

Questions relating to premenstrual asthma

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Abstract

The study of asthma in fertile women needs to consider its potentially recurrent exacerbation in a specific phase of the menstrual cycle. Premenstrual asthma (PMA)

refers to the deterioration of asthma in some women of fertile age during the premenstrual phase. Prevalence varies considerably according to studies (11%-47.44%) mainly because there is no standardized definition of the illness. There is a possible link between PMA and premenstrual syndrome, which is a set of physical and psychic manifestations that occur in some fertile women during the same premenstrual phase. This relation has been widely studied but there are still several unknowns. PMA etiopathogeny is not known. It involves possible causes such as hormonal variations in the premenstrual phase, the coexistence of atopy, variations during the cycle in substances related to inflammation, like LTC₄ leukotrienes, catecholamines, E₂ and F₂ α prostaglandins and certain cytokines. Also considered are psychological factors related to this phase of the menstrual cycle, a high susceptibility to infection or increased bronchial hyperreactivity prior to menstruation. Yet no factor fully explains its etiology, consequently no specific treatment exists. Researchers have investigated hormones, anti-leukotrienes, prostaglandin synthesis inhibitors, diuretics, phytoestrogens and alternative therapies, but none has been shown to be effective.

Key words: Premenstrual asthma; Definition; Etiology; Risk factors; Treatment

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Core tip: Premenstrual asthma (PMA) refers to the exacerbation of asthma in women of fertile age during the premenstrual phase. Whether or not it is an asthma phenotype, its definition, etiopathogeny and treatment are issues still to be resolved. PMA seems to be a female asthma phenotype despite contradictory results. It can occur at any level of asthma severity and it is usually associated with poorer disease control. Its etiology is not well known, and there is no specific widely recognized treatment. We need new well-designed studies to compare asthmatic women with or without PMA, and good quality clinical trials.

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INTRODUCTION

Unfortunately, there are illnesses or phenotypes of illnesses whose etiopathogeny remains unknown and for which specific treatment is still not available. One such is premenstrual asthma (PMA).

Bronchial asthma in women of fertile age has several specific connotations that include factors such as female sexual hormones and the variations they undergo in the menstrual cycle, women's psychology and metabolism, aspects related to reproduction and the influence of external factors on certain genetic characteristics, among others.

Several authors have investigated the cyclical exacerbation of asthma in fertile women in a specific phase of menstrual cycle. Deterioration has been described in the periovulatory phase^[1,2], in the middle of the preovulatory or luteal phase^[3,4] and more frequently in the premenstrual phase, an entity defined as premenstrual asthma^[5-9].

As well as PMA, other exacerbations in the premenstrual phase have been described, in acne, psoriasis, porphyria, epilepsy, nasal symptoms^[10], multiple sclerosis, migraine, urticarial, Behçet syndrome and myasthenia gravis, among others^[11].

All this seems to indicate that there are still more questions than answers concerning the possible influence of the menstrual cycle on women and their health, especially in terms of bronchial asthma.

QUESTIONS RELATING TO PREMENSTRUAL ASTHMA

A definition

The classic definition of PMA continues to be the cyclical deterioration of asthma in some women of fertile age during the premenstrual phase and/or the first days of menstruation^[6,7]. Although it can occur at any level of asthma severity according to the Global Initiative for Asthma classification^[12], it is usually associated with poorer disease control.

Definition of deterioration

Deterioration refers to the worsening of the symptoms of asthma, lung function and inflammation markers, or all of these factors together. As a result, the definition of premenstrual asthma varies in the studies of this entity. Early research^[7,9,13,14] defined PMA merely on the basis of a "Yes" answer by a female asthma sufferer to the question, "Does your asthma get worse during the premenstrual phase?" This definition is clearly

subjective, referring to the patient's own perception of her asthmatic symptoms in this phase. Authors such as Balzano *et al.*^[15] comment in their conclusions that it is not clear whether the asthma exacerbation occurring in many women during the premenstrual period is due to an objectively measurable intensification of the disease or to an increased perception of symptoms caused by the particular psychological state occurring shortly before menstruation. Our research group^[1] defines this as "PMA from a subjective perspective".

Later authors sought a definition by formulating a methodology that gathered data on the symptoms and then subjected them to a structured analysis in order to consider whether a patient's condition conformed to PMA criteria^[8,16]. These definitions still retained a subjective component since they asked women about their personal "perception" of asthmatic symptoms. Our research group^[17] defines this as "semi-objective PMA".

Other researchers applied criteria that were more obviously objective. These included the observation of a premenstrual exacerbation in lung function through peak flow^[17-19] or spirometry^[20] (a reduction in lung volume and flow, or lung diffusing capacity, bronchial hyperreactivity^[21] to methacholine or to physical exercise), an increase in inflammation markers such as Nitric Oxide (NOx)^[22] or eosinophils in the sputum in the premenstrual phase^[23]. There is also some controversy over the level of exacerbation that needs to occur in the premenstrual as opposed to the preovulatory phase. Some authors^[16] require more than 20% in the objective parameters while for others it must be 40%^[19].

Our research group^[16] has categorized these three possible definitions of PMA as "PMA from a subjective perspective", "semi-objective PMA" and "PMA defined by objective criteria", and analyzed the relation between all three. We found that the biggest differences between the preovulatory and premenstrual phases in asthmatic females occurred within the semi-objective PMA category. On the other hand, there is a greater correlation between the semi-objective exacerbation of the symptoms and perception of the exacerbation of the asthma before menstruation when considering one single menstrual cycle than requiring semi-objective exacerbation in two consecutive cycles. We believe it is too stringent to require that semi-objective criteria apply in two consecutive cycles. Objective criteria, which demand a peak flow variation of 20%, are much more restrictive. Our results lead us to think that the definition by semi-objective criteria in a menstrual cycle is what best defines the problem of PMA.

These disparate definitions are seen in the variation in figures for PMA prevalence that appear in studies (from 11% to 47%) and highlight the need to standardize criteria.

Another aspect that further confuses the issue is the relation between subjective, semi-objective and objective criteria. Pauli *et al.*^[24] found that 11 asthmatic women who had stated that their asthma did not

deteriorate prior to menstruation (non-compliance with subjective criteria) in fact had more symptoms before menstruation when these same symptoms were later analyzed (semi-objective criteria); they also experienced deterioration in premenstrual peak flow (objective criteria according to peak flow). However, there was no deterioration in spirometry or in bronchial hyperreactivity (objective criteria according to other parameters different from peak flow).

How many cycles?

While some authors only require that deterioration occurs in a single cycle^[17,25,26], others believe that exacerbation of symptoms must be present in several consecutive cycles^[14], the question being whether women with PMA fulfill PMA criteria in all menstrual cycles. With this in mind, Agarwal *et al.*^[9] studied a group of women over four consecutive menstrual cycles and found that 61% of those with PMA showed deterioration in almost every cycle, 39% had worsening once every 2-3 cycles while one patient had an increase in symptoms every 3-4 cycles. These data question how many cycles are required for PMA criteria to be satisfied. They also make us think about whether PMA sufferers vary in their symptoms during different cycles in the same year or whether these symptoms can change over several years. We consider the semi-objective criteria in a complete menstrual cycle as the most valid approximation to real PMA^[16].

At which point in the cycle?

Why do some women experience deterioration in some pre-existing illnesses during the premenstrual phase and others do not? Why do some women suffer this exacerbation in other phases of the menstrual cycle? Such questions remain to be answered convincingly.

Questions on the relation between premenstrual asthma and premenstrual syndrome

Premenstrual syndrome is the cyclical recurrence of a set of physical and psychic symptoms that occur in some women of fertile age following ovulation, in the luteal phase of the menstrual cycle and, in particular, before menstruation, and which is resolved at the beginning of the next menstrual cycle^[27,28].

More than 150 clinical manifestations of the syndrome have been described^[14,29,30], with congestive and edematous symptoms being predominant in the physical aspect, and mood changes in the psychic aspect. These premenstrual symptoms are relatively frequent in fertile women although their intensity and possible repercussion on quality of life vary significantly (80% experience a slight exacerbation and 3% a severe exacerbation)^[31-33]. Their true etiology and physiopathology are unknown^[34-36], although the alterations in the balance between sexual hormones and neurotransmitters are noteworthy^[37].

Several works have found links between PMA and premenstrual syndrome^[17,38]. Our research group^[39]

has shown a clear connection between PMA and premenstrual syndrome. A detailed analysis of the various symptoms related to premenstrual syndrome reveals that the relation is particularly intense in psychic and edematous symptoms such as abdominal and mammary tension. This could be due to the fact that the generalized nature of the edema in women also occurs in nasal and bronchial mucosa^[10] leading to a deterioration of nasal and asthmatic symptoms, and lung function in this premenstrual phase.

Although we believe there exists a relation between PMA and the symptoms related to premenstrual syndrome, the etiology and physiopathology of both is unknown, and not all women with PMA necessarily present with premenstrual syndrome and vice versa.

Questions relating to the etiology of premenstrual asthma

Premenstrual asthma's true etiology is still in doubt. Some authors stress the influence of hormonal factors (premenstrual decline in estrogens or progesterone, or variations in the estrogen/progesterone relation in the premenstrual phase^[25,40-46], LH^[41], FSH^[41]), atopy^[47-51], variations during the menstrual cycle of inflammation-related substances [leukotrienes (LTC) 4^[19,52], the E2 and F2 α ^[53] prostaglandins and cytokines^[54]], psychological factors, diminished resistance to infections or increased bronchial hyperreactivity (Table 1)^[8,55,56]. The results of studies that have analyzed the possible factors vary and are occasionally contradictory.

For the possible genetic factors involved, Gorovenko *et al.*^[57] studied aspects related to asthma genetics and found that women with PMA showed a greater frequency of functioning alleles in Glutathione transferase T1. This genetic polymorphism (in terms of inactive GSTM1 alleles) relates to the metabolism of prostaglandins (PG), LTC and the sexual hormones. The genetic component associated to the atopy could also influence the relation found in some studies between levels of total IgE and premenstrual asthma^[47].

Other factors such as sensibility to aspirin (ASS)^[48], use of aspirin or non-steroidal anti-inflammatory drugs^[58] or body mass index (BMI)^[48] have been related to premenstrual asthma. No clear link has been found between ASS and PMA, and although Rao *et al.*^[48] found higher BMI scores in asthmatics with PMA, other authors found no link between obesity and premenstrual asthma^[59].

A priori, the varying behaviors of the sexual hormones in the premenstrual phase compared to the preovulatory phase would seem to be the best explanation of the mechanism by which to describe why some women with bronchial asthma have PMA and others do not. However, the studies have found no difference between the blood levels of the different hormones between women with and without PMA^[40]. Researchers have always explored this relation *via* hormone levels in the blood but perhaps this relation is more complex, and is found in intermediary mechanisms such as the cyclical variations

Table 1 Etiological factors in premenstrual asthma

Group	Factor	Ref.	Design	Level of factor in PMA	Level of factor in non PMA	P value	Evidence level ¹
Hormones	Estrogen	Pasaoglu <i>et al</i> ^[41]	Pre-post study	PM: 89.3 pg/mL	PM: 72 pg/mL	N/A	4
	Estrogen	Pereira <i>et al</i> ^[40]	Cross-sectional study	PO: 111.49 pg/mL PM: 95.9 pg/mL	PO: 131.31 pg/mL PM: 123.83	(for change) 0.845	4
	Progesterone	Pasaoglu <i>et al</i> ^[41]	Pre-post study	PM: 7.3 pg/mL	PM: 9.2 pg/mL	N/A	4
	Progesterone	Pereira <i>et al</i> ^[40]	Cross-sectional study	PO: 0.83 pg/mL PM: 6.82 pg/mL	PO: 1.39 pg/mL PM: 6.31	(for change) 0.225	4
	Estrogen/ Progesterone	Pereira <i>et al</i> ^[40]	Cross-sectional study	PO: 219.26 pg/mL PM: 35.53 pg/mL	PO: 356.6 PM: 355.22	0.865 0.371	4
	LH	Pasaoglu <i>et al</i> ^[41]	Pre-post study	PM: 3.5 mU/mL	PM: 4.9 mU/mL	N/A	4
	FSH	Pasaoglu <i>et al</i> ^[41]	Pre-post study	PM: 13.3 mIU/mL	PM: 3.3 mIU/mL	N/A	4
Inflammation	LTC4	Nakasato <i>et al</i> ^[19]	Pre-post study	PO: 24.0 pg/mL PM: 69.0 pg/mL	PO: NA ¹ PM: NA ¹	NA	4
	LTC4	Pereira <i>et al</i> ^[52]	Cross-sectional study	PO: 1.5 ng/mL PM: 1.31 pg/mL	PO: 1.4 ng/mL PM: 1.29	NS	4
	Prostaglandin F2 α	Eliasson <i>et al</i> ^[53]	Cross-sectional study	Early cycle: 143 pg/0.1 mL Late cycle: 15.9 pg/0.1 mL	169.3 pg/0.1 mL 9.5 pg/0.1 mL	NS ¹ NS ¹	4
Atopy	Total IgE (geometric mean)	Pereira <i>et al</i> ^[47]	Cross-sectional study	206.31	87.99	0.01	4
	Total IgE (% > 100 kU/L)	Pereira <i>et al</i> ^[47]	Cross-sectional study	84	43	0.001	4
	Total IgE (mean)	Rao <i>et al</i> ^[48]	Cross-sectional study	208.4	292.2	0.06	4
	Phadiatop (% +)	Pereira <i>et al</i> ^[47]	Cross-sectional study	68	50	0.17	4
	Skin prick test +	Rao <i>et al</i> ^[48]	Cross-sectional study	60 (76%)	297 (88%)	0.01	4
Others	Aspirin sensitivity	Rao ^[48]	Cross-sectional study	23 (39%)	36 (10%)	< 0.0001	4
	Use of aspirin or non-steroidal anti-inflammatory drugs	Forbes ^[58]	Cross-sectional study	14/38 (36.8%)	172/421 (40.9%)	NS	4

¹Oxford Centre for Evidence-based Medicine-Levels of Evidence (March 2009, <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>). N/A: Not available; PMA: Premenstrual asthma; NS: Not significant; LTC: Leukotrienes.

of substances like cytokines (CK) or LTC, among others, which are, in turn, influenced by hormone variations.

In short, despite the studies carried out so far and the reviews published on the subject^[60-65], the research results are inconclusive and the causal factors of this entity remain unknown.

Questions related to treatment

Some women with PMA experience a slight worsening of their asthmatic symptoms before menstruation, which is resolved by increasing the dosage of base medication. However, other women suffer severe exacerbation that require frequent visits to hospital emergency rooms or even hospitalization^[48,66]. The latter cases would be those most urgently requiring a treatment specific to the patient's condition^[40,52,67]. Various specific treatments for PMA have been analyzed (Table 2) without agreement as to which is the most effective. Study results continue to be contradictory. The most attractive hypothesis to explain the cause of PMA is hormonal variations in the premenstrual phase, and the proposed treatments involve oral or intramuscular^[68] progesterone, estrogens^[25,69] and oral contraceptives^[18,44,70]. Other treatments tested

include gonadotropin analogues^[71], which can cause uncomfortable side effects such as amenorrhea or osteoporosis, leukotrienes antagonists^[19,41] and sodium medlofenomate^[72] among others.

Our research group is currently carrying out a randomized double-blind placebo-controlled clinical trial to analyze the possible benefits of phytoestrogens (Genistein) in cases of premenstrual asthma^[73]. Phytoestrogens are natural estrogens that present fewer side effects than human estrogens. They can have an agonistic or antagonistic effect according to the tissue on which they act^[74]. It is shown to be useful in treating postmenopausal symptoms^[75], premenstrual syndrome^[76] and asthma^[77,78]. Our study is based on the relation that we have found between PMA and symptoms related to premenstrual syndrome, and it is boosted by the fact that the side effects of these substances are few. The results have not been published yet.

So we can say that due to the absence of a definitive PMA etiology, and despite the various therapeutic interventions proposed^[19,25,41,42,70,71], the best approach for this entity remains unknown. Treating this condition requires well-designed randomized double-blind placebo-

Table 2 Specific treatments used in premenstrual asthma

Group	Treatment	Ref.	Design	patients	Outcome	Results	P value	Evidence level
Hormonal	Oral or intramuscular progesterone Estrogen	Beynon <i>et al</i> ^[66]	Case-series	3	Premenstrual dips in peak flow	3 eliminated premenstrual dips in peak flow	NS	4
		Ensom <i>et al</i> ^[25]	Cross-over trial	12 (mild severity)	Asthma Quality of Life Questionnaire, FEV1	No differences	NS	1b
		Ensom <i>et al</i> ^[69]	Case report	1 (severe asthma)	Symptoms, pulmonary function, peak flow	Improved	N/A	4
	OC	Murphy <i>et al</i> ^[18]	Case-series	28 (16 with PMA)	OC use (%)	5.42% in Non PMA 6.38% in PMA	NS	4
		Tan <i>et al</i> ^[44]	Cross-sectional study	18 (9 taking OC)	Changes between follicular and luteal phases in airway reactivity and peak flow	Changes in patients not taking OC; No changes in patients taking OC	0.03 NS	4
		Derimanov <i>et al</i> ^[70]	Case report	1	Deterioration of asthma, decline of pulmonary function tests	After discontinuing the contraceptives, her condition returned to baseline	N/A	4
	Gonadotropin analogues	Murray <i>et al</i> ^[71]	Case report	1	Respiratory symptoms, PEFR dips premenstrual and prednisolone dosage and hospital admissions	Improvement	N/A	4
Anti-inflammatory	Anti-leukotrienes: pranlukast	Nakasato <i>et al</i> ^[19]	Pre-post study	5	Respiratory symptoms, PEFR	Improved asthma symptom scores, inhibited maximal decreases in PEFR	< 0.05 < 0.01	4
	Anti-leukotrienes: montelukast	Pasaoglu <i>et al</i> ^[41]	Pre-post study	24 mild asthma-tics (11 with PMA)	PEFR and symptom scores	Improvement in PEFR variability and symptom scores in women with PMA. No differences in women without PMA	0.005 0.002	4
	Prostaglandin synthesis inhibitors: sodium meclofenomate	Shimoda <i>et al</i> ^[72]	Cross-over trial	17 PMA	Peak flow, symptoms score	Improvement in peak flow during the early premenstrual period. No effect on the exacerbation of asthma during the late premenstrual period and early menstruation	0.025 NS	2
Others	Phytoestrogens soy genistein	Bime <i>et al</i> ^[77]	Case series	300 poorly controlled asthma	FEV1 and asthma control	Participants with little or no genistein intake had a lower baseline FEV1 and poorer asthma control than those with a moderate or high intake	0.01 0.001	4
	Phytoestrogens soy isoflavone	Smith <i>et al</i> ^[78]	Clinical trial	386 poorly controlled asthma	FEV1 at 24 wk symptoms, episodes of poor asthma control, asthma control test score	Not result in improved lung function or clinical outcomes	NS	1b

N/A: Not available; NS: Not significant; PEFR: Peak expiratory flow rate; PMA: Premenstrual asthma; OC: Oral contraceptives.

controlled clinical trials.

order for results to be compared.

CONCLUSION

Definition

The definition used in studies needs to be clarified in

Relation between premenstrual asthma and premenstrual syndrome

Although a relation between both events seems to exist, there are still doubts about the type of premenstrual

syndrome-related symptoms that can be clearly linked to PMA; and doubts persist as to the etiology of both phenomena.

Etiology of premenstrual asthma

The type of relation that exists between hormonal changes throughout the cycle and PMA has yet to be established; this relation would be the most likely hypothesis. Investigators have searched for this link in hormone levels of the blood but the relation seems to be more complex. There are still doubts about PMA etiology, and like Skoczynsky *et al.*^[23], we believe that close collaboration between medical specialities such as pneumology, gynaecology and endocrinology, among others, could shed light on this issue.

Specific treatment for premenstrual asthma

Although there are several works published on the subject, there is currently no treatment specifically designed for PMA. More studies are needed in this area.

Final conclusion

Although the results are contradictory, it seems that PMA can be considered a phenotype specific to asthma in women. Although it can occur at any level of asthma severity classification^[16] it is usually associated with poorer disease control^[50,79,80]. We still do not know its etiology entirely and no specific treatment exists that has been widely accepted. All this requires new studies to compare groups of asthmatic women with or without premenstrual asthma, with clear criteria regarding definition of the entity.

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