EFFECT OF ENDOGENOUS FEMALE HORMONES ON LUNG FUNCTIONS

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ABSTRACT: Background and Objectives: The characteristic rhythmic changes in the rate of secretion of ovarian hormones produce corresponding changes not only in the reproductive system but in other organ systems as well. This study was intended to evaluate the variation in the pulmonary functions during different phases of menstrual cycle in healthy females. Methods: This was a prospective, observational study performed on 50 healthy, regularly menstruating subjects. Their lung functions were measured during various phases of menstrual cycle and the various parameters were compared. Results: FVC and FEV₁ were significantly higher during the luteal phase as compared to menstrual and follicular phases. PEF was increased in the luteal phase as compared to menstrual and follicular phase but was not statistically significant. This study indicates that changes occur during different phases of menstrual cycle and that endogenous female hormones have measurable influence on lung mechanics. Conclusion: The pulmonary functions were better during the luteal phase of menstrual cycle thus suggesting a possible beneficial role of progesterone in the management of respiratory diseases.

KEYWORDS: Menstrual cycle, pulmonary functions, Spirometry, Progesterone.

INTRODUCTION: Female reproductive phase comprises menstrual cycle which is an integral part of their lives. A normal menstrual cycle is dependent on the fluctuation in the ovarian hormones (oestrogen and progesterone) during different phases of menstrual cycle – menstrual, follicular and luteal phases. The characteristic rhythmic changes in the rate of secretion of ovarian hormones produce corresponding changes not only in the reproductive system but in other organ systems as well. It is suggested that lung functions exhibit not only diurnal variations but also show changes dependent on different phases of menstrual cycle.¹ Women, for largely unknown reasons, are increasingly becoming more affected with inflammatory lung diseases such as asthma, chronic obstructive pulmonary disease and cystic fibrosis and are experiencing excess morbidity and mortality from these disorders. It is being increasingly recognized that about a third to half of women experience worsening of asthma symptoms during the premenstrual or menstrual phase of their menstrual cycle.² Although men have higher prevalence of COPD than women, the increased rates of cigarette smoking in females in the last decade have been associated with steadily increasing rates of COPD in females.³ Even in cases in which cigarette smoking is implicated, women develop COPD after smoking fewer number of cigarettes per lifetime (i.e., less pack-years of smoking) and are two to three times more likely to experience hospitalization than are male patients.^{4,5} These epidemiologic data suggest that female gender is a significant risk factor for morbidity and mortality in inflammatory lung diseases and that sex hormones may be important in their pathogenesis, though the mechanisms by which they act may differ between these disorders. Some of the investigators also proposed to supplement progesterone hormone along with other bronchodilators and found better results in female patients suffering from bronchial asthma with acute exacerbations.⁶

On the contrary, different observations have shown that after addition of exogenous progesterone no further increase of the lung function parameters occur during the different phases of menstrual cycle.⁷

Thus the information on the effect of sex hormones on lung functions are controversial and hence require further evaluation so as to enable the physicians to formulate better treatment regimes. Therefore, the present study was attempted to observe the variation in pulmonary functions during different (menstrual, follicular and luteal) phases of the menstrual cycle in healthy adult females.

MATERIALS AND METHODS: The study was conducted in the Department of Physiology, Bangalore Medical College and Research Institute after obtaining the clearance of ethical committee. 50 healthy subjects of age group 18-35 years were selected from volunteers to participate in the study using the following criteria: healthy physical condition, non-smoker, no hormone or respiratory drug use, non athlete with no history of dysmenorrhoea, menorrhagia, obesity and anaemia. The women had to have regular menstrual cycle of 25-35 days in addition to not being pregnant or using oral contraceptives.

A detailed questionnaire was used to assess the pattern of menstrual cycle, the regularity of the cycles and the last menstrual period. The preliminary clinical examination of respiratory system was carried out and written informed consent was obtained. Age, height, weight, body surface area were recorded. Each subject was instructed to visit the respiratory laboratory on a specific date. Subjects were instructed to visit the laboratory for pulmonary function testing during each phase of menstrual cycle: 1-5th day during menstrual phase, 9-12th day during follicular phase and 19-22nd day during luteal phase as estimated from their menstrual histories for the preceding 3 months. Phases were corroborated with the period of ovulation, as judged from daily basal oral temperature of subject throughout the study. Follicular scanning was done only on days nearing ovulation as indicated by temperature chart because of practical difficulties. Different subjects started their pulmonary function tests in different phases of menstrual cycle to rule out training effect, if any. The manoeuvres were evaluated by a single examiner who initially explained what a correct manoeuvre consisted of. The subjects were made to undergo pulmonary function tests using the KIT MICRO RS 232C Computerized Spirometer for 3 times at every 15 minutes interval. The FVC, FEV₁, PEF and FEV₁/FVC% were recorded. The best of the 3 recordings was taken into account. All the tests were done at the same time of the day to avoid possible diurnal variation.

The data obtained was subjected to statistical treatment using SPSS version 11.0. Analysis of variance was used to find the significance of PFT for different phases of menstrual cycle. Bonferroni test was used to find the significance of PFT for pair wise comparison of different phases.

Significance level interpretation (p: probability):

p<0.01	highly significant (probability is <1%)
0.01<p<0.05	significant (probability <5%)
0.05<p<0.10	near significant
0.10<p<0.50	possible trend but without significance
p>0.50	no trend at all

RESULTS: When the pulmonary function tests in different phases were studied, FVC showed an increase in the luteal phase as compared to menstrual and follicular phases which was statistically highly significant with p value <0.00 . FEV_1 was increased in luteal phase as compared to menstrual and follicular phase which was statistically highly significant with p value <0.01 . PEF was increased in the luteal phase but was not statistically significant with p value >0.40 . $FEV_1/FVC\%$ was unaffected by all the 3 phases and was not statistically significant with p value >0.52 .

Pair wise comparison of different phases was done using Bonferroni test and only those p values less than 0.05 were deemed to be significant. When FVC was compared in menstrual and follicular phase, there was an increase in menstrual phase as compared to follicular phase, the mean difference was 0.09 but the difference was not statistically significant, the p value being >0.50 . When FVC was compared in the menstrual phase and luteal phase, there was an increase in the luteal phase, the mean difference was 0.20 and was statistically significant with p value at <0.01 . When FVC was compared in the follicular phase and luteal phase, there was increase in the luteal phase, the mean difference was 0.29, and was statistically highly significant at p value of <0.001 . When FEV_1 was compared in the menstrual phase and follicular phase, there was increase in the menstrual phase as compared to the follicular phase but was not statistically significant (mean difference: 0.10, p value: >0.44). When FEV_1 was compared in the menstrual phase and luteal phase, there was increase in the luteal phase but was not significant (mean difference: 0.11, p value: >0.30). When FEV_1 was compared in the follicular phase and luteal phase, there was an increase in the luteal phase as compared to the follicular phase which was significant (mean difference: 0.21, p value <0.01). When PEF was compared in the menstrual phase and follicular phase, there was an increase in the menstrual phase as compared to follicular phase but was not statistically significant (mean difference: 0.30, p value 1.00). Comparison between menstrual phase and luteal phase shows an increase in the luteal phase as compared to the menstrual phase but was not statistically significant (mean difference: 0.18, p value 1.00). When follicular phase and luteal phases were compared, PEF was increased in the luteal phase though the increase was not statistically significant (mean difference: 0.48, p value >0.54). When $FEV_1/FVC\%$ was compared in the menstrual phase and follicular phase, there was no significant changes (p value 1.00), when compared in menstrual phase and luteal phase there was no significance (p value >0.77), when compared in follicular phase and luteal phase again there was no significance (p value >1.00).

DISCUSSION: The present study was undertaken to evaluate the effect of endogenous female sex hormones on pulmonary function parameters during the 3 phases of menstrual cycles in healthy female adults at rest. Majority of the studies have evaluated the effects on follicular and luteal phases without any evaluation done on menstrual phase. In this study the effect on menstrual phase was also evaluated and pair wise comparisons were made. This study demonstrated better lung volumes during luteal phase of menstrual cycle as compared to those in follicular and menstrual phases. Though PEF was increased in luteal phase, it did not show statistical significance. These findings were consistent with reports of Pai R.S et al, Dabhoiwala S et al, and Arora D et al.^{8, 9, 10} But Arora et al found higher values in secretory phase followed by follicular phase and lowest in menstrual phase. This was not corroborated in the present study which demonstrated higher values in secretory phase followed by menstrual and lowest in follicular phase.

This present study shows that respiratory parameters of women in reproductive age group show significant variations during different phases of menstrual cycle which could be due to the hyperventilation caused by increased levels of progesterone in the luteal phase as suggested by Das et al and Rao et al.^{11, 12} Progesterone induces hyperventilation through both the central medullary and peripheral receptors. According to Bayliss D.A and Millhorn D.E the respiratory response to progesterone is mediated at hypothalamic sites through an oestrogen (E2) dependent progesterone receptor (PR) mediated mechanism requiring RNA and protein synthesis i.e., gene expression. The neural mechanisms underlying the stimulation of respiration by progesterone are similar to those mediating its reproductive effects.¹³

On the other hand, Williams JS et al, Chong et al and Bruno da Silva et al observed that there were no significant differences in different phases of menstrual cycle for any spirometric variables and concluded that menstrual cycle phases did not influence ventilator responses at rest.^{14, 15, 16} This present study does not agree with these studies.

CONCLUSION: The results indicated that pulmonary functions were better during the luteal phase of menstrual cycle as compared to those in follicular and menstrual phases in regularly menstruating women, which suggested a possible role of the increased levels of progesterone during this phase on the respiratory system.

Limitations and issues for further study:

Female sex hormones were not measured during the menstrual cycle phases due to practical constraints. However, all the subjects reported a normal regular menstrual history. A well designed study with healthy females in different age groups and different phases of reproductive life as volunteers with measurement of ovarian hormones and pulmonary function parameters could determine the consistency of the relationship.

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Table 1: Comparison between different phases among subjects

Control	Menstrual phase		Follicular phase		Luteal phase		F-value*	p-value
	Mean	SD	Mean	SD	Mean	SD		
FVC (L/sec)	2.47	0.33	2.38	0.30	2.67	0.37	9.90	<0.00
FEV1 (L/sec)	2.17	0.35	2.08	0.34	2.29	0.32	4.87	<0.01
PEF (L/sec)	4.79	1.82	4.50	1.76	4.98	1.79	0.93	>0.40
FEV1/FVC%	0.88	0.08	0.87	0.09	0.86	0.09	0.66	>0.52

* F-value is obtained from ANOVA

Note: Menstrual phase corresponds to days 1-5, follicular phase to days 9-12 and luteal phase to days 19-22 of the case group.

Table 2: Pair wise comparison of different phases in subjects using Bonferroni test

	Phase	Mean Difference	p-value
FVC	Menstrual phase vs. Follicular phase	0.09	>0.50

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	Menstrual phase vs. Luteal phase	0.20	<0.01
	Follicular phase vs. Luteal phase	0.29	<0.001
FEV1	Menstrual phase vs. Follicular phase	0.10	>0.44
	Menstrual phase vs. Luteal phase	0.11	>0.30
	Follicular phase vs. Luteal phase	0.21	<0.01
PEF	Menstrual phase vs. Follicular phase	0.30	1.00
	Menstrual phase vs. Luteal phase	0.18	1.00
	Follicular phase vs. Luteal phase	0.48	>0.54
FEV1/FVC%	Menstrual phase vs. Follicular phase	0.01	1.00
	Menstrual phase vs. Luteal phase	0.02	>0.77
	Follicular phase vs. Luteal phase	0.01	1.00

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