

REVIEWS

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Perimenstrual Asthma as a Gynecological and Pulmonological Clinical Problem

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Abstract

Asthma is one of the most common chronic diseases of the respiratory system. It is estimated that up to 40% of asthmatic women of childbearing age may experience a cyclical exacerbation of asthmatic symptoms during the perimenstrual period, which is called perimenstrual asthma (PMA). The precise prevalence of this particular phenotype of asthma is difficult to determine due to a lack of explicit diagnostic criteria and appropriate epidemiological surveys. According to one of the best documented hypotheses regarding perimenstrual exacerbations of asthma, the impact of female steroid sex hormones on the function of the respiratory system and inflammations in the bronchi may play a central role in this phenomenon. Although the basic medical approach to PMA is similar to that used in other asthma phenotypes, unconventional methods of “experimental” treatment have also been tried. Unfortunately, current knowledge about the pathogenic mechanisms of this phenotype of asthma is incomplete and inconsistent, which justifies the need for further interdisciplinary studies with the participation of specialists in both gynecology and lung diseases. The knowledge thus acquired will help to individualize and focus future therapy on specific cellular and/or hormonal mechanisms to optimize asthma control in patients with PMA (*Adv Clin Exp Med* 2014, 23, 4, 665–668).

Key words: perimenstrual asthma, gonadal steroid hormones, inflammation, peak expiratory flow rate.

Asthma, one of the most common chronic respiratory diseases, can deteriorate during the perimenstrual period, which is a phenomenon known as perimenstrual asthma (PMA). PMA occurs in up to 40% of asthmatic women of childbearing age [1]. The case of a woman with severe, recurrent perimenstrual asthma attacks was first described in 1931. Inhibition of ovarian function stopped the asthma attacks; however, with the return of hormonal function the asthma symptoms reappeared [2]. These findings revealed the importance of menstrual cycle-related changes in sex hormones in the pathogenesis of PMA. Although several later studies confirmed this relationship [1, 3, 4],

present knowledge of PMA is incomplete and requires further research.

Definition and Incidence

PMA is usually described as cyclical deterioration of asthma during the luteal phase and/or during the first days of menstruation [1, 3–5]. This deterioration is defined as a worsening of asthma symptoms and/or deterioration of lung function tests, such as a decrease of ≥ 20 –40% in the peak expiratory flow (PEF) [3, 5, 6]. Most authors diagnose PMA on the basis of either asthma

questionnaires [1, 7–12], PEF measurements [5, 8] or questionnaires combined with PEF measurements [6]. Chandler et al. accepted a $\geq 20\%$ PEF decrease and/or exacerbation of asthma symptoms before menstruation as diagnostic criteria for PMA [3], while Nakasato et al. regarded a perimenstrual decrease of morning PEF $\geq 40\%$ as diagnostic of PMA [5]. Magadle et al. recognized PMA as $\geq 20\%$ PEF decrease within ten days before menstruation [13]. The precise incidence of PMA has not been determined yet, due to a lack of large epidemiological studies, but in a study by De Marco et al. [14] PMA incidence was reported to be about 19% of asthmatic women, while other studies reported the incidence to be as high as 25% to 40% [2, 5, 8–10].

Etiology and Pathogenesis

There is no coherent explanation of the pathogenesis of PMA. The available data link the endocrine system with the influence of female sex hormones on inflammatory mediators and asthma symptoms. The incidence of asthma in puberty and in reproductive age is significantly higher in women than in men [9–11]. According to Romieu et al., postmenopausal hormone replacement therapy (HRT) with estrogen (but not estrogen combined with gestagen) is associated with an increased risk of developing asthma [10], while Barr et al. [11] and Troisi et al. [12] found an increased risk of asthma due to estrogen or estrogen-gestagen HRT. Gomez et al. confirmed an increased risk of asthma in a group of 540 women on HRT in the perimenopausal period [13]. The influence of estradiol on the production of inflammation factors is easy to predict. Data regarding the effect of oral contraceptive pills (OCPs) on asthma are also inconsistent, reporting both positive effects [14] and deterioration [15]. However, in the majority of patients OCPs do not significantly affect the course of asthma [16]. Murphy and Gibson failed to confirm any effect of OCPs on PMA [8]. Theoretically, blocking the hypophyseal-ovarian axis could decrease sex hormone levels and cause a secondary decrease of inflammatory marker concentration, improving asthma control in PMA patients. This hypothesis was partially confirmed by Mandhane et al. [17], where low exhaled nitric oxide (NO) was observed in women using OCPs, and only a subclinical decrease in asthma control was noted. It seems that not only sex hormone level changes, but also other factors like receptor distribution or human variability are important in asthma control. Summarizing, during the natural ovulatory cycle, sex hormone changes stimulate

inflammatory factors that affect asthma control in the perimenstrual period. Women on OCP therapy have somewhat better asthma control, whereas postmenopausal women on HRT experience more asthma exacerbations.

Estrogen and progesterone receptors (ER- α , ER- β , PR-A, PR-B) are widely distributed in the lower airways [18]. Progesterone causes bronchorelaxation, increases mucous secretions and respiratory drive, modulates the activity of beta-2-adrenergic receptors (β_2 AR) [19], facilitates catecholamine-related bronchodilatation, and increases the number of progesterone receptors on the surface of leucocytes. Miyaura and Iwata showed that the increased concentration of progesterone in the luteal phase increases the Th2/Th1 lymphocyte ratio [20]. Estradiol, in turn, increases the number of leukocytes in peripheral blood and decreases the expression of E-selectin in the lower respiratory tract [21]. During the luteal phase, low estradiol concentrations may affect the influx of leukocytes into the airways. Estradiol has also been shown to reduce bronchial hyperreactivity (by increasing the activity of acetylcholine esterase in bronchial epithelium nerve endings) [22], and to reduce the accumulation of collagen in the airway wall [23]. Estradiol has been shown to stimulate mast cell degranulation [24], leading to the release of histamine, tryptase, serotonin, heparin, thromboxanes, prostaglandins and leukotrienes [25]. De Oliveira et al. found fewer inflammatory cells in the airways of ovariectomized rats than in the intact controls [26]. Administration of estradiol has been associated with an influx of inflammatory cells into the bronchoalveolar lavage (BAL), decreased secretion of IL-10, and increased secretion of IL-4, IL-1 β and TNF [33]. Conversely, progesterone administration reduced the number of inflammatory cells, increased the concentrations of IL-10, IL-1 β , TNF in BAL and IL-4 blood concentration [33]. In the same study, bronchial mast cell degranulation was reduced after ovariectomy and reverted by estradiol (but not progesterone) administration. Oguzulgen et al. revealed higher levels of exhaled NO and increased induced sputum and peripheral blood eosinophil count before menstruation in PMA patients [27].

Clinical Features

Unfortunately, although it is important and difficult to deal with, PMA has not been widely accepted as real clinical problem. Clinicians dealing with asthma most frequently base their treatment on current international guidelines such as those set by the Global Initiative for Asthma (GINA)

[28]. Although in such reports one can easily find detailed information on co-existing allergies, obesity, air pollution, tobacco smoking or gastroesophageal reflux, there is usually only minimal information about PMA. The GINA definition states that under 14 years of age, asthma is more common in boys than girls, but after reaching this age, the epidemiology is reversed and asthma is more frequent in women. However, this phenomenon is not well explained in the document, and the statement proposing lung capacity as a factor seems doubtful, since lung capacity favors males throughout life. Moreover, despite the epidemiology and clinical importance of PMA presented in this review, PMA is not mentioned in GINA chapters such as Special Mechanisms, Classification of Asthma: Phenotype or Special Considerations [35].

Suzuki et al. [12] states that PMA often has a more severe course than other asthma phenotypes, and that achieving and maintaining control over the symptoms is more difficult than in non-PMA asthma. PMA often requires aggressive treatment, including systemic glucocorticosteroids. Additionally, Barkmann described two deaths in the course of asthma attacks on the day before menstruation was expected [29], while Lenoir described three cases of PMA patients requiring mechanical ventilation due to asthma exacerbations during the perimenstrual period [30]. That is why, in the current authors' opinion, PMA should not only be considered in scientific research, but also – most importantly – in clinical practice.

Treatment of Exacerbations

There are no specific guidelines for treating PMA [35]. In some (but not all) cases of PMA, the

anti-inflammatory drugs recommended by the GINA guidelines [35] – mostly inhaled glucocorticosteroids – allow good symptom control during the perimenstrual period as well. Beyon et al. reported a significant improvement in asthma control after intramuscular progesterone administration in three women with life-threatening PMA, in whom conventional therapy had not been sufficient [31]. Data on the use of OCP therapy in treating PMA is ambiguous. Some studies have reported positive effects from the use of estradiol [3, 32], but other studies have not confirmed this effect [6, 33]. Gonadotropin-releasing hormone analogs (GnRH analogs) constitute another approach to PMA therapy. Murray et al. described the case of a 32-year-old asthmatic female in whom PMA treatment had been ineffective. When goserelin was added to the baseline therapy, it stopped menstruation, significantly improved asthma control and increased PEF values [34]. Pasaoglu et al. found that montelukast administration helps to achieve asthma control and increases PEF values in PMA patients [35], which indicates that the use of leukotriene receptor antagonists (LTRA) in PMA also seems to be justified.

Summary

PMA is a commonly observed, difficult-to-treat asthma phenotype. The concept that sex hormones aggravate airway inflammation, resulting in deterioration of asthma symptoms, requires further interdisciplinary studies using advanced immunology and molecular biology techniques. This might help to focus therapy on specific cellular and/or hormonal mechanisms. Until then, inhaled glucocorticosteroids combined with hormonal therapy and/or LTRA seems to be the optimal treatment.

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