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Evaluation of sensitivity, motor and pain thresholds across the menstrual cycle through medium-frequency transcutaneous electrical nerve stimulation

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OBJECTIVES: The aim of this study was to identify variations in nervous thresholds in different phases of the menstrual cycle in eumenorrheic women and users of oral contraceptives.

METHOD: An observational study was performed including 56 volunteers, consisting of 30 eumenorrheic women who were non-users of oral contraceptives and 26 users of oral contraceptives. An electrical stimulator was employed to assess their nervous thresholds, with pulses applied at a fixed frequency of 2,500 Hz, modulated at 50 Hz, with phase variances of 20 μs, 50 μs and 100 μs. Sensitivity, motor and pain thresholds were evaluated during five menstrual cycle phases: phase 1 - menstrual, phase 2 - follicular, phase 3 - ovulatory, phase 4 - luteal and phase 5 - premenstrual.

RESULTS: The results indicated low sensitivity thresholds of 100 μs for non-users of oral contraceptives and 50 μs for oral contraceptive users in phase 5. Low motor thresholds of 20 μs, 50 μs and 100 μs were observed for non-users of oral contraceptives in phase 5, while that of oral contraceptive users was 100 μs. Finally, a low pain threshold of 100 μs was observed in phase 5, but only in the oral contraceptive group.

CONCLUSION: Nervous thresholds vary systematically across the phases of the menstrual cycle, with or without the use of oral contraceptives. These variations should be taken into account during research performed in women.

KEYWORDS: Hormones; Menstrual Cycle; Pain Threshold; Sensory Thresholds.

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INTRODUCTION

Changes in sexual hormones can affect various body responses. Behavioral, biochemical and physiological data obtained from animal studies indicate that beyond their reproductive function, ovarian hormones can influence sensory, motor and pain responses, depending on the menstrual cycle (MC) phase of the woman. As such, these hormones could account for certain responses that are specific to females (1-5).

The evidence of such effects is even stronger when considering the high prevalence of reproductive-aged woman presenting with chronic and behavioral diseases such as fibromyalgia, rheumatoid arthritis, temporomandibular dysfunctions, chronic pain and mood disorders compared to males (6).

The stimulation of sensory and motor nerves as well as nociceptive phenomena can influence the rehabilitation process, especially for diseases in which the existence of variations in the MC may either impair or facilitate the treatment procedure. Therefore, obtaining a better understanding of female physiology, including changes related to the MC, may enable more specific, safer and more effective therapeutic interventions to be applied in women of childbearing age.

Researchers have attempted to analyze the variations in physiological, physical and behavioral responses throughout the phases of the MC. However, their results have varied considerably due to the different methodologies applied in terms of the number of MC phases examined, stimulus modalities, type of response investigated and test parameters and protocols. This variation makes it difficult to compare and reproduce previously reported findings (4). Moreover, most studies have only assessed pain response

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across MC phases (1,2,4,7,8), without evaluating other parameters, such as sensitivity and motor responses.

Thus, the aim of the present study was to evaluate sensitivity, motor and pain thresholds during the different menstrual phases in eumenorrheic women and women using an oral contraceptive (OC). This evaluation was carried out through the application of medium-frequency excitatory motor currents and the subsequent measurement of various physical parameters.

MATERIALS AND METHODS

Subjects

A total of 70 women were recruited to the initial sample population. However, 14 women were excluded for the following reasons: four for irregularity in their menstrual cycles; seven due to missing some of the collection sessions (drop-out); two due to a high body mass index (BMI); and one for a surgical reason. Thus, 56 volunteers ultimately participated in the study, all of whom were aged between 18 and 40 years (21.27 ± 3.53) and presented a BMI between 18.5 and 25 kg/m^2 (21.11 ± 2.15) and an MC of 21-35 days. The inclusion criteria were as follows: absence of endocrine, neurological, psychiatric and urogynecological diseases and chronic musculoskeletal dysfunction of the upper limbs; absence of pregnancy or breast feeding in the past six months; and absence of drug use, except for OCs. All of the subjects signed an informed consent form. The study was approved by the local human ethics research committee (protocol number 64/05).

The volunteers were divided into two groups: eumenorrheic women with a regular and constant menstrual cycle ranging from 21-35 days (9,5) using no OC (non-oral contraceptive group - NOCG) (n = 30, mean age of 23.7 ± 3.60 years); and women using an OC regularly for at least 6 months (oral contraceptive group - OCG) (n = 26, mean age of 23.03 ± 3.53 years).

Instrumentation

To analyze the somatic and physiological symptoms associated with the MC, the participants were given a questionnaire based on the Menstrual Distress Questionnaire - MDQ (10). In this questionnaire, each volunteer evaluates her own experience regarding her symptoms in each phase of the cycle according to a 6-point scale as follows: 1 = without symptoms; 2 = minimal symptoms; 3 = mild symptoms; 4 = moderate symptoms; 5 = intense symptoms; and 6 = overwhelming symptoms. The questionnaire was administered during each data collection session immediately before the procedure (11).

For data collection, a pulse generator (Quark® Dualpex 961, Piraciaba-SP, Brazil) was used. It was operated with a biphasic pulsed current, symmetric square wave, medium frequency of 2,500 Hz and with the electric current modulated at a low frequency of 50 Hz. Phase variances of 20 μs (M20), 50 μs (M50) and 100 μs (M100) were employed. Two silica-carbon electrodes, measuring 5x3 cm, were connected to the skin using 1 mL of a hydrosoluble gel on both the flexor muscle of the wrist and the fingers of the non-dominant limb. The electrodes were placed longitudinally on the muscle fibers, with the first being placed at a distance of 4 cm from the joint line of the medial epicondyle and the second attached 4 cm from the first electrode by means of hypoallergenic adhesive tape, according to dermatome C6-8 (12). The device was calibrated before, during and after the experiment using a digital oscilloscope (Tektronix TDS 210 - Beaverton, OR, USA).

Procedures

Each volunteer was evaluated in five different MC phases, which were defined relative to the first day of menstruation as follows: menstrual phase, corresponding to days 1 to 5 (P1); follicular phase, days 6 to 11 (P2); ovulatory phase, days 12 to 16 (P3); luteal phase, days 17 to 23 (P4); and premenstrual phase, days 24 to 28 (P5) (13). In the case of longer or shorter cycles within the range of normality, proportional and individual differentiation was carried out by adding or subtracting days during the follicular period, which was considered the variability period of the MC (14).

The method used to identify the MC phases in each volunteer followed Lamprecht and Gummer-Strawn, based on information about at least the six preceding MCs (15), and Arevalo et al., based on fixed days (16). Regularity was confirmed for at least six posterior MCs, and an estimate was obtained from the average of all the cycles analyzed.

To maintain the same standards of experimental data collection and the consistency of the analysis across the groups within a given number of sessions, the MCs of the women in the OCG were also divided into five different phases. This methodology was applied despite the fact that these women present constant hormonal conditions during the use of OCs and that they only display low hormonal levels when the contraceptives are withdrawn to allow menstrual bleeding.

The MCs in OCG were evaluated by examining the contraceptive package, with the cycle being considered to begin on the first day of menstruation, based on a calendar of 28 days. All of the OC pills used by these women were single-phase, i.e., being composed of estrogen and progesterone in equal concentrations and characterized by the cyclic ingestion of 21 pills, one per day, followed by a gap of seven days to allow menstrual bleeding.

After defining the MC phases, the experiment was always conducted during the middle day(s) of each phase, and there were therefore specific data collection days for each volunteer. The phase in which the first test was initiated was randomized: 15 volunteers began in the menstrual phase, nine in the proliferative phase, 11 in the ovulatory phase, 14 in the luteal phase and seven in the premenstrual phase.

All of the volunteers were informed about the application of electric stimulation and were asked to report both the sensation of the current and the muscular contraction evoked by the stimulation during the different test conditions. All participants received previous training so that they were familiar with the procedure and displayed optimal judgment of the thresholds (17-20).

The volunteers were advised not to be on a diet and not to ingest products with caffeine, such as coffee, tea, chocolate and sodas, alcoholic beverages or systemic medicines in the 24 hours prior to data collection.

During the procedure, the volunteers remained comfortably seated, with the non-dominant arm positioned in a supine position on the examination table. Local asepsis with 70% alcohol was applied to the skin prior to the placement of the electrodes.

Data collection was always performed in the afternoon to minimize the effects of morning hormonal variations and circadian fluctuations (17,21). The data were collected at

approximately the same time for each volunteer at a room temperature of 23±2℃ and an air humidity of 70%.

Prior to initiating data collection, the sequential order for the application of electric currents was chosen randomly. Then, the volunteer was instructed to report any sensation associated with the current in response to the increase in amplitude. The first identified sensation was defined as the sensitivity threshold (ST). Next, the amplitude was increased to identify minimal clear muscular contraction, based on visual inspection or palpation, which was defined as the motor threshold (MT). Finally, the amplitude was increased until the first pain sensation was observed, which was defined as the pain threshold (PT). The increase in amplitude was maintained at the same rhythm, and the thresholds were defined based on the amperage of the device, which varied from 0 to 60 mA.

After the initial evaluation of the three nervous thresholds, the amplitude was reduced to zero, and the same procedure was repeated immediately after a one-minute rest period. During this period, the parameters were modified in accordance with the second current. This procedure was repeated successively until the three different types of electrical currents were applied.

At the end of the complete sequence of stimulation with the different current parameters, there was an interval of 15 minutes after which the procedure was repeated. This process was carried out twice. Average values from the duplicate measures were obtained.

Statistical Analysis

The sample size was calculated previously based on the standard deviation data obtained from a pilot study. The results indicated that 25 volunteers were required per group to achieve a test power of 80% and an alpha error of 0.05 (Statmate; GraphPad Software Inc, La Jolla, CA, USA).

All of the collected data were considered non-normally distributed, according to the Shapiro-Wilk test. For intra-group analysis of the threshold response across the MC phases, the Friedman test, followed by the rank test, was performed. To carry out comparisons of the thresholds between the groups, the Mann-Whitney test was used. To verify possible variations in MDQ scores and potential differences between the menstrual phases within the same group, the Friedman test was applied. All of the tests were performed using Bioestat 4.0 (Brazil) software. A significance level of 5% was used for all analyses.

RESULTS

In the NOCG, the ST associated with the M100 electric current was significantly different ($p<0.05$) in P1, P2, P3 and P4 compared to P5. In the OCG, the M50 current was different between P2 and P5 (Figure 1).

Regarding the MT, for M20 and M50 currents, variations were observed between the first four phases and P5. For the M100 current, the only difference was found between P2 and P5. The OCG only displayed differences for the M100 current between P2 and P5 (Figure 2).

For the PT, the only difference identified was between P2 and P5 in the OCG for the M100 current (Figure 3).

When the MDQ scores were evaluated, there was no difference observed between the groups. However, intra-group analysis showed differences between the phases. In both groups, it was observed that the menstrual (P1) and premenstrual (P5) phases were associated with a greater intensity of the signs and symptoms of menstrual distress compared to the other menstrual phases (i.e., the proliferative (P2), ovulatory (P3) and luteal (P4) phases).

DISCUSSION

The data collected in this study indicated that nervous thresholds vary systematically during the different phases of the menstrual cycle (MC), which is in accordance with the findings of several other studies (1-5,22).

In the NOCG, the obtained ST values were higher when the level of estradiol (E_2) was elevated, with or without reaching statistical significance. One previous study (23) in which transcutaneous electric stimulation was used to evaluate the variations in sensorial perception associated with three different currents (5 Hz, 250 Hz and 2,000 Hz) showed no difference in response between the proliferative and luteal phases. However, when the participants were pregnant, the threshold was increased due to the high levels of progesterone (P_4) and endogenous opioids present. While increases in E_2 and P_4 can influence the endogenous opioid system by acting as analgesics, decreases in these hormones, such as those observed during the premenstrual phase, can also increase pain sensitivity (18).

It is believed that the decrease in P_4 observed at the end of the luteal phase and during the premenstrual phase increases the symptoms of premenstrual syndrome (PMS), thus negatively influencing sensorial perception due to increased production of the alpha sub-unit-4 of the receptor, GABA, and/or an increase in the biosynthesis of alpha PGF2 (1,24). E_2 levels and the interaction of this hormone with the limbic system are also closely associated with the increased ST and PT observed in the proliferative phase. However, the decrease in these thresholds that occurs during the premenstrual phase in response to high levels of E_2 affects emotional and behavioral activities (25).

In the OCG, it was observed that a balance in the ST, MT and PT was maintained throughout the phases of the MC, except in P5, when a lower threshold was observed. Such findings are in accordance with those of Abraham et al. (26), who observed that women who use an OC present with variations in the symptoms of premenstrual syndrome during the premenstrual and menstrual phases.

The results obtained specifically for the MT associated with the M50 current may have occurred because this current is considered to be optimal for muscular stimulation. This effect is because the type I and II muscle fibers are intensively recruited, thus guaranteeing a more efficient and vigorous contraction, which is dependent on the number of activated motor units. Therefore, the threshold is reached more quickly than when using a current with a smaller pulse duration and in a more selective manner than when using a longer pulse.

The MT presented the greatest variation among the menstrual phases. A possible explanation for this finding may be related to the genomic effects of E_2 and its excitatory function in cortical regions linked to muscular contraction (27-29).

Inghilleri et al. (30) observed that the evoked motor potential increased gradually depending on the elevation of E_2 across MC phases. The interaction between E_2 and glutamate receptors increases the excitability of the hippocampus by opening sodium channels and increasing the

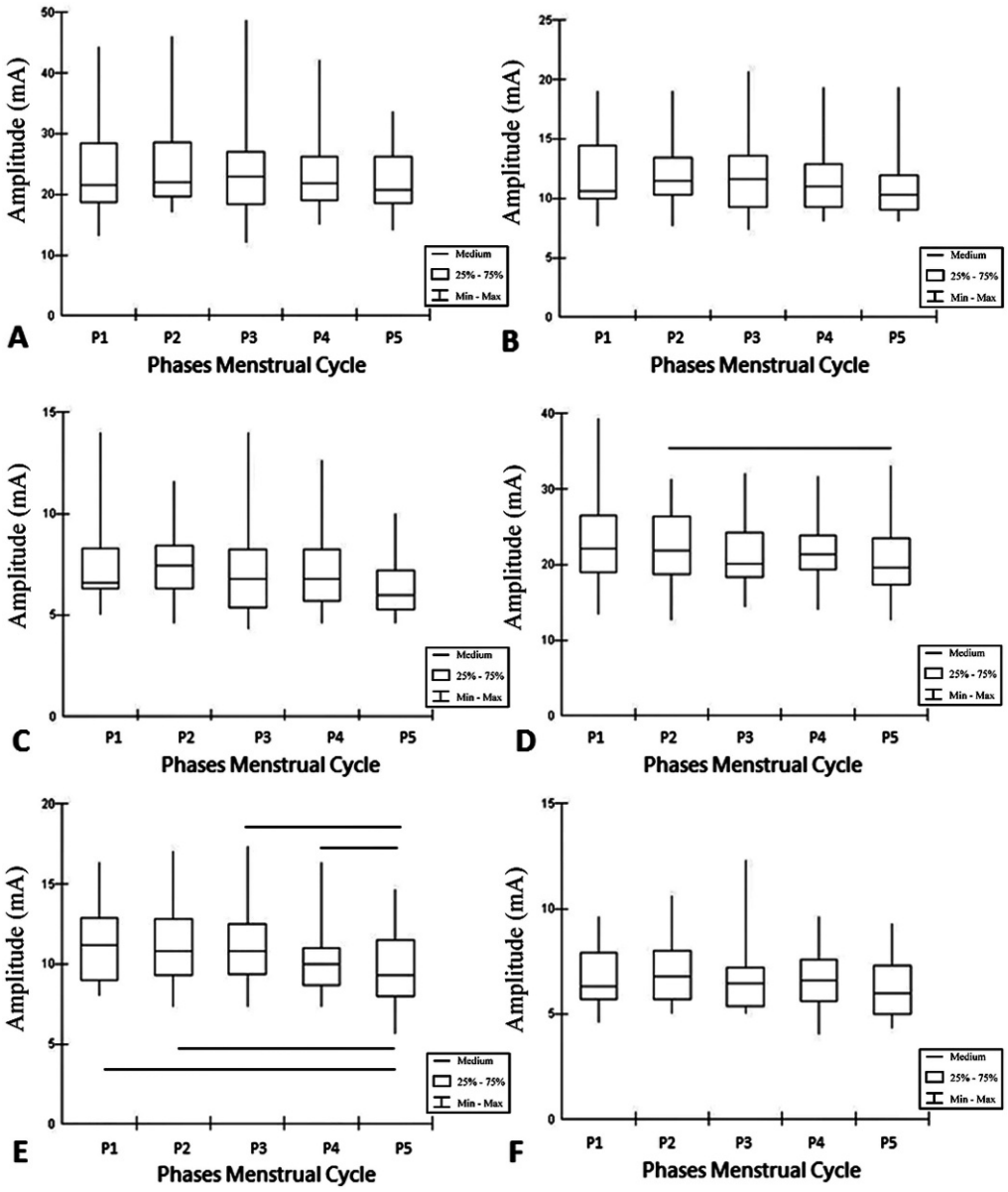

Figure 1 - The sensitivity threshold (ST) across the following five phases of the menstrual cycle (MC): menstrual (P1), follicular (P2), ovulatory (P3), luteal (P4) and premenstrual (P5). A current of 2,500 Hz was applied in phases of 20 μs (A and B), 50 μs (C and D) and 100 μs (E and F). A, C and E represent the non-oral contraceptive group (NOCG), and B, D and F represent the oral contraceptive group (OCG). The connections indicate statistical significance ($p<0.05$).

density of dendritic spines and specific synapses. The rise in E_2 levels during the proliferative phase and their peak in the ovulatory phase influence motor behavior by allowing the excitatory mechanisms of the motor cortex to act (31). This increases sensory-motor functions, including activities that demand attention and coordination (32).

The pain thresholds observed in the present study did not vary significantly between menstrual phases with respect to the experimental currents. One exception was found in the OCG between P2 and P5 in relation to the M100 electric current. As observed for the ST and MT, lower values were obtained in P5 because the hormone levels were very low in this phase. Conversely, higher values were observed for P2 and P3 because of the high estrogenic concentration and estrogenic peak in these phases, respectively. It is important to highlight that no difference was observed when using the M20 and M50 currents due to limitations in the amplitude of the pulse supplied by the device, thus restricting the evaluation of the pain threshold.

Herren (33) was the first author to evaluate alterations in pain perception in women during the MC by means of pain induction through pressure. His findings revealed lower thresholds during the premenstrual phase compared to the other phases. In addition, Robinson and Short (34) applied experimental pain induced through pressure and detected peaks of pain sensitivity in women during the menstrual and premenstrual phases.

Other studies using electric stimulation to induce pain have obtained results similar to those of the present study. Veith et al. (35) compared the five menstrual phases and

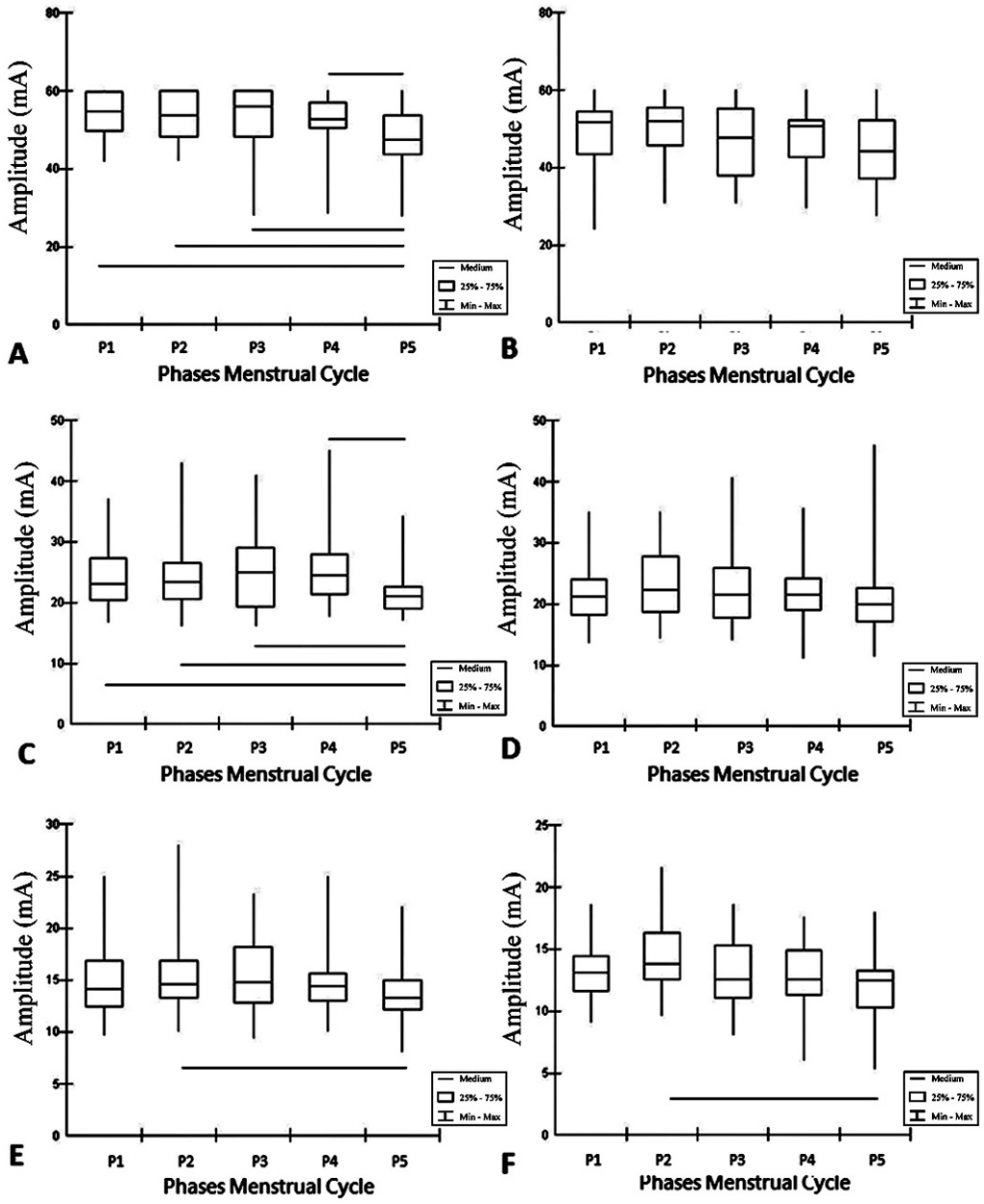

Figure 2 - The motor threshold (MT) across the following five phases of the menstrual cycle (MC): menstrual (P1), follicular (P2), ovulatory (P3), luteal (P4) and premenstrual (P5). A current of 2,500 Hz was applied in phases of 20 μs (A and B), 50 μs (C and D) and 100 μs (E and F). A, C and E represent the non-oral contraceptive group (NOCG), and B, D and F represent the oral contraceptive group (OCG). The connections indicate statistical significance ($p<0.05$).

found no significant difference in eumenorrheic women. Tedford et al. (36) observed lower thresholds during the phases associated with lower plasma hormonal concentrations. Young-Hee et al. (37) applied continuous current and evaluated three MC phases. These authors reported lower thresholds in the luteal phase compared to the menstrual phase, which is in accordance with the results from the present study.

The relationship between the amplitude of the current and phase duration influences the sensory, motor and pain thresholds. Specifically, the shorter the phase duration, the greater the amplitude required to reach these thresholds (38,39). Our results showed that sensitivity increased in the premenstrual phase (P5) for all of the examined physical parameters.

However, the present findings differ from those obtained in the study that was most methodologically similar to ours, carried out by Giamberardino et al. (40). These authors examined the menstrual variation of pain thresholds by means of electric stimulation applied to different locations and types of tissues in the body in the four following phases: menstrual (days 2-4), peri-ovulatory (days 12-16), luteal (days 17-22) and premenstrual (days 25-28). They recorded higher pain thresholds during the luteal phase and lower thresholds during the ovulatory phase. The proliferative phase was not evaluated in their study.

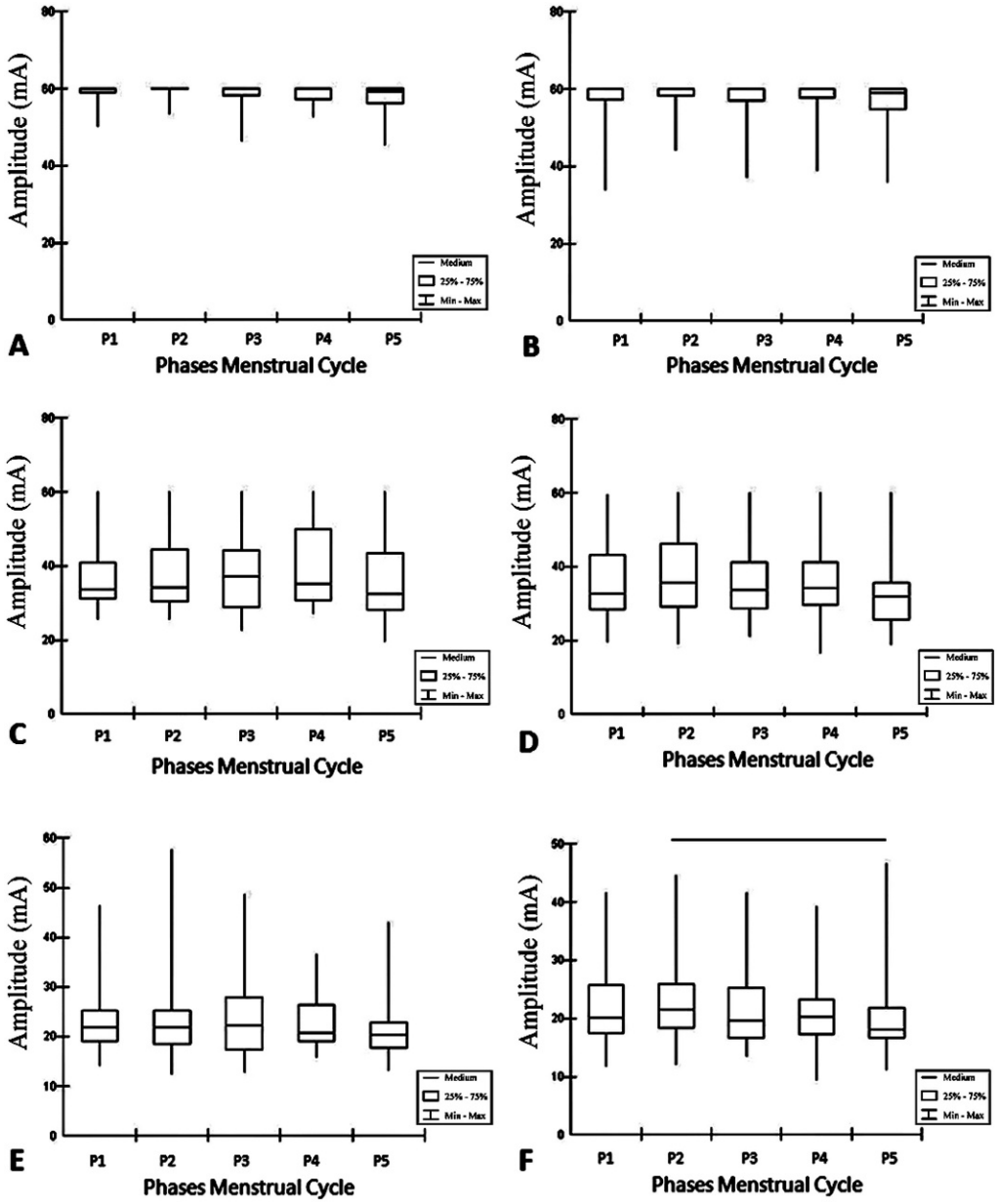

Figure 3 - The pain threshold (PT) across the following five phases of the menstrual cycle (MC): menstrual (P1), follicular (P2), ovulatory (P3), luteal (P4) and premenstrual (P5). A current of 2,500 Hz was applied in phases of 20 μs (A and B), 50 μs (C and D) and 100 μs (E and F). A, C and E represent the non-oral contraceptive group (NOCG), and B, D and F represent the oral contraceptive group (OCG). The connections indicate statistical significance ($p<0.05$).

The previous studies described above display numerous methodological differences from the present work. These differences include variations in the number of MC phases examined, the modality of electrical stimulation, the types of responses and parameters investigated and the applied test protocols. These factors may account for the varying results and difficulties encountered in comparing the findings of these studies.

According to Wiesenfeld-Hallin (6) and Riley III et al. (5), who reviewed studies performed in both humans and animals, higher thresholds are observed in the proliferative phase and lower thresholds are recorded during the phases preceding a new cycle. These conclusions support the findings of the present study, regardless of the statistical significance of the results.

Dao et al. (41) reported that female hormones can directly modulate the release of nitric oxide from muscles, possibly causing vasodilatation, inflammation and pain. Moreover, Silberstein (42) observed that serotonin levels are higher when there is more estrogen circulating in the bloodstream, thus explaining the increase in the incidence of chronic headache complaints during the premenstrual phase.

Isselée et al. (43) recorded lower pain thresholds during the premenstrual phase in women who use OCs compared to non-users. It is possible that in OC users, in whom synthetic estrogens are maintained at high doses throughout the cycle to suppress GnRH and ovulation, a significant drop in hormonal levels may result in increased pain perception (44). Moreover, Teepker et al. (45) concluded that

compared to non-users, OC users exhibit more intense migraines at the end of the menstrual phase.

Oelkers (46) found that women taking single-phase pills present with increased water retention during the phases that precede a new cycle compared to eumenorrheic women. This additional extracellular liquid generates greater impedance when a current is applied and results in higher pain sensitivity in the premenstrual phase compared to other MC phases (36).

High indices of behavioral variations such as stress, fatigue, anxiety and mood alterations may also influence the pain response through several different neural and physiological mechanisms. This type of effect was observed in the results obtained via the tMDQ.

One possible limitation of this study is the lack of blood tests to evaluate hormone levels. However, to ensure the accuracy of the results, the MCs of the volunteers were observed for 6 months before and 6 months after collecting the data to confirm the regularity of their cycles.

The present findings suggest that the hormonal oscillations observed across MC phases influence sensory, motor and pain responses in women. These modifications should be taken into account when designing therapeutic interventions because women may present better therapeutic evolution depending on the MC phase.

AUTHOR CONTRIBUTIONS

Barbosa MB executed the project and participated in the study design, data collection and analysis, and manuscript writing. Guirro EC guided and supervised the development of the work and participated in the study design, statistical analysis, discussion of results and manuscript writing. Nunes FR participated in the statistical analysis, discussion of the results and manuscript writing.

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