Pulmonary Function Variability in AsthmaticFemales during different phases of menstrual cycle

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Background*: Peri menstrual asthma (PMA), is a clinical situation that occurs in the luteal phase of the menstrual cycle, leading to worsening of asthma symptoms. The question of whether PMA is an under- or over-recognized condition has not been adequately addressed. Various studies, however, seem to suggest that 30 to 40% of female asthmatics experience a premenstrual worsening of symptoms. Whatever the true prevalence and true significance of PMA, most experienced clinicians recall various female patients whose asthma would significantly worsen on a monthly basis. A number of mechanisms have been postulated and investigated, such as "allergy to endogenous hormones,"psychological changes associated with the premenstrual syndrome,progesterone-induced hyperventilation, low progesterone levels at the onset of menses leading to bronchial smooth muscle constriction, progesterone potentiation of an unidentified bronchodilator, progesterone- mediated loss of microvascular integrity with subsequent oedema leak, dynamic fluctuations of oestrogen levels after sustained but static elevation,increase in mucous secretions, and variation in prostaglandin synthesis. Therefore the current study was done to evaluate the effects of menstrual cycle on various parameters of the lung functions .*
Materials and Methods*: The present study involved 20 known asthmatic and 20 non-asthmatic women in menstruating age group. Women in age group 30–45 years were included in the study.All the participants were asked to report thrice in the Respiratory research laboratory in the Department of Physiology for pulmonary function test and according to their phases of menstrual cycle (once in each phase).*
Results*: The mean values of all the parameters were higher in Group I as compared to Group II. The mean values of VC and FVC in all the four groups were highest in secretory phase followed by follicular phase and lowest in menstrual phase.*
Conclusion*: Asthma can deteriorate during the perimenstrual period, a phenomenon known as perimenstrual asthma (PMA) which is usually much more severe and troublesome than the periovulatory worsening which is probably due to the smooth muscle relaxant effect of progesterone and probably oestrogen*
Key words*: Perimenstrual asthma, Pulmonary functions, progesterone*

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I. Introduction

Asthma is a chronic lung disease characterized by airway obstruction, inflammation, and hyper-responsiveness[1,2]. A broad range of factors has been identified that can make asthma worse. These factors are often referred to as "asthma triggers." Trigger exposure may occur on a chronic or episodic basis. Identifying and avoiding asthma "triggers" is essential to preventing asthma flare-ups. One of the common triggering factors in women is the monthly menstrual cycle which is referred to as Perimenstrual asthma.

Menstrual cycle is divided into three phases : menstrual, follicular and luteal. The course and timing of menstruation is steered through a multifaceted endocrine interplay. Oestrogen level increases during follicular phase until ovulation. Follicle Stimulating Hormone (FSH) level rises, and then has a short dip before a new rise, around ovulation. Luteinizing Hormone (LH) that initiates ovulation has a large surge in its level around ovulation. The serum levels of progesterone are very low during the follicular phase, but high during the luteal phase. These hormonal variations are responsible for various physiological changes as well as psychological changes[3].

Worsening of asthma symptoms prior to or during menstruation, known as perimenstrual asthma, has been reported in 17 to 40 percent of women (ages 12 to 50) with asthma .Emergency department visits due to asthma occurred slightly more often during the preovulatory phase (days 5 to 11) and the perimenstrual phase of the cycle (day 26 to day 4 of the next cycle)[4].The pathophysiology responsible for this phenomenon is unclear, although changes in oestradiol, progesterone, and testosterone levels have been associated with changes in markers of atopy and asthma (e.g, fractional exhaled nitric oxide and skin test diameters), upregulation of

eosinophils and mast cells, and increased bronchial reactivity[5-8]. Women with hormonally-associated asthma tend to have more severe disease than women whose asthma is unaffected by hormone levels, and patients with severe and fatal attacks in association with menstruation have been reported[7,9].

II. Subjects And Methods

The present study involved 20 known asthmatic and 20 non-asthmatic women in menstruating age group. The study design was approved by the Ethical Committee of the Institute. Informed consent was taken from all subjects. Women in age group 30–45 years were included in the study. The different phases of menstrual cycle were estimated according to the menstrual history related questionnaire and date of last menstrual period, as follows:

* During the first or second day of the menstrual bleeding (referred as menstrual phase).
* 3-4 day after complete stoppage of bleeding (referred as follicular phase).
* 2 weeks after the mid follicular phase (referred as luteal phase).

All the participants were asked to report thrice in the Respiratory research laboratory in the Department of Physiology for pulmonary function test and according to their phases of menstrual cycle (once in each phase).

Group-I included 20 non-asthmatic women in age group >30 years;
Group-II had 20 asthmatic women in age group >30 years.

Vital Capacity (VC), Forced Vital Capacity (FVC), Forced Expiratory Volume in 1^{st}second (FEV$_1$), FEV$_1$/FVC, Peak Expiratory Flow Rate (PEFR), Maximal Expiratory Flow Rate (MEFR, FEF$_{200-1200}$), Maximal Mid-expiratory Flow Rate (MMFR, FEF$_{25-75}$%) were calculated for each subject.

Statistical analysis was done using student's *t*-test. Three pairs were made for analysis of the data as Pair I (Follicular and Menstrual phases), Pair II (Secretory and Menstrual phases), and Pair III (Follicular and Secretory phases).

III. Results

The mean values of all the parameters were higher in Group I as compared to Group II. The mean values of VC and FVC in all the four groups were highest in secretory phase followed by follicular phase and lowest in menstrual phase. The mean values of all the lung functions, i.e., FEV$_1$, PEFR, FEF$_{25-75}$%, PEF$_{200-1200}$, in all groups were higher in secretory phase followed by follicular phase and the lowest in menstrual phase. The mean value of lung functions were significantly lower in asthmatic women as compared to the normal women in the three phases especially during menstrual and premenstrual phase

Table-1: Lung functions in asthmatics and non-asthmatics in 30–45 year age group (group I and II) in three phases of menstrual cycle (Mean±SD)

Pulmonary Function test	Follicular phase		Secretory phase		Menstrual phase	
	Group-I N=20	Group-II N=20	Group-I N=20	Group-II N=20	Group-I N=20	Group-II N=20
VC (L)	2.77±0.28	2.41±0.38	2.89±0.33	2.47±0.41	2.61±0.28	2.29±0.38
FVC (L)	2.75±0.32	2.41±0.36	2.89±0.36	2.44±0.4	2.63±0.32	2.26±0.32
FEV$_1$ (L)	2.55±0.28	1.87±0.30	2.71±0.29	1.93±0.27	2.36±0.33	1.76±0.29
FEV1/FVC (%)	93.25±9.04	79.95±10.44	94.4±5.71	80.85±9.28	89.90±7.33	80.70±11.86
PEFR (L/Min)	339.80±79.96	275.35±68.54	363±70.54	281.05±50.63	323±72.97	255±73.63
FEF$_{25-75}$% (L/Sec)	3.84±0.73	2.13±0.54	4.06±0.75	2.24±0.37	3.56±0.76	2.04±0.51
PEF$_{200-1200}$ (L/Sec)	4.91±1.16	3.18±0.69	5.25±1.05	3.24±0.71	4.73±1.19	2.99±0.68

Table 2: Comparison of PFTs during three phases of menstrual cycle in asthmatics and non-asthmatics in 31–45 year age group

Pulmonary function test	Comparison Groups	*t*-test		
		Asthmatic	Non-Asthmatic	Non-Asthmatic
VC (L)	Pair I	-6.365	-4.884	0.000
	Pair II	-8.304	-2.589	0.018
	Pair III	-4.085	-0.997	0.331
FVC (L)	Pair I	-4.023	-4.698	0.000
	Pair II	-7.119	-2.415	0.026
	Pair III	-4.731	0.446	0.661
FEV$_1$ (L)	Pair I	-5.497		

			-4.514	0.000
	Pair II	-10.68	-3.199	0.005
	Pair III	-6.782	-1.288	0.213
FEV₁/FVC (%)	Pair I	-1.781	-0.691	0.498
	Pair II	-3.028	-0.082	0.936
	Pair III	-0.886	-0.609	0.550
PEFR (L/Min)	Pair I	-3.961	-6.984	0.000
	Pair II	-5.735	-3.192	0.005
	Pair III	-4.225	-0.831	0.416
FEF25–75% (L/Sec)	Pair I	-4.245	-2.045	0.050
	Pair II	-6.178	-2.872	0.010
	Pair III	-5.887	-1.215	0.239
FEF200–1200 (L/Sec)	Pair I	-3.222	-6.547	0.000
	Pair II	-4.317	-3.316	0.004
	Pair III	-3.975	-0.831	0.416

IV. Discussion

The present study showed that various pulmonary function indices show significant variation during different phases of menstrual cycle of women in reproductive age group. The cyclically fluctuating hormone levels during the menstrual cycle might play on the bronchomotor tone and hence the respiratory function tests.

The results of this study were consistent with the results of previous studies by Rao *et al* [10] The most probable cause for this increase in the lung function parameters during the secretory phase of menstruation is the hyperventilation associated with increased levels of progesterone secretion in this phase. Rajesh *et al* reported that periodic hyperventilation improves respiratory muscle strength and lung capacities[11].Progesterone induces hyperventilation through both central medullary and peripheral receptors and by increasing the sensitivity of respiratory receptor during the secretory phase. The fact that progesterone could cause relaxation of smooth muscles was studied by intramuscular injections of progesterone in patients with severe asthma[9].

Lymphocyte beta 2 adrenoreceptors in normal women are under the cyclical influence of ovarian sex hormones. Greater receptor density and cyclic adenosine monophosphate response to isoprenaline occurred during the luteal phase, in association with increased postovulatory levels of progesterone and estrogen, as compared with the follicular phase of the menstrual cycle[11].In contrast, asthmatic women fail to show a similar cyclical pattern in that there is no luteal phase rise in beta 2 adrenoreceptors density despite an appropriate postovulatory hormone response[12].

The plasma progesterone in menstrual phase is near about zero level. These changes of hormone levels associated with menstrual cycle are known to affect different organ systems, including the respiratory system. Significant increase in PEFR was observed during the luteal phase where the progesterone level is higher in comparison to those of menstrual and follicular phases of menstrual cycle. Progesterone may also has a role in relaxation of the bronchial smooth muscle which ultimately causes improvement of lung functions during this phase· Some of the investigators also proposed to supplement progesterone hormone as one of the important regimen along with other bronchodilators and they found better results in female patients suffering from bronchial asthma with acute exacerbations[13-17]. Moreover progesterone may potentiate prostaglandin induced relaxation of bronchial smooth muscles. This relaxation is well marked during luteal phase. The present study showed that respiratory parameters of young healthy women and asthmatic women in reproductive age group show significant variation during different phases of menstrual cycle. Similar results were reported by Rumball J [18] and Rao VSJ *et al* [19]. It also showed that the lung function parameters are of lower value in asthmatics as compared to normal women. These results are in agreement with Weinberger SE *et al* [20], and Pai SR *et al* [21]

V. Conclusion

Asthma exacerbations begin more often during the preovulatory (28 %) period in women with this chronic condition. Ovulation associated sex hormones' fluctuations may trigger asthmatic crisis in vulnerable women.Menstrual fall of estradiol and progesterone triggers asthmatic crises in vulnerable women . The lung function parameters in asthmatics were of lower value compared to normal women which are probably due to the smooth muscle relaxant effect of progesterone, and probably of oestrogen too. This study was done to reduce the exacerbations during perimenstrual phase by using new preventive strategies which are pathophysiologically oriented, such as stabilizing estradiol and progesterone/progestins levels and reducing the hormone free interval by giving hormonal therapy

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