RESEARCH ARTICLE

PEAK EXPIRATORY FLOW RATE DURING VARIOUS PHASES OF MENSTRUAL CYCLE IN ASTHMATICS PRESENTING TO A TERTIARY CARE CENTRE

Dr. Lubaiba K.[1], Dr. Rajani M.[2], Dr. Manoj D.K[3], Dr. Muhammad Shafeek K.[4] and Dr. Padmanabhan K.V[5]

1. Senior Resident, Dept of Respiratory Medicine, Govt Medical College, Kannur.
2. Professor Dept of Respiratory Medicine, Govt Medical College, Kannur.
3. Professor and HOD Dept of Respiratory Medicine, Govt Medical College, Kannur.
4. Assistant Professor Dept of Respiratory Medicine Govt Medical College, Kannur.
5. Assistant Professor Dept of Respiratory Medicine Govt Medical College, Kannur.

………………………………………………………………………………………………....

Manuscript Info

……………………..

Abstract

………………………………………………………………………………

Introduction: Asthma is a chronic inflammatory lung disease characterized by airway hyper responsiveness and reversible airway obstruction. Worsening of asthma symptoms and pulmonary functions in relation to menstruation has been documented by some authors.
Objectives: To determine peak expiratory flow rate during various phases of menstrual cycle among adult asthmatic women.
Methods: A Prospective studyof1 year duration (July 2020 to June2021)
A consecutive series of 100 patients with asthma, attending the outpatient clinic of department of chest diseases, satisfying inclusion criteria were included in the study. The socio demographic details and the relevant clinical details was collected using the socio demographic Performa prepared specifically for the study, Patients asked to record asthma symptom scores, morning Peak Expiratory Flow Rate (m-PEFR) (best out of 3 readings taken) daily during the one month screening period to identify women with and without pre-menstrual asthma
Results And Discussion: From our study we found highest mean PEFR value is during post ovulatory phase. Lowest during perimenstrual phase. Fall in PEFR seen mostly during perimenstrual phase (43%). Then during preovulatory phase (34%). No such fall seen during periovulatory and postovulatory phase. Severe symptoms were present during perimenstrual phase (19%) and preovulatory phase (14%) only. Similarly, moderate symptoms also during perimenstrual (22%) and preovulatory phase (21%). Both severe and moderate symptoms were not seen during periovulatory and postovulatory phase.
Conclusion: Premenstrual exacerbation of asthma occurs in a significant proportion of female adult asthmatics. Thus proper history including menstrual variation of asthma of all these patients should be taken for effective management.

………………………………………………………………………………………………....

Corresponding Author:- Dr. Lubaiba K.
Address**:-** Senior Resident, Dept of Respiratory Medicine, Govt Medical College, Kannur.

Introduction:-

According to GINA asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation.(1) Global Burden of Disease Study (GBD) estimated that in 2019, there were 262 million people affected by asthma, equating to an age-standardised rate of 3416 cases per 100,000 population.(2).Amongst India's 1.36 billion people, about 35 million suffer from asthmaand asthma is responsible for significant morbidity. More than 25% of patients are hospitalised at least once a year probably due to inadequate treatment.

Worsening of asthma symptoms and pulmonary functions in relation to menstruation has been documented by some authors. This syndrome is being increasingly recognized as premenstrual asthma (PMA) Premenstrual asthma (APM) is defined by the exacerbation of asthma before menstruation (3) requiring fast-acting beta 2 mimetics (4) . Also defined by a 20% or more fall in PEFR and / or change by 20% or more of daily symptom score. Patients with PMA present with worsening of asthmatic symptoms and pulmonary functions in the late luteal phase of the menstrual   cycle
Fluctuations in female sex hormone levels play an important role in exacerbations of symptoms although the underlying mechanisms through which these hormones influence asthma symptoms remain unclear (5).

Aim of the study was to to determine peak expiratory flow rate during various phases of menstrual cycle l among adult asthmatic women

Relevance of the study:
Even though it is generally accepted that PEFR variation during various phase of menstrual cycle in normal females, variations in asthmatic population is less studied. Finding association of worsening asthma with various phases of menstrual cycle, help patients to become more vigilant and careful during these periods to avoid exacerbation.

So far no studies have been conducted to find the Peak expiratory flow rate during various phases of menstrual cycle in   asthmatics   in   SouthIndia.   Our   study   aims   to   bring   light   to   this   issue.

Materials & Methods:-

Study Design:
Hospital based prospective study

Study Setting:
This observational comparative study was conducted on female patients in the reproductive age group attending the outpatient department of respiratory medicine Government Medical College Kannur, with a diagnosis of asthma

Study Period:
The study was conducted for a period of 1 year, (July 2020 to June2021)

Sample Size:
Sample size calculated from reference article (6)

$$N_{pairs} = \frac{\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\Delta^2} + \frac{z_{1-\alpha/2}^2}{2}$$

$$\Delta = \frac{(\mu_2 - \mu_1)}{\sigma} \qquad \sigma = \frac{\sigma_1 + \sigma_2}{2}$$

Where,

μ_1	:	Pre-test mean
μ_2	:	Post-test mean
σ_1	:	Standard deviation in the pre-test
σ_2	:	Standard deviation in the post-test
Δ	:	Effect size
α	:	Significance level
$1-\beta$	:	Power

pretest mean =55   posttest mean =50   standard deviation in pretest =22
standard deviation in. in posttest =18   effect size =0.25   , power =80
significance level =5
Hence sample size =128

Inclusion Criteria
• Female subjects of age group 18-49 with regular menstrual cycle (24-38 days cycle with flow 4-8 days) with a diagnosis of Asthma (GINA 2019) ie, history of respiratory symptom such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity AND evidence of Variable expiratory airflow limitation.

Exclusion Criteria
• Pregnant
• Exacerbation or Respiratory Infection or antibiotic use within the last 30 days
• Current Smoker
• Use of hormonal contraceptives other than monophasic OCPs
• Postmenopausal (either surgical or physiological menopause)

Methodology:-
Subjects were selected according to inclusion and exclusion criteria. The written informed consent was obtained from them and a complete clinical history and physical examination of patients were done. Data collected from each patient include age, occupation, duration of asthma attack, details of the current asthma episode, past medical history (including asthma triggers), personal history including menstrual history, which include date of last menstrual period, interval between menstrual periods. Treatment history including current medications, compliance etc. Physical examination done including general examination and system examination

For every patient presenting peak expiratory flow rate recorded. Patient was taught peak expiratory flow meter usage which was provided during enrolment in the study and asked to keep diary recording morning peak expiratory flow rate. Diaries started on the first day of menstrual periods. The menstrual cycle was assumed to have a duration of 28 days and women were divided into the following four categories with day 1 considered to be the onset of menstruation: preovulatory (days 5 to 11), periovulatory (days 12 to 18), postovulatory (days 19 to 25), and perimenstrual (days 26 to 4).

Patients asked to record asthma symptom scores, morning Peak Expiratory Flow Rate (m-PEFR) (best out of 3 readings taken) and rescue asthma medication (β2-agonist) used daily during the one-month screening period to identify women with and without pre-menstrual asthma. Cost of peak flow meter required for the study beared by investigator

Record asthma symptoms (shortness-of-breath, wheezing, chest tightness, and cough) at the same time each day and score these as: 3 = severe, 2 = moderate, 1 == slight, and zero = not present.

Data Analysis:
Descriptive statistics like mean and standard deviation used for describing PEFR.

Inferential statistics like Repeated measures Anova test used for testing significant difference in mean PEFR at different phases, a p value of <0.05 considered significant.

Result:-
Total no of patients 100

Table1:

| PROFILE OF ASTHMA PATIENTS		
VARIABLE	NUMBER	%
SYMPTOMS		
COUGH	79	79
DYSPNOEA	60	60
CHEST X RAY		
normal	100	100
TREATMENT RECEIVED		
LABA plus ICS	45	45
LABA PLUS LAMA	16	16
SABA plus ICS	31	31
ICS+oral Steroids+SABA	8	8
CO-MORBIDITIES		
No comorbidities	68	68
comorbidities	32	32
SEVERITY OF ASTHMA		
Well controlled	54	54
Not well controlled	23	23
Very poorly controlled	23	23

79% of the asthmatics had cough, and about 60% of them had dyspnea.
• 51 patients were on regular follow up.
• In our study about 54 patients had well controlled symptoms, and 23 patients each were moderately controlled and very poorly controlled.
• About 45% used LABA plus ICS, only 8% used ICS+ oral Steroids SABA
• 13% had a normal BMI between 18.5 to 24.9.
• 51 patients were overweight. 28 patients had BMI >30

Figure 1:- Comparison of Mean PEFR during various phases of menstrual cycle.
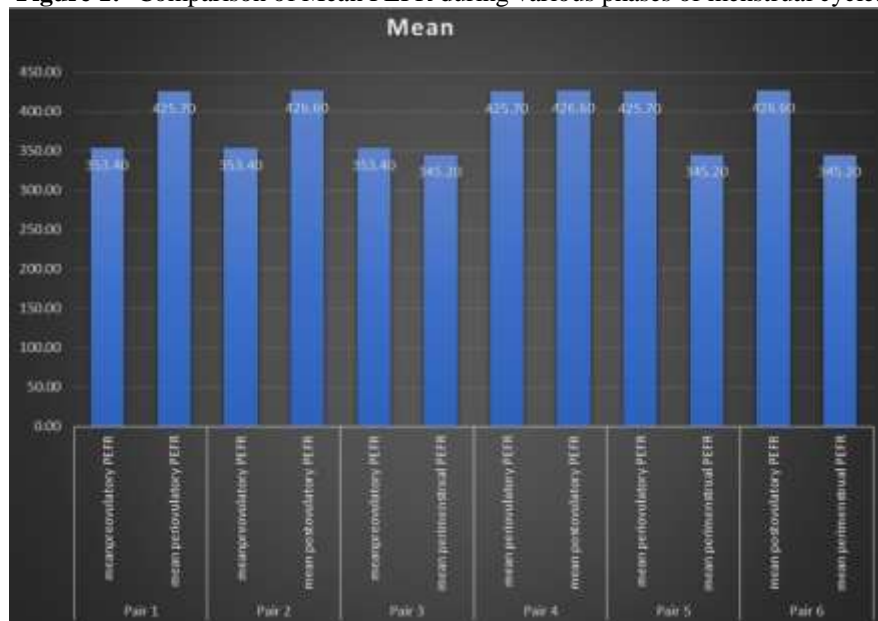

On comparison of the mean values of mean preovulatory PEFR and mean periovulatory PEFR the PEFR fall is more during preovulatory phase with a difference of 72.3 is statistically significant with a p value of <0.001.On comparison of the mean values of mean preovulatory PEFR and mean postovulatory PEFR the PEFR fall is more during preovulatory phase with a difference of 73.2 is statistically significant with a p value of <0.001.

On comparison of the mean values of mean periovulatory PEFR and mean perimenstrual PEFR the PEFR fall is greater during perimenstrual phase with a difference of 80.5 is statistically significant with a p value of <0.001. On comparison of the mean values of mean postovulatory PEFR and mean perimenstrual PEFR the PEFR fall during perimenstrual phase is higher with a difference of 81.4 is statistically significant with a p value of <0.001.

Fig2:- Fall in PEFR and age during perimenstrual phase.
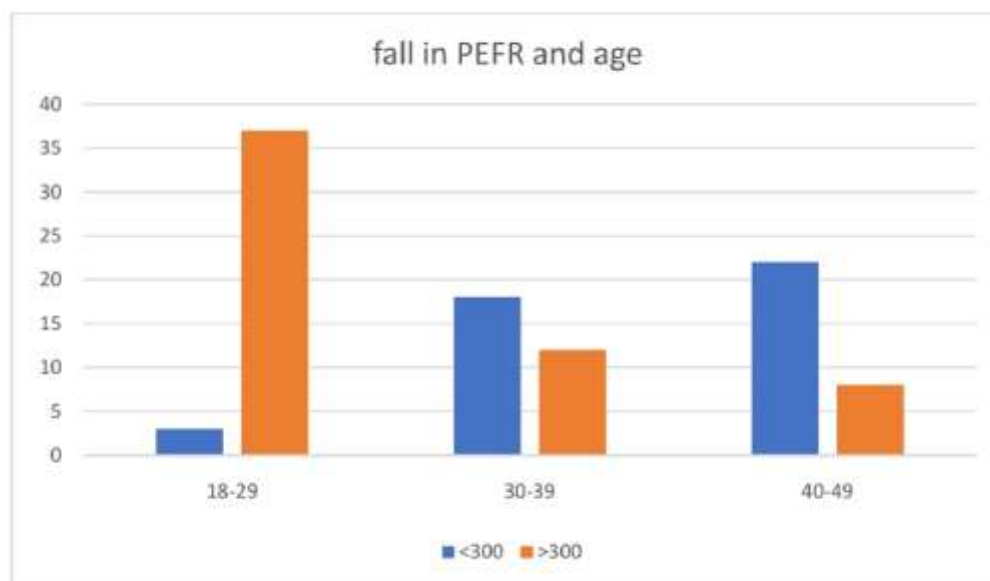
In the perimenstrual phase significant fall in PEFR noted mainly in older age group which is statistically significant with p value <0.001

Fig 3:- Fall in PEFR and age during preovulatory phase.
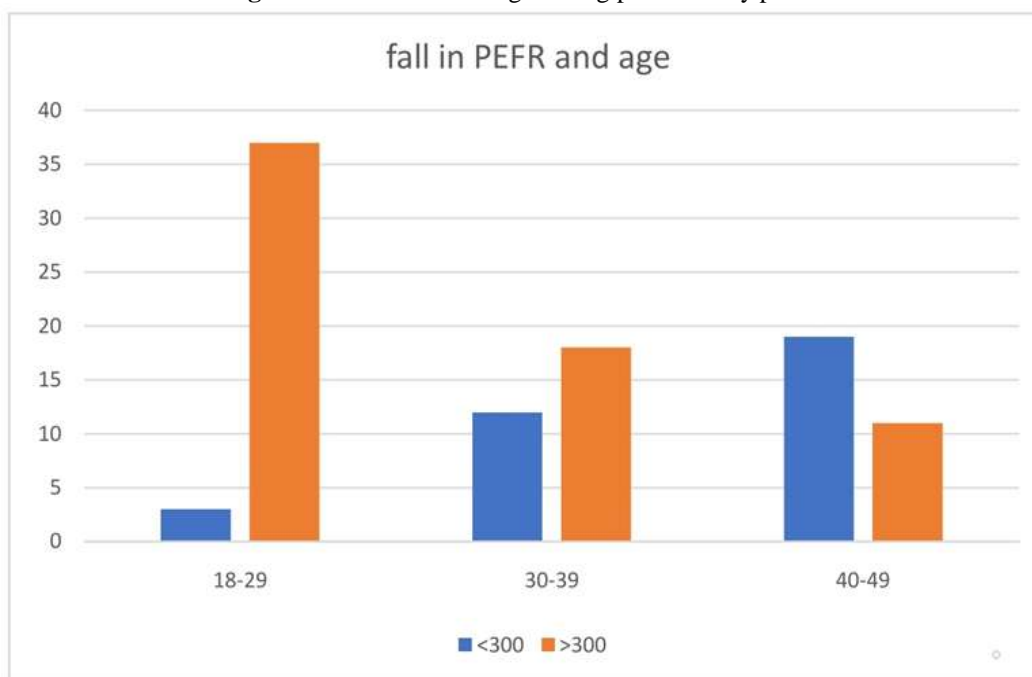
Similarly, in the preovulatory phase as age increases significant fall in PEFR noted which is statistically significant with p value <0.001

Table 2:- Fall in PEFR and symptoms during perimenstrual phase.
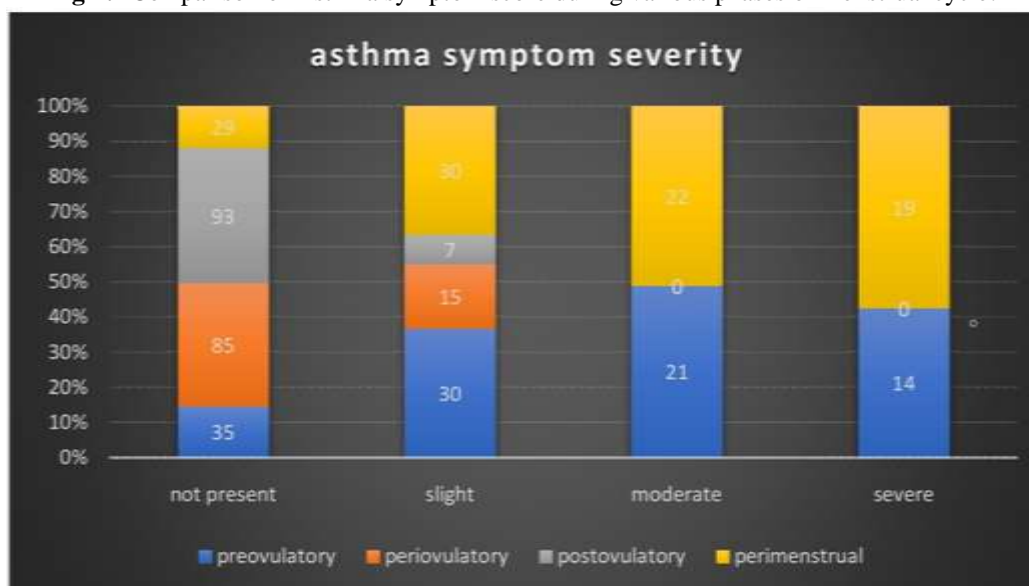
PERIMENSTRUAL PHASE				
		TOTAL NO	**PEFR<300**	**PEFR>300**
cough	No	21	9 (20.9)	12 (21.1)
	Yes	79	34 (79.1)	45 (78.9)
dyspnea	No	40	16 (37.2)	24 (42.1)
	Yes	60	27 (62.8)	33 (57.9)

Most of the patients with perimenstrual fall in PEFR were with cough than dyspnea which is statistically not significant (p 0.988 and 0.621 respectively.

Table 3:- Fall in PEFR and symptoms during preovulatory phase.

PREOVULATORY PHASE				
		TOTAL NO	**PEFR<300**	**PEFR>300**
cough	No	21	**7**	**14**
	Yes	79	27	**52**
dyspnea	No	40	11	29
	Yes	60	23	37

Similarly, most of the patients with preovulatory fall in PEFR were with cough than statistically not significant (p 0.942 and 0.263 respectively.

Fig 4:- Comparison of Asthma symptom score during various phases of menstrual cycle.

Severe and moderate symptoms were present during perimenstrual phase and preovulatory phase only.

Discussion:-

In our study fall in PEFR seen during both perimenstrual (43%) and preovulatory (34%) phase. Whereas Agarwal and Shah found significant cyclical differences in PEF in asthmatic women who perceived a menstrual linked deterioration which was not noted in women without such deterioration (7).
• In a small study Chandler et al noted that, although only a small percentage of patients noted a prior premenstrual exacerbation, all had a fall in PEF or exacerbation in symptoms which improved with estradiol.(8)In a prospective study Shames et al found increased use of bronchodilators and decreased morning PEF during the perimenstrual phase in women with reported menstrual asthma compared with women without menstrual asthma. However, daily symptom scores, evening PEF, differences in forced expiratory volume in 1 second between the luteal and follicular phases, and results of methacholine challenge were not significantly different for the two groups. (9)
• Objective evaluations of airway function during the menstrual cycle in women with stable asthma have yielded inconsistent results. Some studies have noted worsening symptoms and decreases in PEF in the premenstrual and menstrual period (10,11,12) while others found no changes in symptoms or spirometry parameters. (13)
• Brenner et al found ED visits for acute asthma are slightly more common during the preovulatory (28%) and perimenstrual (27%) phases of the menstrual cycle. (14). Our study also showed PEFR fall in same phases.
• Skobeloff et al (15) who found that almost 50% of 182 ED visits for acute asthma occurred during the perimenstrual phase. • Study by Zimmerman et al (16) on behalf of the Multicenter Airway Research Collaboration

(MARC) investigators. They found that only 21% of 288 ED visits for acute asthma exacerbation occurred in the perimenstrual phase, whereas 33% occurred in the preovulatory phase. This is also in consistent with our result.
• Aissani et al study showed Premenstrual asthma in 40 patients with asthma among the 95 premenopausal patients (42.1%).(17) Vega series [18] which published the highest rate of 52.54%.

The symptoms of premenstrual asthma are variable. In our series, most common symptom found to be cough. Aissani et al observed premenstrual asthma was expressed only by respiratory discomfort in 85% of cases. (17) AGARWAL who studied the different symptoms in premenstrual asthma. He found dyspnea in 96% with wheezing in 52% of cases, chest tightness in 43% of cases, cough in 39% of cases and sputum in 13% of cases [7].

Severity of asthma in premenstrual asthma. We noted moderate to severe asthma symptoms during both perimenstrual (41%) and preovulatory (35%) phase. Most patients in Aissani et al study with premenstrual asthma have moderate asthma in 52.5% of cases, or mild in 35% of cases. There was no high incidence of severe asthma in asthmatics with premenstrual asthma (7.5%). (17) The same finding was reported by VEGA [18]. In contrast, Rao reported severe asthma in 50% of women with premenstrual asthma [19]. Several other studies have found a link between premenstrual asthma and the severity of asthma [14,16,20,21].

Limitation
• Sample was obtained from a single centre, thereby selection bias is possible
• Small sample size due to covid pandemic situation.
• Other parameters like premenstrual syndrome not considered.

Conclusion:-
To conclude, premenstrual exacerbation of asthma occurs in a significant proportion of female adult asthmatics. Thus, proper history including menstrual variation of asthma of all these patients should be taken for effective management our data do not support claims that asthma exacerbations markedly increase during the perimenstrual phase. It is possible that both preovulatory and perimenstrual phases may have some adverse impact. For specific subsets of women, these phases could be actual triggers of an asthma exacerbation or they might serve as ''co-factors'' that worsen other recognized triggers of acute asthma.These menstrual phase findings, support efforts to explore hormonal influences on asthma in women.

References:-
1.GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION [Internet]. [cited 2022]. Available from: www.ginasthma.org
2.Global_Asthma_Report_2022.pdf.
3.Shames RS, Heilbron DC, Janson SL, Kishiyama JL, Au DS, et al. Clinical differences Among Women with and Without Self-Reported Perimenstrual. Ann Allergy Asthma Immunol.1998,81; 65-72
4.Magadle R, Berar-Yanay N, Weiner P. Long-acting bronchodilators in premenstrual exacerbation of asthma. Respir Med .2001,95;740-743
5.Vriege A, Postma DS and Kerstjens HAM. Perimenstrual asthma: A syndrome without any cause or cure. J Allergy ClinImmunol.2003,112; 271-282
6.Zimmerman JL, Woodruff PG, Clark S, et al. Relation between phase of menstrual cycle and emergency department visit for acute asthma. Am J Respir Crit Care Med 2000; 162:512–5.
7.Agrawal AK, Shah A. Menstrual-linked asthma. J Asthma .1997,34;539–45
8.Chandler MHH, Schuldheisz S, Phillips BA, et al. Premenstrual asthma: the effects of estrogen on symptoms, pulmonary function, and b2-receptors. Pharmacotherapy .1997,17;224–34
9.Shames RS, Heilbron DC, Janson SL, Kishiyama JL, Au DS, et al. Clinical differences Among Women with and Without Self-Reported Perimenstrual. Ann Allergy Asthma Immunol.1998,81; 65-72
10.Hanley SP. Asthma variation with menstruation. Br J Dis Chest .1981, 75;30608
11. Gibbs CJ, Coutts H, Lock R, etal Premenstmal exacerbation of asthma. Thorax 1984,39;833-36
12.Juniper EF, Kline PA, Roberts RS, et al. Airway responsiveness to methacholine during the natural menstrual cycle and the effects of oral contraceptives. Am Rev Respir Dis 1987; 135:1039–42.
13.Weinmann GG, Zacur H, Fish JE. Absence of changes in airway responsiveness during the menstrual cycle. J Allergy Clin Immunol 1987; 79:634–8
14.Brenner BE, Holmes TM, Mazal B, Camargo CA Jr. Relation between phase of the menstrual cycle and asthma presentations in the emergency department. Thorax. 2005 Oct;60(10):806-9. doi: 10.1136/thx.2004.033928. PMID: 16192365; PMCID: PMC1747196.

15.Skobeloff EM, Spivey WH, Silverman R, et al. The effect of menstrual cycle on asthma presentations in the emergency department. Arch Intern Med 1996; 156:1837–40.

16.Zimmerman JL, Woodruff PG, Clark S, et al. Relation between phase of menstrual cycle and emergency department visit for acute asthma. Am J Respir Crit Care Med 2000; 162:512–5.

17.Aissani S, Ararem I, Haouichat H, Haffaf ME, Zitouni A (2019) Clinical and Spirometric Characteristics of Premenstrual Asthma. Int J Aller Medications 5:041. doi.org/10.23937/2572-3308.1510041

18.Pereira Vega A, Sanchez Ramos JL, Maldonado Perez JA, Alvarez Gutierrez FJ, Ignacio Garcia JM, et al. (2010) Variability in the prevalence of premenstrual asthma. Eur Respir J 35: 980-986

19.Rao CK, Moore CG, Bleecker E, Busse WW, Calhoun W, et al. (2013) Characteristics of perimenstrual asthma and its relation to asthma severity and control: Data from the Severe Asthma Research Program. Chest 143: 984-992.

20.Thornton J, Lewis J, Lebrun CM, Licskai CJ (2012) Clinical characteristics of women with menstrual-linked asthma. Respir Med 106: 1236-1243.

21.Sabry EY (2011) Relation of perimenstrual asthma with disease severity and other allergic co-morbidities-the first report of perimenstrual asthma prevalence in Saudi Arabia. Allergol Immunopathol (Madr) 39: 23-26.