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Research article

A STUDY OF CARDIAC AUTONOMIC CONTROL AND PULMONARY FUNCTIONS IN DIFFERENT PHASES OF MENSTRUAL CYCLE.

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ABSTRACT

Introduction: Menstrual cycle is a physiological cyclical occurrence in women. This is associated with variations in metabolism and associated endocrine fluctuations. Among other things, the cardio respiratory changes too have been observed. In the present study, we investigated the autonomic control of heart, and concurrent changes in the respiratory system. **Material and methods:** Forty seven normally menstruating women were recruited from a group of 80 subjects reported for this study voluntarily. ECG was recorded from limb lead II time domain and frequency domain analysis of Heart rate Variability (HRV) was done. Their respiratory parameters namely PEFR, FEV_1 were determined. **Results:** The results of this study were analysed by applying Wilcoxon's signed rank sum test. In Time domain analysis RMSSD (36.91±2.73, $p<0.05$) showed significant decrease during ovulation, while other parameters did not show significant variation among the three phases. Frequency domain analysis yielded results to suggest that there is increased variability during Ovulatory and Luteal phase ($p<0.05$). PEFR and FEV_1 increased in luteal phase ($p<0.05$).**Conclusions:** The results of our study reiterated the findings of reports of previous studies on the heart rate variability suggesting that the HRV was more during ovulatory and luteal phase. This is suggestive of the role of Progesterone on the HRV. Similarly the respiratory parameters too showed an increased PEFR and FEV1 suggesting a decreased airway resistance, while other parameters remained unchanged.

Key words: Heart rate variability, pulmonary function, menstrual cycle.

INTRODUCTION

Menstrual cycle is a physiological cyclical occurrence in women. This is associated with variations in endocrine fluctuations and associated metabolism. Among other things, the cardio respiratory changes too have been observed. A number of research articles have thrown light into the effects on heart and respiration during menstrual cycle. Some previous studies reported a sympathetic predominance in the luteal phase [Sato et al. 1995], whereas others reported vagal predominance in the luteal phase [Princi T et al. 2005]. Heart rate variability has been proved to be useful tool to assess the autonomic influence on heart. The recording and analysis of heart rate variability has become a popular method to study the physiological mechanisms responsible for the control of heart rate fluctuations, autonomic neuropathy, congestive heart failure, myocardial infarction and other cardiac and non-cardiac diseases [Stys A& Stys T, 1998]. HRV is a strong and independent predictor of mortality after acute myocardial infarction [Umetani K et al. 1998].

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Autonomic nervous system activity may be altered in the phases of menstrual cycle [Matsumoto T et al. 2006]. A study by Leicht et al [2003] found no significant differences in heart rate variability in all three phases of the menstrual cycle. Wenner and associates also did not observe any demonstrable variations in heart rate and blood pressure when studied in relation to changing levels of hormones during the menstrual cycle [Wenner MM et al. 2006, Sansores MH et al. 1995]. Study report by several authors reportedly found pulmonary function test parameters in various phases of menstrual cycle were significantly higher in the luteal phase of the menstrual cycle [Rao GS et al. 1991; Rajesh CS et al. 2000; Pai SR et al. 2004]. It has been shown that ventilation is significantly greater in the luteal phase than the estrogen dominated follicular phase [Milne JA, 1979]. Some studies indicated that progesterone caused hyperventilation and hypocapnea in the luteal phase of a menstrual cycle [Rajesh CS et al. 2000]. Luteal phase appears to show significantly elevated respiratory parameters as compared to the menstrual and follicular phases [Das TK, 1998].

The results of many studies made contradictory findings on cardiac and respiratory parameters. Therefore a relook into the cardiorespiratory changes during menstrual cycle was done here. In the present study, we investigated the autonomic control of heart, and concurrent changes in the respiratory system. We analyzed the HRV in normal women in phases of menstrual cycle and compared the data with concomitant changes in the respiratory parameters.

MATERILS AND METHODS

Sample size: Forty Seven subjects with normal menstrual cycles were recruited and they were charted over two cycles to confirm regularity. Early follicular phase was calculated as the fourth day of the cycle. The ovulatory phase was 14 days prior to the onset of next cycle, the mid luteal phase as 7th day from day of ovulation.

Inclusion criteria

Healthy women in the age group of 20 – 30 years having normal regular menstrual cycles were included in the study.

Exclusion criteria

- Lactating women.
- Subjects on oral contraceptives/medication for Respiratory (RS), Cardiovascular (CVS) and Central nervous system (CNS) disorders.
- Subjects with past/present history of RS, CVS disorders, diabetes.
- Subjects with H/O smoking.

Plan of study

Eighty young females, between the age group of 20-30 years, attended the study voluntarily. The menstrual history was charted for two months and healthy women having regular menstrual cycles were chosen for the study. Out of the 80, twenty had irregular cycles. Among the 60 in whom heart rate variability and lung functions were performed, thirteen opted out of study. The results from 47 volunteers are presented here.

A detailed clinical history of these subjects was taken. Relevant past history, family history, any drug history, personal history like smoking, alcoholism etc. was also taken, and details were noted on the proforma. Early follicular phase was calculated as the fourth day of the present cycle, the ovulatory phase as 14 days prior to the onset of next cycle, and the mid luteal phase as 7th day from the day of ovulation.

Measurement of HRV- Recording of ECG:

The instrument used in this study was computerized ambulatory ECG system (Niviqure, Pune). A high quality ECG recording was taken for 5 minutes after 10 minutes of supine rest, under standardized conditions to minimize artifacts. ECG signal was obtained using Limb lead II. Subjects were instructed to close the eyes and to avoid talking, moving of hands, legs and body, coughing and sleeping during the test.

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Analysis of this was done using time domain and frequency domain methods. Recording was done in the morning hours between 9:00A.M and 11:00A.M.

The subjects were given the following instructions.

- To avoid food two hours prior to testing
- To avoid coffee or alcohol 24 hours prior to testing
- To wear loose and comfortable clothing during the test

Acquisition: The ECG signal was continuously amplified, digitized and stored in the computer for offline analysis. The RR peak detector was adjusted appropriately.

The participants were informed when they were to come next. In a similar way HRV recording and analysis was performed in the next two phases of the menstrual cycle.

Time domain: RMSSD, NN50 and pNN50

Frequency domain: LF power, HF power, LF (normalized) power, HF (normalized) power, LF/HF.

Pulmonary function tests

Peak Expiratory Flow rate (PEFR) and FEV_1/FVC of each subject were recorded. Prior to that all demographics and related information were noted and recorded which included: age, height, weight and race. The test was performed in erect position with no tight clothing around the neck. A demonstration was given to the subject before performing the tests.

Statistical analysis: Results were tabulated and analyzed using Wilcoxon signed rank sum test.

The test was considered significant if it yielded $p<0.05$.The rest of the results are expressed as Mean ± Standard error of mean (SEM). This study was conducted on healthy females after ethical clearance from the ethical committee and a signed informed consent was obtained before recruiting the subjects.

RESULTS

Frequency Domain analysis of HRV (Table 1) yielded results suggesting that high frequency power had a higher mean in phase 1 (early follicular) The lowest value was observed in the ovulatory phase (phase2) no statistically significant difference was found between the three phases.Mean low frequency in normalized units was highest in the mid-luteal phase and the lowest value was observed in the early follicular phase. A significant increase was seen in ovulatory phase and mid luteal phase compared to follicular phase [*$p< 0.05$].

The highest mean SDNN value was observed in the ovulatory phase and the lowest in the early follicular phase. No statistically significant difference between any of the phases.

The highest mean NN50 value was observed in the early follicular phase and lowest in the mid luteal phase no statistically significant difference between the phases. * $p<0.05$.

The highest mean PEFR value was seen in the mid luteal phase and the lowest value in the ovulatory phase. The PEFR in the midluteal phase was significantly more compared to other two phases. ($p< 0.001$).The highest mean value for FEV_1/FVC was observed in the mid-luteal phase was significantly higher than early follicular phase ($p<0.01$). There was no much difference in the other phases. †* $p<0.05$ 1 Vs 2; 1 Vs 3 $p<0.05$.

Table 1: HRV – Frequency domain analysis in three phases of menstrual cycle. (* p<0.05; Phase 1 Vs Phase 2&3)

Phases of observation	High Frequency Power (ms^2) Mean ± SE	Low Frequency Power (ms^2) Mean ± SE	High Frequency in normalized units (nu) Mean ± SE	Low Frequency in normalized units (nu) Mean ± SE
1.Early Follicular	226.82 ± 33.26	65.51±5.74	69.02±2.70	30.98 ± 2.70
2. Ovulatory	190.85 ± 30.28	72.12±7.24*	64.80±2.41	35.20 ±2.41*
3.Mid luteal	200.34 ± 26.32	83.29±8.85*	64.59±2.62	35.41 ±2.62*

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Table 2: HRV analysis: Mean Standard deviation of all NN intervals (SDNN), Mean NN50, RMSSD (ms), LF /HF in the three phases of observation, values in the three phases of observation (Phase 1 Vs Phase 2; p<0.05)

Phases of observation	**Standard deviation of all NN intervals (ms)** Mean ± SE	**NN50 (ms)** Mean ± SE	**RMSSD (ms)** Mean ± SE	**LF /HF** Mean ± SE
1. Early Follicular	71.67±2.78	24.75±2.76	41.17±3.21	0.57±0.07
2. Ovulatory	75.53±3.70	23.66±3.77	36.91±2.73*	0.68±0.08*
3.Mid luteal	73.65±2.40	21.99±2.99	40.47±3.45	0.70±0.08*

Table 3: Mean Peak expiratory flow rate (PEFR) values in the three phases of observation; Mean FEV_1/FVC values in the three phases of observation (* p<0.05 Phase 1 Vs 3; † p<0.05, Phase 2 Vs Phase 3)

Phases of observation	**Peak expiratory flow rate (L/sec)**	**FEV_1/FVC**
1. Early Follicular	5.00 ± 0.18	0.86 ±0.01
2. Ovulatory	4.96 ± 0.16	0.87±0.01
3.Mid luteal	5.52 ± 0.17*†	0.89±0.01*

DISCUSSION

The fluctuation in hormonal concentrations during the menstrual cycle is very well known. The female sex hormones have profound influence on autonomic and metabolic activities. In the present study we examined the correlation of cardiovascular autonomic control and respiratory activity in three phases of menstrual cycle in normal women. We found a small but significant variation in the HRV and respiratory parameters during menstrual cycle.

Results of our study suggested a sympathetic predominance in the luteal phase. This is in agreement with previous studies, which have shown that progesterone in physiological doses, acts as adrenergic agonist by inducing an increase in norepinephrine level. [Bernardi F et al, 1999; Guasti L, et al 1999; Eskin BA et al. 2003]; also comparison of HRV in follicular phase with luteal phase, showing a sympathetic predominance in the luteal phase. Previous study suggested that low frequency (LF) component in the HRV was higher and HF component in the HRV was lower during the luteal phase than during the follicular phase. The LF/HF ratio was also significantly greater in the luteal phase[Sato N et al. 1995].

Apart from these observations, on healthy eumenorrheic women, muscle sympathetic nerve activity and plasma norepinephrine were lower during the early follicular phase compared with the midluteal phase [Hirshoren N et al. 2002]. Some studies suggest that estrogen may influence the ANS function by up regulating parasympathetic activity and down regulating the sympathetic nervous system activity. Estrogen stimulates the release of nitric oxide (NO) from the endothelium by increasing NO synthase activity. Estrogen is also associated with lower levels of endothelin and a decreased sensitivity to its vasoconstrictor effects [Schwertz DW, et al. 2001]. However, studies examining the influence of estrogen on the cardiovascular responses to stress have produced mixed results, with some studies showing a protective effect, and others showing no effect [Matthews KA et al. 2001]. The presence of estrogen receptors in the heart, vascular smooth muscle and autonomic brain centers (eg., Nucleus TractusSolitarius, ventrolateral medulla) and hormone mediated changes in adrenergic receptor density, [Wilkinson M et al. 1982] cAMP [Alonso-Solis R, et al. 1996] levels and nitric oxide synthase,[Virdis A et al. 2000] suggest a possible involvement of estrogen in the regulation of cardiovascular system. In the follicular phase estrogen causes an upregulation in the cardiovascular, myometrialadrenoreceptors [Hirshoren N et al. 2002].

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The LF component corresponds to 0.04-0.15 Hz, and is jointly modulated by the sympathetic and parasympathetic nervous systems. The mean LF component in normalized units (nu) showed a difference which was not statistically significant between early follicular phase and midluteal phase. A statistically significant increase ($p < 0.05$) was found between early follicular and the ovulatory phase.

It has been shown that ventilation is significantly greater in the luteal phase of the ovulatory cycle than the estrogen dominated follicular phase; there was an increase in the resting minute ventilation in the luteal phase. Progesterone was implicated as the agent causing hyperventilation both in pregnancy and luteal phase of menstrual cycle [Schoene RB et al. 1981]. FVC showed a gradual and significant increase from menstrual to follicular to luteal phases. FEV1 was significantly higher in the luteal phase. Plasma progesterone level was positively correlated with FVC and FEV1 [Mannan SR et al, 2007].The results of present study was comparable with the previously published articles [Rao GS et al. 1991; Rajesh CS et al. 2000; Pai SR et al. 2004.- 9,10,11], where FVC, TLC, FRC was found to be significantly higher in the luteal phase. They had also reported a significantly lower value of FEF 25-75% in the follicular phase of the menstrual cycle.Higher value for respiratory parameters in the luteal phase was reported earlier too [Das TK, 1998].

CONCLUSION

From the present study we could conclude that the HF component of HRV was higher in follicular phase and LF component was found to be higher on the ovulatory and luteal phases. These results suggested a parasympathetic predominance during follicular phase and sympathetic activity in the luteal phase. Respiratory parameters showed that the PEFR was higher in mid luteal phase. But other parameters did not show any statistically significant changes.

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