful test.

In a 1995 article, Nguyen et al. examined esophageal sensory and pain thresholds in 10 females during two phases of the menstrual cycle, days 5–7 and days 20–22. Pain was induced with an esophageal balloon distention technique and measures of threshold were assessed. Sensory and pain perception was identical for each phase of the menstrual cycle. While previous studies had relied on the calendar method or recording cycle phase, serum progesterone levels verified that nine of the 10 women were in the luteal phase of their cycle. Pain stimulation of this nature constitutes visceral pain that may have different response parameters than cutaneous induced pain in relationship to menstrual cycle phase (Robbins et al., 1992).

Recently, Giamberardino et al. (1997) examined pain threshold variations in parietal tissues as a function of menstrual cycle, segmental site and tissue depth. Only the cutaneous sites will be reviewed here. Their sample included 11 females ranging in age from 19 to 36 recruited from a medical center in Chieti Italy. Electrical stimulation was used to induce pain at four sites (arm, leg, and bilateral sides of abdomen). Pain thresholds were measured four times during the course of one menstrual cycle. The cycle was calculated from the onset of menses and defined as menstrual (days 2–6), periovulatory (days 12–16). Luteal (days 17–22) and premenstrual (days 25–28). Analyses revealed the highest thresholds occurred in the luteal phase regardless of segmental site with the lowest thresholds occurring in the periovulatory stage. It should be noted that these differences did not reach statistical significance.

Filligim et al. (1997) improved upon methodological limitations of previous studies by measuring hormone levels in urine and plasma. Filligim et al. used a repeated measure design to evaluate changes in thermal and ischemic pain responses during three phases of the menstrual cycle.

Cycle phases were defined as midfollicular (days 5–8), ovulatory (mean day of 14.7), and mid-to-late luteal (days 19–27) in eleven normally menstruating women. Thermal and ischemic pain threshold and tolerance were measured and a magnitude matching procedure was used to examine responses to graded thermal stimulation. Ovulatory phase was defined by positive tests using ovulation kits rather than relying on the traditional calendar method. They found statistically significant differences for ischemic pain with higher tolerances during the follicular phase in comparison with ovulatory and luteal phases. However, statistical differences were not found across phases for thermal pain.

Filligim et al. (1997) were the first researchers to examine the relationship between circulating hormone levels and pain sensitivity. They assessed plasma levels of estrogen, progesterone, luteinizing hormone, testosterone, and b-endorphins during each experimental session. Correlations between hormones and pain measures revealed that higher estrogen seemed to be associated with increased thermal pain sensitivity. No association between hormone levels and ischemic pain responses were observed.

Pfleger et al. (1997) investigated the relationships among menstrual cycle, blood pressure and ischemic pain sensitivity in women. Eleven normally menstruating women volunteers were assessed twice for ischemic pain sensitivity during the follicular phase (days 4–9) and the mid-late luteal phase (5–10 days after ovulation) using measures of threshold and tolerance. This study also incorporated a urine test to confirm ovulation. Blood pressures were recorded to examine blood pressure pain sensitivity associations. Results revealed significantly longer pain tolerance and threshold times in the follicular phase. Blood pressures were positively correlated with pain threshold and tolerance times assessed during both cycle phases.

3. Methods

3.1. Sample of studies

Computer-based information searches were conducted on the MEDLINE (1996)–1998) and PSYCHLIT (1887–1998) databases. The keywords used in the searches included pain, experimental pain, hormone, menstrual cycle, menstrual phase, estrogen, and progesterone. In addition, the reference sections from published articles identified in these searches were used as an additional source of studies. We believe these studies represent a comprehensive selection of empirical studies. Only published research was included in the analysis, which may have biased the results as non-significant results are less likely to be published than those with significant findings. Overall, sixteen studies were identified. When studies did not provide adequate statistical information for the calculation of effect sizes, authors were contacted via mail, telephone, and electronic mail. Sufficient data was not available for seven studies

(Procacci et al., 1974; Robinson et al., in press; Tedford et al., 1977; Goolkasian, 1980, 1983; Aberger et al., 1983; Rao et al., 1987) and were eliminated. The studies of Herren, 1933 (two-point discrimination) and Nguyen et al., 1995 (esophageal pain from balloon inflation) provided adequate data, however, they used methodologies which we believe could not be compared directly with data from other studies. Consequently these nine studies were included in the literature review, with results discussed in a descriptive manner. The seven studies included in this analysis consisted of 63 subjects in within subject methodology and 43 subjects involved in a single between-subjects study.

3.2. Statistical analysis

The effect size computed for each study was d , defined as the mean for *phase a* – the mean for *phase b*, divided by the pooled within-phase standard deviation ($d = \text{equation/pooled standard deviation}$). Thus d is a standardized mean difference that can be interpreted in the same manner as any standard score. Phase comparison calculations were all made such that the chronologically earlier phase is phase *a* and the later phase is phase *b*.

3.3. Division of studies

The seven studies were divided by type of pain induction stimulation. There were seven studies with a total of 106 subjects that reported pain threshold measures. Of these studies, two used pressure stimulation, two used the cold pressor pain task, one used thermal heat stimulation, three used the ischemic muscle pain paradigm, and two used electrical stimulation. There were six studies with a total of 96 subjects which reported pain tolerance, of which two used pressure stimulation, two used the cold pressor pain task, one used thermal heat stimulation, three used an ischemic muscle pain paradigm, and one used an electrical stimulation.

3.4. Definition of phase

After reviewing the above studies and hormone fluctuation literature (Ferin et al., 1993), the following divisions were used for menstrual cycle phasing: Phase 1, days 1–5, menstrual phase; Phase 2, days 6–11, follicular phase; Phase 3, days 12–16, periovulatory phase; Phase 4, days 17–23 luteal phase; and Phase 5, days 24–28, premenstrual phase. The data from the reviewed studies were assigned to one of the above phases based on the middle day of the reported time period in which a pain measurement was reported. For example, studies reporting data for days 12–16 was assigned the value of 14 and assigned to the periovulatory phase. When studies reported the actual mean value for days of that particular cycle, this value was used for phase identification.

The method used for identifying subject's individual cycle phase was generally subject self-report. In all studies, the first day of a subject's cycle began upon self-report of onset of menses. Phases were then quantified by counting forward the days from this point in time. Hapidou and De Catanzaro (1988) also reported counting backwards from the onset of the next menses for confirmation of phases in the later half of the menstrual cycle. Further control was exercised by identifying ovulation and counting forward for later phases using fluctuation in basal temperature by Veith with the use of urine testing kits by Fillingim et al. (1997) and Pflieger et al. (1997).

4. Results

4.1. Convention for interpreting effect size

For ease in presenting the data in tabular format we have used the following format. Menstrual cycle phase comparisons are ordered (e.g. 1 vs. 2; menstrual phase compared with follicular phase) such that positive values for d indicate higher values of threshold or tolerance for the earlier phases (e.g. 1 > 2) and negative values indicate higher values for later phases (e.g. 1 < 2).

4.2. Pressure pain

Kuczmeirczyk and Adams (1986) and Amodei and Nelson-Grey (1989) used pressure pain to test for differences across the menstrual cycle phases (see Table 1). Unfortunately there was no phasing overlap in these two studies so no across study comparisons are possible. Kuczmeirczyk reported a moderate effect size with the follicular phase showing increased threshold ($d_{\text{thr}} = 0.48$) in comparison to the premenstrual phase whereas Amodei and Nelson-Grey (1989) found a higher threshold for the periovulatory phase than the menstrual phase ($d_{\text{thr}} = 0.42$) or premenstrual phase ($d_{\text{thr}} = 0.43$). Differences across phase on tolerance measures were trivial for both studies. For pressure stimulation, the highest thresholds were observed during the follicular phase.

4.3. Cold pressor

Two studies, Veith et al. (1984) and Hapidou and De Catanzaro (1988), tested pain sensitivity using the cold pressor paradigm (see Table 2). The Hapidou findings suggest a mild effect with the follicular phase having higher thresholds than the luteal phase ($d_{\text{thr}} = 0.41$, $d_{\text{tol}} = 0.25$). Hapidou found somewhat smaller effects for tolerance than threshold scores across phase. Veith reported trivial differences for tolerance measures across all time periods with the largest effect ($d_{\text{thr}} = 0.13$) for follicular compared with luteal phases. For cold pressor pain, the highest threshold and tolerance times were observed during the follicular phase.

Table 1

Threshold and tolerance measures of pressure pain across menstrual phase. Phase 1, menstrual phase; Phase 2, follicular phase; Phase 3, periovulatory phase; Phase 4, luteal phase; Phase 5, premenstrual phase

Study	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Pressure pain: threshold											
Kuczmeirczyk and Adams, 1986	10							0.48			
Amodei and Nelson-Grey, 1989 low pressure	12		-0.42		0.05					0.43	
Amodei and Nelson-Grey, 1989 high pressure	12		0.04		0.32					0.30	
Collapsed × study	22		-0.23		0.16			0.48		0.37	
Pressure pain: tolerance											
Kuczmeirczyk and Adams, 1986	10							-0.03			
Amodei and Nelson-Grey, 1989 low pressure	12		-0.09		0.04					0.11	
Amodei and Nelson-Grey, 1989 high pressure	12		0.06		0.15					0.06	
Collapsed × study	22		-0.01		0.10			-0.03		0.09	

4.4. Thermal heat

Fillingim et al. (1997) was the only study to report testing for differences across menstrual cycle phase using thermal heat (Table 3). They reported the follicular phase showed a higher threshold and tolerance than the periovulatory phase ($d_{thr} = 0.32$, $d_{thr} = 0.38$) with smaller effects for differences with the luteal phases ($d_{thr} = 0.13$, $d_{thr} = 0.28$). The effects for periovulatory phase compared with luteal was very small ($d_{thr} = -0.19$, $d_{tol} = -0.07$). For thermal heat stimulation, the highest tolerance and thresholds were observed during the follicular phase.

4.5. Ischemic pain

Three studies, Amodei and Nelson-Grey (1989), Fillingim et al. (1997) and Pflieger et al. (1997) used ischemic pain to test for differences across menstrual phase (see Table 4). Amodei found the largest differences for comparisons between the premenstrual phase and the periovulatory phase ($d_{thr} = 0.25$, $d_{mi} = 0.23$) or menstrual phase ($d_{thr} = 0.32$). However they did not test either follicular or luteal phases. The staging used by Fillingim and Pflieger were similar and allow useful comparisons. They found higher threshold and tolerance times for the follicular phase compared to the luteal phase (Fillingim, $d_{thr} = 0.48$, $d_{thr} = 0.42$; Pflieger, $d_{thr} = 0.58$, $d_{thr} = 0.68$). Fillingim also reported higher threshold and tolerance for comparisons between the follicular phase and the periovulatory phase ($d_{thr} = 0.36$, $d_{thr} = 0.28$). Threshold and tolerance measures were

similar for Fillingim and Pflieger within phase. Collapsing across threshold and tolerance measures suggests that for ischemic muscle pain, the follicular and premenstrual phases were less sensitive than the ovulatory and luteal phases. The largest effect was for the follicular phase having a higher threshold and tolerance than the luteal phase.

4.6. Electrical stimulation

Two studies, Veith et al. (1984) and Giamberardino et al. (1997) tested for phase differences using electrical stimulation as a pain stimulus (Table 5). The staging used by Veith allowed collection of data from all five phases. They report trivial differences with the exception of finding follicular ($d_{thr} = 0.30$) and periovulatory ($d_{thr} = 0.40$) phases had higher thresholds than the luteal phase.

The study of Giamberardino et al. (1997) tested three different segmental sites (arm, leg, and abdominal region). Rather than report data from each site, we have pooled effect sizes across site by phase. This methodology had little overall influence on the results, as the effects were relatively consistent across site. Giamberardino found the luteal phase had higher thresholds in comparison with periovulatory ($d_{thr} = -0.82$), menstrual ($d_{thr} = -0.37$), and premenstrual ($d_{thr} = 0.35$) phases. In addition, the menstrual phase showed a higher threshold than the periovulatory phase ($d_{thr} = 0.26$). The pattern found by Giamberardino was similar to that found by Veith, only with generally larger effects. The pattern for electrical stimulation was opposite than for the other four types of pain stimuli. With electrical stimulation, the

Table 2

Threshold and tolerance measures of cold pressor pain across menstrual phase. Phases as for Table 1

Study	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Cold pressor pain: threshold											
Hapidou and De Catanzaro, 1988	20/23						0.41				
Cold pressor pain: tolerance											
Veith et al., 1984	9	-0.07	0.03	0.06	0.00	0.10	0.13	0.07	0.03	-0.03	-0.06
Hapidou and De Catanzaro, 1988	20/23						0.25				
Collapsed × study	52	-0.07	0.03	0.06	0.00	0.10	0.19	0.07	0.03	-0.03	-0.06

Table 3

Threshold and tolerance measures of thermal heat across menstrual phase. Phases as for Table 1

Study	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Thermal heat: threshold											
Filligim et al., 1997	10					0.32	0.13		-0.19		
Thermal heat: tolerance											
Filligim et al., 1997	10					0.38	0.28		-0.07		

luteal phase had the highest thresholds and the periovulatory phase the lowest thresholds.

4.7. Pooled effect sizes across pain measure

We then combined studies reporting threshold measures across pain stimulus (Table 6). The two studies using electrical stimulation reported a different pattern of results than the other studies. This suggests some fundamental uniqueness for electrical stimulation. Because of this difference, electrical stimulation is listed separately. The relative magnitude of the differences in effect sizes between electrical stimulation and the pooled effect sizes from the other stimulus modalities was considerable, $d_{\text{electrical}} - d_{\text{pooled}}$ for $\Delta 1v3 = 0.38$, $\Delta 1v5 = 0.05$, $\Delta 2v3 = -0.20$, $\Delta 1v4 = -0.67$, $\Delta 2v5 = -0.58$, $\Delta 3v4 = -0.56$, $\Delta 3v5 = -0.27$.

For the pooled threshold values (pressure pain, cold pressor, thermal heat, and ischemic muscle pain the largest differences appear in comparisons of the follicular phase with the periovulatory ($d_{\text{thr}} = 0.34$), luteal ($d_{\text{thr}} = 0.37$), and premenstrual ($d_{\text{thr}} = 0.48$) phases and indicate that the follicular phase has higher thresholds. Effect sizes for electrical stimulation indicate that the luteal phase showed the highest threshold in comparison to all other phases; menstrual ($d_{\text{thr}} = -0.37$), follicular ($d_{\text{thr}} = -0.30$), periovulatory ($d_{\text{thr}} = -0.61$) and premenstrual ($d_{\text{thr}} = 0.35$).

When the effect sizes for tolerance measures across pain stimulation were combined (Table 7) a somewhat similar, but weaker pattern is observed than for threshold. Tolerance values suggest that the notable differences appear in comparisons of the follicular phase with the periovulatory ($d_{\text{thr}} = 0.25$) and luteal ($d_{\text{thr}} = 0.32$). No studies using electrical stimulation resorted tolerance values.

Table 4

Threshold and tolerance measures of ischemic pain across menstrual phase. Phases as for Table 1

Study	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Ischemic pain: threshold											
Amodei and Nelson-Grey, 1989	12	-0.11	-0.32								-0.25
Filligim et al., 1997	11	0.36	0.48						0.08		
Pfleeger et al., 1997	11	0.68									
Collapsed × study	23	-0.11			-0.32	0.36	0.58		0.08		-0.25
Ischemic pain: tolerance											
Amodei and Nelson-Grey, 1989	12		0.22		-0.01						-0.23
Filligim et al., 1997	11					0.28	0.42				0.14
Pfleeger et al., 1997	11						0.58				
Collapsed × study	23		0.22		-0.01	0.28	0.50		0.14		-0.23

4.8. Threshold versus tolerance

Five studies collected data on both tolerance and threshold measures for a common pain stimulus (Amodei, Filligim, Pfleeger, Hapidou, and Kuczmeirczyk). When the effect size values are pooled across study and phase for these five studies, threshold measures had an average effect size of 0.28 compared with 0.14 for tolerance. When differences in effect size between threshold and tolerance was calculated across stimulation modality the following results were observed: ischemic pain, 0.02; pressure pain, 0.21; thermal pain, 0.02; and cold pressor (one study), 0.17. This suggests that comparisons between threshold and tolerance differ depending on pain stimulus with differences only for pressure and cold pressor induced pain.

5. Discussion

The purpose of this study was to organize and review the sixteen existing studies that examine fluctuations in a woman’s perception of experimentally induced pain as a function of menstrual cycle phase. We have also performed a meta-analysis on the data reported in these studies. The results suggest that there are relatively consistent patterns in the sensitivity to painful stimulation of healthy menstruating women. These patterns are similar across stimulus modality with the exception of electrical stimulation. The magnitude of the effect size for the fluctuation between the relatively most sensitive and least sensitive phases was approximately 0.40 across all stimulation. In addition, pain response measures of threshold and tolerance are similar, with differences somewhat larger for threshold.

Table 5

Threshold measures of electrical stimulation across menstrual phase. Phases as for Table 1

Study	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Electrical stimulation: threshold											
Veith et al., 1984	9	0.04	0.17	0.15	-0.01	0.14	-0.30	-0.10	-0.40	-0.24	0.16
Giamberardino et al., 1997	10		0.26	-0.58	-0.06				-0.82	-0.17	0.54
Collapsed × study	19	0.04	0.21	-0.37	-0.03	0.14	-0.30	-0.10	-0.61	-0.21	0.35

For stimuli other than electrical, a clear pattern emerges for pain threshold with the follicular phase demonstrating higher threshold than later phases (perioviatory, luteal and premenstrual). The largest effect sizes were always observed in comparisons involving the follicular phase. When the effect size was pooled across studies (excluding electrical) comparisons involving the follicular phase were in the small to moderate range (perioviatory phase, $d_{thr} = 0.34$; luteal phase, $d_{thr} = 0.37$; premenstrual phase, $d_{thr} = 0.48$). The pattern of effects was similar for tolerance measures.

The results for electrical stimulation were very different than the other stimulus modalities. This stimulus seemed to interact with menstrual phase in the opposite manner. The largest effect sizes were observed in comparisons involving the luteal phase. For electrical stimulation, the luteal phase demonstrated higher thresholds than all other phases with the largest difference when comparisons are made between the luteal with perioviatory phases. When the effect size was pooled across studies for electrical stimulation, effect sizes were in the small to moderate range (menstrual $d_{thr} = -0.37$), follicular ($d_{thr} = -0.30$) perioviatory $d_{thr} = -0.61$), and premenstrual ($d_{thr} = 0.35$) phases. No studies reported collecting tolerance measures using electrical stimulation.

It is unknown why the studies reviewed would find different effects for electrical stimulation in comparison to the other stimulation modalities. In discussing the results of their study, which used electrical stimulation, Giamberardino et al. (1997) stated that 'it may be that the impact of pain sensitivity is different for different types of stimulation' (p. 194). The lack of generalization across all stimuli for the menstrual cycle effect argues against a common psychophysiological mechanism of action. Rather, it is far more likely that multiple factors co-determine the differences between modalities of stimulation and between dependent measures of pain responsiveness.

Studies have shown that sex hormones such as estradiol and progesterone effect beta-endorphin and met-enkephalin which are known to mediate response thresholds to aversive stimulation (Medina et al., 1993; Dawson-Basoa and Gintzler, 1996, 1997; Gordon and Soliman, 1996). Thus, the influence of hormone levels (menstrual cycle phase) on opioid pain modulating systems could produce the observed differences between stimulus modalities. Morphine inhibits pain evoked by input from unmyelinated C nociceptive afferents more than A-delta nociceptive afferents and it is reasonable to surmise that this difference applies to endogenous opioid modulatory mechanisms as well. Since electrically evoked pain is likely the main result of A-delta nociceptive afferent stimulation (Gracely, 1994) and since exogenous and endogenous opioids have either very small or negligible effects on A-delta mediated pain (Cooper et al., 1986; Price, 1988) then sex differences observed for electrically induced pain are unlikely the result of factors related to endogenous opioid mechanisms. Rather, it is more likely that sex differences in response to electrically evoked pain are the result of autonomic nervous system-mediated responses to an acute painful electrical stimulation or the result of factors related to overall perceived unpleasantness associated with electric shock.

Related to the autonomic nervous system changes that may be associated with menstrual changes are cardiovascular changes that also occur with the menstrual phase. Changes in core of peripheral temperature associated with menstrual phase could influence those types of stimuli that use applied heat or cold. These changes are less likely to influence electrical stimulation. Monitoring basal body temperature changes is a common means of detecting ovulation and empirical evidence has shown that the thermal conductance and core body temperature differs between phases (Frascarolo et al., 1990, 1992). Changes in thermal pain perception has been demonstrated to be associated with

Table 6

Effect size for threshold pooled across pain stimuli. Phases as for Table 1

Stimuli	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Pressure pain	22		-0.23		0.16			0.48		0.37	
Cold pressor pain	43						0.41				
Thermal heat	10					0.32	0.13		-0.19		
Ischemic pain	23		-0.11		-0.32	0.36	0.58		0.08	-0.25	
Pooled effect size	98		-0.17		-0.08	0.34	0.37	0.48	-0.06	0.06	
Electrical stimulus	19	0.04	0.21	-0.37	-0.03	0.14	-0.30	-0.10	-0.61	-0.21	0.35

Table 7

Effect size for tolerance pooled across stimuli. Phases as for Table 1

Study	<i>n</i>	1v2	1v3	1v4	1v5	2v3	2v4	2v5	3v4	3v5	4v5
Pressure pain	22		−0.01		0.10			−0.03		0.09	
Cold pressor pain	52	−0.07	0.03	0.06	0.00	0.10	0.19	0.07	0.03	−0.03	−0.06
Thermal heat	10					0.38	0.28		−0.07		
Ischemic pain	23		0.22		−0.01	0.28	0.50		0.14	−0.23	
Pooled effect size	107	−0.07	0.08	0.06	0.03	0.25	0.32	0.02	0.03	−0.06	−0.06

phases of the menstrual cycle (Kenshalo, 1996). In addition, blood pressure changes have also been documented across menstrual phase (Dunne et al., 1991; Mehta and Chakrabarty, 1993; Miller and Sita, 1994). Other evidence (Pfleeger et al., 1997) has demonstrated a relationship between blood pressure and pain responsivity. These cardiovascular changes associated with menstrual cycle and presumably associated hormonal changes may contribute to the differences between type of stimulation employed in the reviewed studies.

Another hypothesis is that an electrical stimulus has different perceptual-emotional dimensions of pain. Certain stimulation may elicit a greater affective (unpleasantness) pain response compared to the sensory aspect, which in turn could interact with hormone level. It has been demonstrated that intensity and unpleasantness of pain are processed differently (Rainville et al., 1997; Morin and Bushnell, 1998) and respond differently to drugs (Price et al., 1985, 1986). Rainville et al. (1992) compared sensory and affective qualities of four experimental pain modalities and reported that the cold pressor and ischemic muscle pain were given higher relative unpleasantness ratings than electrical or thermal stimulation. This finding supports the hypothesis that perceptual-emotional dimensions are different across stimulus modality but does not address the question of a gonadal hormone \times perceptual-emotional dimension \times stimulus modality interaction.

It is also possible that humans are more emotionally reactive to electrical stimulation than other modalities. This exaggerated autonomic response could be a function of social learning (fear of electrical shock) or physiological in nature. That naive subjects are very fearful of electrical shock is suggested by the observation that individuals who undergo training as subjects for electrical stimulation have increased their threshold as high as 300% and tolerances 350% (Vierck et al., 1983). A number of physiological events such as thermal conductance (Frascarolo et al., 1990), blood flow (Bartelink et al., 1990), and blood pressure (Dunne et al., 1991; Miller and Sita, 1994) are known to vary as a function of menstrual cycle. Furthermore, Miller and Sita (1994) reported a history of hypertension by menstrual cycle interaction for psychological reactivity to stress. As argued by Giamberardino et al. (1997), these sympathetically mediated variables (and others) could interact with stimulus modality differently across phases to produce the results reviewed above. This could account for some sex

differences in pain responsivity because there is evidence that females show greater emotional reactions to stimulation that are generally aversive in nature (Lang et al., 1993). Therefore, large sex differences in response to electrically evoked pain are more likely due to psychological factors that determine perceived aversiveness than physiological differences in afferent mechanisms of pain processing or in modulatory mechanisms that are selective for controlling perceived pain intensity.

Although some quantitative differences can be seen within stimuli, these differences may well be a function of other factors such as sample selection, instructional set, gross intensity of stimulation, or phases tested. Electrical stimulation provides an example of across study variability. Giamberardino et al. (1997) reported systematically larger phase differences than Veith et al. (1984), with some effects nearly four times higher (−0.15 to −0.58 and 0.16 to 0.54). Nevertheless, all effects were in the same direction.

The overall largest effect size reported for each study are fairly similar (Veith et al., 1984 electrical stimulation, $d_{thr} = 0.40$; Kuczmeirczyk and Adams, 1986 pressure pain, $d_{thr} = 0.48$; Hapidou and De Catanzaro, 1988 cold pressor, $d_{thr} = 0.41$; Amoedi and Nelson-Grey, 1989 pressure, $d_{thr} = 0.43$; Fillingim et al., 1997 ischemic pain, $d_{thr} = 0.48$; Pfleeger et al., 1997 ischemic pain, $d_{thr} = 0.68$; Giamberardino et al., 1997 $d_{thr} = 0.82$). The three most recent studies have reported the largest effect sizes (Fillingim et al., 1997 ischemic pain, $d_{thr} = 0.48$ for 2 vs. 4; Pfleeger et al., 1997 ischemic pain, $d_{thr} = 0.68$, 2 vs. 4; Giamberardino et al., 1997 $d_{thr} = \text{minsu}0.82$, 3 vs. 4 and $d_{thr} = -0.58$, 1 vs. 4). These increased differences may be the results of better operational definition of phase and more precise staging methodology (i.e. use of ovulation testing kits). Given that the largest variability in the menstrual cycle occurs between menses and ovulation (Ferin et al., 1993), accurate identification of ovulation may have significantly reduced error in staging.

This paper serves to emphasize the implications of hormonal fluctuations in females for future research on pain or in clinical practice. Although the task of interpreting this group of studies was made difficult by the variability in methodology, the results reflect relatively consistent patterns. For pressure induced pain, the cold pressor task, thermal heat stimulation, or ischemic muscle pain, healthy menstruating females demonstrate less pain sensitivity during the follicular phase, with some inconsistency across the

other phases. For electrical stimulation, the luteal phase was the least sensitive, again with little variability across other phases. An important issue is which phases are necessary to test to best characterize the pain level of female subjects in the age range where menstruation is a high probability? It appears the answer is that the variability is adequately captured if measures are taken in both follicular and luteal phases.

Notwithstanding the relative consistency of these results, future studies must attempt to replicate the findings reviewed above. The use of within-subject designs and multiple pain stimulation modalities and multiple dependent measures including direct scaling of multiple dimensions of pain would best serve this purpose. Studies addressing issues of validity and reliability of methods for determining cycle phase are also needed. Although a blood draw provides accurate measurement of current blood levels of hormones or their metabolites, this method is invasive, making repeated assessment costly and at best unpleasant. The use of ovulatory test kits may offer a reasonable alternative. Further, as the exact mechanism is unknown, whether levels at a single time are sufficient to predict this effect or whether this is a dynamic process, more influenced by hormone level change than absolute levels are unknown.

One question that this review should address is whether the menstrual cycle related variability in pain perception is sufficient to account for differences between males and females in past studies of experimental pain. On average, fluctuation between the relatively more sensitive and less sensitive phases were approximately 0.40. The existing literature (Riley et al., 1998) indicates that the effect size for sex was 0.55 for threshold measures and 0.57 for tolerance measures. These values would suggest that hormone variability could account for substantial portions but not all of the observed sex difference in response to experimental pain.

This paper raises several questions for which the definitive answer is yet to be determined. How much and in what way does this menstrual cycle effect bias studies of female subjects participating in clinical trials? Furthermore, how should studies of clinical pain samples control for menstrual related differences in pain ratings and do they exist in clinical pain syndromes? What this paper does suggest is that the menstrual cycle effect on pain perception is too large to ignore.

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