

Cardiovascular reactivity and pain perception to thermal noxious stimuli across different phases of Menstrual Cycle

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Abstract

Epidemiological studies on animal and human participants have failed to reach a consensus regarding the interaction of the autonomic nervous system with the female gonadal hormones and this paucity in research is important for a number of reasons since an alarming number of females complain of chronic pain and cardiovascular diseases throughout their reproductive lifespan the results of this complex interaction will help unraveling strategies for planning as well as implementation.. The aim of the present study was to examine whether the different phases of menstrual cycle alter the cardiac functioning as well as the pain nociception tested using the Cold Pressor test. Thirty eumenorrhic females were recruited and examined during the follicular and luteal phases of menstrual cycle for changes in the heart rate, systolic and diastolic blood pressures as well as for pain threshold, tolerance and its perception during Cold Pressor test. The results from our study proved that the heart rate, systolic and diastolic blood pressures were higher while the pain threshold and tolerance was lower during the luteal phase. We hence conclude that the luteal phase induces a greater cardiovascular reactivity and pain nociception as a result of greater sympathetic arousal due to interaction of the Autonomic nervous system with the endogenous gonadal hormones.

Keyword: Cold pressor test, Estrogen, Menstrual cycle, Vagal.

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Introduction

Menstruation is a regular cyclical sloughing of the uterine lining due to the interactions of hormones produced by the hypothalamus, pituitary, and ovaries which function together as Hypothalamo-pituitary Axis.^(1,2) The cyclical fluctuation in the plasma levels of gonadal steroids estrogen and progesterone underlie the physiology the menstrual cycle. Follicular phase is primarily a phase of increased estrogen levels while the luteal phase shows an increase in the levels of progesterone, these gonadal hormones are modulators of HPA(Hypothalamo-pituitary adrenal axis) axis, which along with ANS, form the stress system which regulates multiple homeostatic mechanisms regulating the cardiovascular system especially its cardiac reactivity.⁽³⁾ Heart is an organ which is controlled by the autonomic nervous system and its functioning shows variations across the normal menstrual cycle which are consistent with established actions of female-sex hormones.^(4,5)

Certain studies conducted have used the heart rate variability as a marker of ANS fluctuation and proved a significantly higher sympathetic activity in the luteal phase^(6,7) while another study proved that cyclic variations in endogenous sex hormone levels during the menstrual cycle were not significantly associated with changes in cardiac autonomic control.^(8,9) It is speculated that the cyclical hormonal profile may affect the ANS with certain consequences on the cardiovascular functioning and is an important indicator of health, because adults with autonomic dysfunction

have higher all-cause and cardiovascular mortality rates.^(10,11,12) Despite that, the literature is not clear about the influence of this relation.

There are documented non reproductive actions of endogenous sex steroids and its interaction with the pain processing and analgesic pathways is just one of them. Animal and human researches have demonstrated fluctuating pain sensitivities and variability in the central modulation of pain across the phases of menstrual cycle which can be attributed to gonadal steroid interactions both at the CNS as well as PNS levels.^(13,14) Though it is well known that there is fluctuation in pain sensitivity across the cycle but its exact effect on responses experienced has not been studied. The 1994-95 National population health survey made certain subtle observations that women have higher subjective pain ratings in response to painful stimuli compared to their counterpart males (20 % vs 16%) and the intensity as well as frequency increase after the age of 15 years.^(15,16) Literature on the interaction of endogenous gonadal hormones with the pain processing systems of the body will pose itself to controversies with some reporting higher pain thresholds at times of the menstrual cycle when the estrogen levels in the body are high since estrogen is involved in modulation of somatic sensory processes while others demonstrate reduced pain sensitivity during menstrual and premenstrual phases compared to mid-menstrual and ovulatory phases of menstrual cycle.^(17,13,14)

Females in the reproductive age group are at higher risk for developing several chronic pain conditions like fibromyalgia, rheumatoid arthritis, temporomandibular dysfunctions, chronic pain compared to males and demonstrate a greater sensitivity to noxious stressor but there is insufficient information regarding the same which is compounded by the less frequent participation of women in such studies with the result that planning preventive strategies or inventing tests for diagnosis pertinent to cardiovascular fitness as well as pain analgesia in women have posed hindrances. Cold Pressor test (CPT), is a well validated test used in the study of cardiovascular reactivity and pain which is characterized by enhanced sympathetic outflow involving both, the PNS which induces peripheral vasoconstriction by release of neurotransmitters like noradrenalin from by the post ganglionic nerve endings as well as activation of thermal- and nociceptive system activation. However, variability in the responses to experimental noxious stimuli and clinical pain in the setting of menstrual cycle have not been well characterized.^(18,19) Pain tolerance, threshold along with its perception have been used as a predictor of outcome involving nociception. There is increasing evidence that females subject themselves to less frequent evaluation and treatment for cardiac and pain relief, as a result of which it is difficult to sort the nexus of complexities involved in gender specific research hence a study of such type is necessary to be undertaken to understand the female physiology and the results derived from the study could be of help in planning multidisciplinary treatment and effective therapeutic applications for chronic pain and cardiovascular conditions.

Aim

The present study was conducted with the aim to verify the influence of the different phases of the menstrual cycle on cardiovascular as well as pain parameters in healthy young women.

Materials and Method

Study Design: Cross-sectional

Duration: December 2011 till February 2012

Source of Data: In the present study the data was collected from the students of 1stM.B.B.S enrolled for the academic year 2011. The source was limited to 1st M.B.B.S since they represent a section which is into one of the most stressful occupations, younger age groups as well the female gender make them more susceptible. If abnormalities are picked up at an earlier stage, implementing curative or preventive strategies can be planned easily.

Sample Size: Thirty eumenorrhic girls aged 17 -20 years of age studying their 1st year MBBS course were selected

Sample size Estimation-

Expected Reduction-(Mean) =d=20

SD=40 = σ

$\alpha = 0.05$ One sided

$Z \alpha = 1.65$

$\beta = 0.2$ Power 80%

$Z \beta = 0.84$

$n = ((Z \alpha + Z \beta) \sigma / d)^2 = 24.8 = 25 = 30$

Based on sample size calculation 30 MBBS phase 1 females aged 17-20 yrs who are eligible were enrolled at the time of data collection.

Thirty eumenorrhic girls aged 17 -20 years of age with regular menstrual cycle duration of 28days at least 2 months prior to the study having no medical or gynecological problems or no well-defined premenstrual tension were enrolled. We excluded subjects who had irregular menstrual cycles, menorrhagia or suffering from any endocrine disorder. The subjects consuming medications likely to influence PNS (diuretics, hormone, etc.) or drugs affecting moods (antidepressant, tranquilizers), oral contraceptive pill, hormonal replacement therapy, drugs that alter the cardiovascular functions were also excluded from the study.

Voluntary Informed written consent was obtained from all participants, and the experiment protocol was approved by Ethics committee of the college. A detailed menstrual history which included the no of days, regularity and total duration of cycle was collected prior to enrollment of every participant.

The entire purpose along with a detailed description of the study protocol was given to all the subjects prior to beginning of the test& examination carried out at same time of the day to avoid diurnal variations along with basal body temperature monitoring. Considering the first day of bleeding as Day 1, the phases marked out were:

1. Follicular (10th day)
2. Luteal (20th day).

Procedure: The subject was instructed about the test and baseline blood pressure (SBP, DBP) and HR measured using Omron semi-automated sphygmomanometer. The subject immersed the dominant hand in cold water maintained at 10 c prepared by adding ice cubes up to the wrist for one whole minute. Temperature of the water measured using a room thermometer Subject was instructed to indicate when he was not able to keep the hand immersed in water for 1 minute. After the hand was removed from the water, it was covered by a towel.

Recordings –

1. Baseline blood pressure.
2. Blood pressure was taken just before the hand is taken out of water.
3. Blood pressure was taken again at 1.5 minute and 5 minute after the hand is withdrawn from the cold water.

Highest DBP=value

Normal Values: Increase in diastolic BP ≥ 10 mm HG
Pain threshold was determined by measuring the amount of time (seconds) from the immersion of the hand in cold water till the first pain sensation was felt.

Pain Tolerance was defined as the total number of seconds elapsed at the time of withdrawal of the hand from the cold water

Pain perception was monitored during the cold pressor test using visual analogue scales (VAS) which are often used in epidemiologic and clinical research to measure the intensity or frequency of various symptoms, particularly pain.

Statistical analysis: The data quantified as mean \pm SD and analyzed statistically using Student's paired t-test $p < 0.05$ was considered to be statistically significant. Statistical software SPSS 18 version was used for the analysis of the data.

Results

In the current study we subjected the participants to Cold Pressor test during the follicular and luteal phase of menstrual cycle and observed for changes in heart rate, SBP, DBP which are markers of cardiovascular reactivity, we also measured the pain threshold, tolerance and perception which are indicators of nociceptive mechanisms. The resting baseline values of heart rate, SBP, DBP were all elevated in the luteal phase, on subjection to Cold Pressor test the values of DBP and heart rate were significantly elevated in the luteal phase as compared to its counterpart follicular phase. The pain threshold as well as tolerance for cold thermal stimuli was higher in the follicular phase while

the perception of pain did not seem to vary significantly between the two phases. The results of the present study points towards a sympathetic dominance in the luteal phase which is characterized by greater cardiac activity and pro-nociception.

1. **Table 1:** Shows baseline parameters like HR, SBP & DBP. The table shows that the HR, SBP & DBP are all statistically higher in the luteal phase.
2. **Table 2:** Shows the changes in HR, SBP & DBP when subjected to Cold Pressor test. It was observed that the changes in SBP & HR were significantly higher in the luteal phase while the change in SBP was insignificant between the two phases.
3. **Table 3:** Shows the pain correlates like Pain threshold, Pain tolerance & Pain perception. It was observed that the Pain threshold as well as Pain tolerance were higher in the follicular phase while the pain perception did not show significant difference between the two phases.
4. **Fig. 1:** Shows baseline SBP & DBP across the menstrual cycle, where it is evident that both SBP & DBP are elevated in the luteal phase as compared to follicular phase.
5. **Fig. 2:** Shows Pain threshold & Pain Tolerance across the menstrual cycle, where it is seen that both the values are higher in the follicular phase.

Table 1: Baseline Cardiovascular parameters

Variables	Follicular	Luteal	Paired t	P value
Heart Rate(bpm)	78.8 \pm 7.48	84 \pm 8.17	3.228	0.003*
Systolic Blood Pressure (mmHg)	113.9 \pm 6.63	115.8 \pm 5.91	3.023	0.005*
Diastolic Blood Pressure (mmHg)	72.8 \pm 6.90	76.5 \pm 6.82	3.354	0.002*

*- statistically significant, NS-not significant

The measurement of baseline cardiovascular parameters included measurements of HR, SBP & DBP. The Table 1 shows that the heart rate was significantly higher ($p=0.003$) in the luteal phase if you compare it to follicular phase of menstrual cycle. The systolic blood pressure measurement also shows higher values in luteal phase ($p=0.005$) and closely following are values of diastolic blood pressure which are also higher in luteal phase ($p=0.002$).

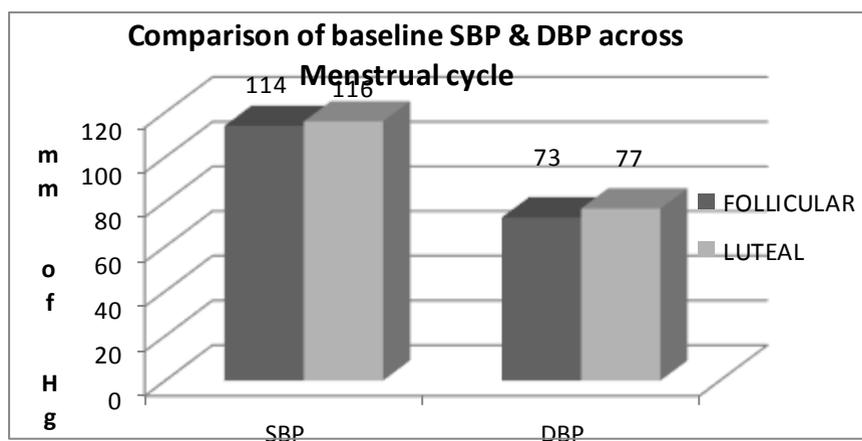


Fig. 1: Baseline SBP & DBP across the menstrual cycle

Fig. 1 shows the baseline SBP & DBP across the phases of menstrual cycle, it is evident that both the SBP & DBP are elevated during luteal phase of menstrual cycle.

Table 2: Changes in the Cardiovascular Parameters with CPT

	Follicular	Luteal	Paired t	P value
CPT(CSBP)(mmHg)	25.7 ±4.51	26.2 ±5.07	0.371	0.13 ^{NS}
CPT(CDBP)(mmHg)	17.4± 2.62	22.6 ±4.30	5.531	0.001*
CPT (Heart Rate) (bpm)	82±2.55	90±4.37	9.82	0.001*

C stands for the change in the variables on CPT, *-statistically significant, NS- not significant

In the Cold Pressor test the values of change in diastolic pressure as well as heart rate were significant ($p \leq 0.001$) in the luteal phase but the same is not true regarding the change in systolic blood pressure which was not statistically significant between the two phases.

Table 3: Pain correlates during CPT

	Follicular	Luteal	Paired t	P value
Pain Threshold(sec)	16.7 ±6.09	12.2 ±5.07	0.731	0.001*
Pain Tolerance(sec)	47.4± 19.62	26.6 ±14.30	3.531	0.001*
Pain perception (VAS Score)	4± 10.54	5± 13.09	0.141	0.10 ^{NS}

***-statistically significant, NS-not significant**

The Table 3 shows the Pain threshold as well as the pain tolerance which were significantly higher ($p=0.001$) in the follicular phase as compared to luteal phase of menstrual cycle while the pain perception using VAS scores was greater during the luteal phase but the value was statistically insignificant.

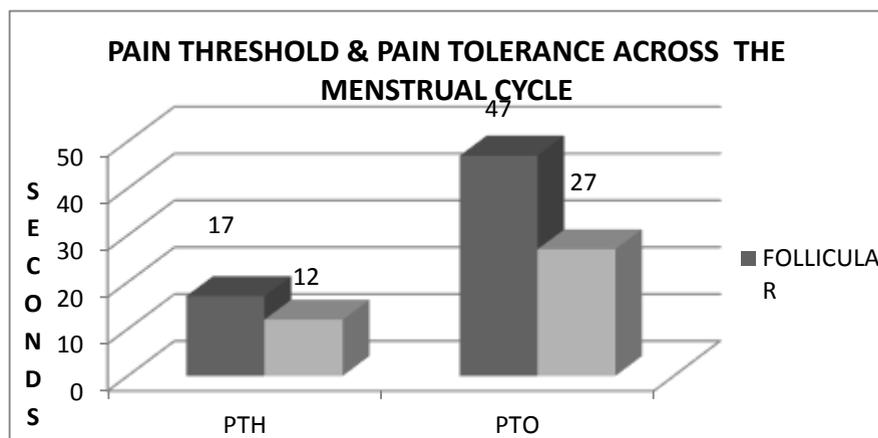


Fig. 2: Pain threshold & Pain Tolerance across the menstrual cycle

PTH-pain threshold, PTO-pain tolerance

Fig. 2: Depicts a reduced pain threshold as well as tolerance to pain during the luteal phase.

Discussion

The menstrual biological rhythm is characterized by secretion of endogenous female hormones which interact with multiple body systems to bring about certain physiological and psychological responses. The purpose of this study was to determine the influence of different phases of Menstrual Cycle i.e.- follicular and the luteal phases on certain select Cardiovascular variables like Heart rate, Systolic and Diastolic Blood Pressure as well as correlates of pain such as pain threshold, tolerance as well as perception when subjected to a physiological thermal stressor, Cold

Pressor test. Contrary to the hypothesis set forward in multiple studies that the phases of menstrual cycle would not have any bearing on the cardiovascular variables the findings of our study point towards an accentuated sympathetic activity, augmented cardiovascular functioning, lower pain threshold and tolerance during the luteal phase of menstrual cycle.

Physiological stressor used in our study namely thermal stimulus mimics conditions of day to day stress which activates the sympathetic nervous system along with hypothalamo-pituitary- adrenal axis with resultant release of neurotransmitters like nor adrenaline, adrenaline, cortisol etc. which lead to elevated heart

rate as well as cardiac output leading to increased systolic blood pressure. The elevated diastolic blood pressure as a result of peripheral vasoconstriction may be the result of action of nor-adrenaline on its corresponding alpha adrenergic receptors located on blood vessels.

The results of our study are coherent with a study conducted where they found a significant correlation between rising estrogen levels and enhanced vagal activity.⁽⁸⁾ The results of our study point towards a sympathetic dominance during the luteal phase which is similar to the results of many other studies^(6,10) where they justified an interaction between fluctuating gonadal hormones across the menstrual cycle and autonomic nervous system. The luteal phase of menstrual cycle is characterized by rising levels of the hormone progesterone which induces salt and fluid retention which may lead to elevated blood pressures.⁽²⁰⁾

Our study has elucidated an increased sympathetic activity during luteal phase findings similar to a study conducted which demonstrated a reduced high-frequency (HF) component in nonlinear HR variability representing parasympathetic activity towards the luteal phase while the low-frequency (LF) component which represents sympathetic activity was significantly elevated. The LF/HF ratio signifying symphatho-vagal imbalance was also altered during the luteal phase.⁽¹²⁾ The luteal phase is characterized by increased progesterone levels which have been implicated as to having a hypertensive effect while on the contrary the estrogen is known to cause vasodilatation through multimodal pathways namely as a result of inhibition of various vasoactive agents like Endothelin and Angiotensin which are potent vasoconstrictors as well as increasing the release of vasodilators like Prostacyclin and Nitric oxide.⁽²⁰⁾ The literature also documents estrogen acting centrally as well as at peripheral levels as a Para sympathomimetic agent which may interfere with the sympathetic outflow and at the same time increase the synthesis of the enzyme acetyl choline transferase.^(21,22) Greater sympathetic activity during the luteal phase poses extra demands on the cardiovascular system as a result of which the entire cardiac functioning is geared up.

In our study the pain threshold & tolerance were lower during the luteal phase which is consistent with other studies which have reported similar findings. Higher pain threshold and tolerance in the follicular phase, a phase of increasing estrogen levels could be due to the role of estrogen in the pain modulation systems of the body.^(14,17,18,23) Pain perception and pain circuitry involve a complex interaction of multiple variables most cited in literature is the interaction between estrogen and CNS opioid analgesia system. Phases associated with high estrogen levels demonstrated a significant increase in the mu-opioid receptor availability and greater interaction between

estrogen and opioid receptor signaling leading to greater facilitation of opioid transmission in the CNS and hence showcase the role of estrogen as an anti-nociceptive agent.⁽²⁴⁾ Molecular mechanisms involving the pain circuitry have documented the role of estrogen in conversion of excitatory neurotransmitter glutamate to an inhibitory neurotransmitter GABA, GABA in turn exerts its role on the descending analgesic pathways and this seems possible because of the role of estradiol in facilitating enzyme glutamic acid decarboxylase.⁽²⁵⁾ The estrogen and progesterone levels keep on fluctuating throughout the cycle, the rising levels of progesterone which dominates the luteal phase is known for increasing the cortical excitability, which reflects as increased pain sensitivity during the same.^(26,27) Controversies still exist wherein another study has demonstrated reduced thermal cold perception threshold across certain phases of the menstrual cycle which are associated with high estrogen levels⁽²³⁾ i.e.-during the latter half of the follicular phase as compared to the early follicular phase which again is related to the rising hormonal levels in the late follicular phase, while there are some⁽¹³⁾ which have failed to prove an association between the gonadal hormones and pain and this difference may exist due to the paradigm employed. Methodological inconsistencies may exist which may depend on the methodology used, type of stressor, and characterization of menstrual phases etc. which be the reason for variability in results obtained.⁽²⁸⁾

According to the results of our study the reduced pain threshold & tolerance during the luteal phase is suggestive of some kind of interaction of pain processing systems and gonadal hormones in healthy women.

Conclusion

We hence conclude from the results of our study that the luteal phase of menstrual cycle was associated with augmented cardiovascular reactivity in the form of increased heart rate, SBP, DBP and altered nociception in the form of reduced pain tolerance and threshold.

Limitations, Practical Implications, and Future Investigations

The limitation of our study was that the phases were based on self-reported data from the participants and actual hormone estimation was not conducted. However, due to technical difficulties and since during the regular menstrual cycle the gonadal hormones vary within well-defined standards; many studies are carried out without actual hormone assessment. It is difficult to ascribe the pro-nociceptive or anti-nociceptive actions to a single hormone because both the gonadal hormones can modulate each other as well as affect the analgesic pathways hence future research should be conducted with actual hormone estimates of the

menstrual phases, for future comparison of results and better clarification.

The practical implication of the study lies in the fact that literature has demonstrated an increased risk of mortality associated with increased heart rates, differences in heart rates which exist between the phases will allow the stakeholders in planning a pragmatic approach with the use of Resting heart rates for exercise prescription in female athletes as well as cardiac invalids.^(29,30) Therefore, any phenomenon that is likely to influence cardiovascular control is an important research question that should be elucidated.

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