Exacerbation of premenstrual asthma caused by an oral contraceptive

Geo Stoyanov Derimanov, MD* and John Oppenheimer, MD

Background: The relationship between sex hormones and asthma has not been clarified. Studies have suggested a potential beneficial effect of exogenous sex hormones and/or contraceptive pills on asthma in premenopausal females whereas the data for postmenopausal females are inconsistent.

Case report: A 33-year-old woman suffering from asthma with premenstrual exacerbations had a stable course until she began taking oral contraceptives. At that time she experienced clinical deterioration of her asthma associated with decline of pulmonary function tests. No other precipitating factors were identified. After discontinuing the contraceptives, her condition returned to baseline.

Conclusion: We found only two reports of worsening of asthma related to hormonal therapy (estrogen in one case, contraceptive pills in the other) in premenopausal women. Our report, together with these observations, suggests that in some premenopausal women exogenous sex hormones and/or contraceptive pills may, contrary to expected, produce exacerbation of asthma.

Ann Allergy Asthma Immunol 1998;81:243–246.

INTRODUCTION

Premenstrual asthma (PMA) denotes worsening of asthma symptoms shortly before and/or during menstruation. While this entity is well recognized, it has not been extensively studied and is not widely known among clinicians. The mechanism of PMA has not been established but it is speculated that hormonal variations during the menstrual cycle play an important role in its pathogenesis. Little is known about the influence of oral contraceptive pills (OCP) on asthma. We report a case of PMA that appeared to be exacerbated by OCP. Our search of the literature found only one case report where OCP were believed to be an aggravating factor in asthma.[1]

CASE REPORT

The patient RQ is a 33-year-old white female with a history of asthma since age 27. She was first seen in our practice in March of 1996 at age 31. Her past medical history was significant for spina bifida for which she underwent surgery in her childhood. She also had seasonal allergic rhinitis and conjunctivitis in the spring and fall. Skin testing had revealed allergy to dust and tree pollens. She had no known latex sensitivity.

Her asthma manifested with attacks of shortness of breath, chest tightness, and wheezing without pronounced cough or sputum production. These were provoked by upper respiratory tract infections, dust, smoke, strong smells, cold air, physical activity and did not show seasonal variation. The strongest trigger, however, were her menses. All of them were associated with worsening of the asthma, typically extending from about 1 week before until 2 to 3 days after the onset of bleeding. The patient had no night awakenings. She had not been hospitalized for asthma but had had an average of 2 to 3 emergency room visits a year, each precipitated by her menstrual periods. She had been treated with inhaled β_2-agonists and sporadic inhaled corticosteroids and had received occasional short courses of oral corticosteroids (usually after an emergency room visit). Her baseline peak flows and spirometry results were within normal range (Table 1).

The patient's menstrual cycles varied in duration (30 to 45 days) with the bleeding usually lasting 4 to 5 days. Since she was not following her basal temperature, it was unclear whether she had anovulatory cycles. She also reported a number of premenstrual syndrome (PMS) symptoms including abdominal cramps, backpain, legpain, fatigue, irritability, depression, bloating, and breast tenderness. On one occasion she had received OCP for a very brief period (a few days) which had been associated with worsening of her asthma. We were not able to identify the type of medication the patient had used.

After she visited our office, her treatment was modified to include continuous inhaled steroids: fluticasone, 220 μg bid; long-acting β-agonist-salmeterol, 2 puffs bid; and albuterol inhaler as needed. She was enrolled in an asthma education program. After these interventions, we observed stabilization of her asthma with no emergency room visits over the ensuing 18 months and only minimal use of supplemental Albuterol (an average of 1 to 2 times weekly).

In October 1997 the patient began taking OCP (0.035 mg ethinyl estradiol/0.180 mg norgestimate). About a week later she noticed deterioration of her asthma but continued the medication. She did not have an upper respiratory tract infection, change in environment, or any other exposure that could have potentially caused an asthma exacerbation. Over the following week her condition worsened significantly, she had night awakenings and had to use albureral every 2 hours

From * Internal Medicine, Morristown Memorial Hospital, Morristown, New Jersey and † Pulmonary Allergy Associates, Morristown, New Jersey.

Received for publication March 23, 1998.
Accepted for publication in revised form June 17, 1998.

Table 1. Pulmonary Function Tests at Baseline (March, 96) and on OCP (1 day after the ER visit)

Measurement*	Baseline	On OCP
FVC (L)	4.15	3.06
FVC % pred	136	98
FEV_1 (L)	3.25	2.32
FEV_1 % pred	123	87
FEV_1/FVC (%)	78	75.8
FEV_1/FVC (%) % pred	90	87
$FEF_{25–75\%}$ (L/s)	2.95	1.79
$FEF_{25–75\%}$ % pred	92	56
PEFR	470	350

* FVC = forced vital capacity; FEV_1 = forced expiratory volume in one second; $FEF_{25–75}$ = mid-forced expiratory flow; PEFR = peak expiratory flow rate; and OCP = oral contraceptive pills.

to control her symptoms. Her peak flows dropped by more than 100 mL/s. About 2 weeks after the beginning of the contraceptive therapy, she experienced severe respiratory distress necessitating evaluation in the emergency room where she received three nebulizer treatments and was placed on oral steroids (60 mg of prednisone). On the next day she was seen in our office. She was still symptomatic, had mildly prolonged expiratory phase on exam and her spirometric results were significantly worse compared with baseline (Table 1). It was decided that she should stop taking the OCP. Over the next few days her condition returned to baseline. Prednisone was tapered and stopped within 5 days. Approximately 1 week after discontinuing the OCP, she had a menstrual bleeding that lasted 9 days which was not associated with change in her asthma.

In order to confirm that the asthma exacerbation was related to the OCP intake, a rechallenge with the same drug was proposed but the patient, in fear of another bad reaction, did not accept it.

DISCUSSION

Premenstrual asthma is not uncommon. According to some surveys 30% to 40% of female asthmatics report worsening of asthma symptoms during the premenstrual and/or menstrual period.[2,3] This observation is supported by the pattern of presentation of women with asthma to the emergency department which shows a 4-fold variation with greatest number of women presenting during the premenstrual and early menstrual interval (days 26 to 04 of the menstrual cycle).[4]

The nature and cause of PMA as well as the role of sex hormones in asthma are poorly understood. There has been debate whether PMA represents a true "physiologic" event or a "psychologic" phenomenon as part of the spectrum of PMS. Gibbs et al[3] found objective difference between women with PMA and those with regular asthma (RA) with the PMA group demonstrating a statistically significant decrease of peak flow in the premenstrual week compared with the midcycle week. Such a change was not present in the RA group. But the authors felt that the observed changes in peak flow were too small to account for the worsening of symptoms. Several studies have failed to demonstrate significant difference in spirometric measurements (FEV_1, FVC, FEV_1/FVC) and airway reactivity to histamine[5] and methacholine challenge[6,7] when comparing the follicular and luteal phases of the menstrual cycle (coinciding with the lowest and highest levels of sex hormones, respectively). The anticipated association between airway responsiveness and hormone levels throughout the menstrual cycle was therefore not confirmed. Similarly, no changes in spirometric values or airway responsiveness was seen with OCP use.[7] It should be noted however, that these studies were not conducted among women with PMA but, rather, among an unselected population of female asthmatics.

These results have lead some investigators to believe that PMA may be due to altered perception of somatic stimuli in the premenstrual period. There have been conflicting data, however, on the association between PMA and the presence of more severe PMS and/or dysmenorrhea in asthmatic women.[2,3] Prostaglandins have been implicated in the pathogenesis of both PMA and dysmenorrhea but treatment with a prostaglandin synthesis inhibitor (meclofenamate) did not prevent premenstrual exacerbation of asthma.[8]

Only recently, Tan et al[9] were, for the first time, able to establish increased airway responsiveness in the luteal phase as compared with the follicular phase in asthmatic females by using adenosine 5′-monophosphate (AMP) challenge. Unlike histamine and methacholine, which act as direct smooth muscle stimulants, AMP causes bronchoconstriction indirectly through mast cell activation. The authors speculated that sex hormones may affect asthma by sensitizing the adenosine receptors on the surface of mast cells but failed to demonstrate a statistically significant correlation between hormone levels and the degree of change in airway responsiveness. Interestingly, a comparison between asthmatic women with natural menstrual cycles and those taking OCP revealed absence of increased airway responsiveness to AMP in the latter during the period corresponding to the luteal phase. Reduced diurnal variation in peak expiratory flow was also noted in this group.[10] This suggests that OCP, presumably by suppressing the endogenous hormonal fluctuations, may be able to bring about a stabilization of airway sensitivity and thus exert a beneficial effect on asthma. Contrary to this observation, a case report described a 26-year-old woman who had marked improvement of her "asthmatic bronchitis" and rhinitis after she stopped taking oral contraceptives.[1]

Several new studies have tried to elucidate the mechanism of PMA and the role of sex hormones in asthma. Tan et al[9] discovered that the up-regulation of lymphocyte β_2-adrenoceptor density and isoprenaline responsiveness, normally present during the luteal phase in healthy women, was absent in women with asthma. Furthermore, administration of exogenous progesterone during the follicular phase (when endogenous sex hormone levels are normally low) resulted in up-regulation of lymphocyte β_2-adre-

noceptors in normal women but produced a paradoxic down-regulation in asthmatic women.[11,12] This phenomenon was not observed with estrogen administration. The authors suggested that progesterone may play an important role in PMA, with high levels of the hormone in the luteal phase suppressing the bronchial β_2-adrenergic response thereby promoting asthma exacerbation. This hypothesis seems to be in discordance with three earlier case reports of therapeutic effect of intramuscular progesterone in patients with severe PMA.[13] It was felt that the precipitous fall of progesterone level during the late luteal phase might be responsible for PMA and IM progesterone was given to avoid this fall with benefit.

Other investigators have focused on the impact of estrogen on asthma. A recent study reported statistically significant improvement of premenstrual symptoms in premenopausal females with mild-to-moderate asthma after administration of exogenous estradiol in the premenstrual period (2 mg of estradiol orally on days 23 to 28).[14] The participating women had a significantly lower baseline PEFR in the premenstrual phase (day 26) than in midcycle (day 13); however, after estradiol administration this difference was no longer evident. A trend toward significant improvement in PEFR and FEV_1 ($.05<P<.2$ for both measurements) in the premenstrual/early menstrual period was noted with estradiol but the β_2-receptor density and function as well as catecholamine concentration were not significantly altered. The authors concluded that in asthma and/or PMA the administration of exogenous estrogen is associated with symptomatic improvement that does not appear to be β_2-receptor mediated. Of interest, one woman in this group had a paradoxic reaction with worsening of asthma symptoms as well as PEFR, and FEV_1 after estradiol administration.

The effect of estrogen on asthma in postmenopausal women has been studied with contradicting results. Case reports have noted either improvement[15] or worsening[16] of asthma with supplemental estrogen. Different studies have documented both subclinical deterioration of asthma[17] and inhibitory effect of estrogen replacement therapy on airway reactivity during estrogen replacement therapy in postmenopausal women.[18] A large prospective survey found higher age-adjusted risk of asthma among postmenopausal women who were former or past users of replacement hormones (conjugated estrogens with or without progesterone) as compared with never-users as well as increased risk of asthma with higher daily dose of estrogens.[19] Furthermore, in this study past use of OCP was independently associated with higher risk of developing asthma.

We feel strongly that in our case OCP was responsible for worsening of patient's asthma. Unlike the case report referenced above in which improvement was noted after OCP was discontinued, we observed both exacerbation with initiation of OCP as well as rapid improvement after it was stopped. Our impression is reinforced by the history of poor tolerance to OCP in the past. Our study was limited by the patient's reluctance to undergo rechallenge and it is not possible to estimate the relative contribution of prednisone and OCP discontinuation on patient's asthma.

CONCLUSION

It appears that the weight of evidence points to a possible beneficial effect of OCP and/or exogenous sex hormones on PMA in the majority of premenopausal women whereas the effect of sex hormones on asthma in postmenopausal women is quite controversial. On the other hand, our report as well as other observations[1,14] suggest that there may be a subset of premenopausal women in whom administration of OCP and/or exogenous sex hormones can potentially produce worsening of asthma. This emphasizes the need for the clinician to be aware of the possible interactions between OCP and/or exogenous sex hormones and asthma.

REFERENCES

1. Horan JD, Lederman JJ. Possible asthmogenic effect of oral contraceptives. Can Med Assoc J 1968;99:130–131.
2. Eliasson O, Scherzer HH, DeGraff AC. Morbidity in asthma in relation to the menstrual cycle. J Allergy Clin Immunol 1986;77:87–94.
3. Gibbs CJ, Coutts II, Lock R, et al. Premenstrual exacerbation of asthma. Thorax 1984;39:833–836.
4. Skobeloff EM, Spivey WH, Silverman R, et al. The effect of the menstrual cycle on asthma presentations in the emergency department. Arch Intern Med 1996;156:1837–1840.
5. Weinmann GG, Zacur H, Fish JE. Absence of changes in airway responsiveness during the menstrual cycle. J Allergy Clin Immunol 1987;79:634–638.
6. Pauli BD, Reid RL, Munt PW, et al. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. Am Rev Respir Dis 1989;140:358–362.
7. Juniper EF, Kline PA, Roberts RS, et al. Airway responsiveness to methacholine during the natural menstrual cycle and the effect of oral contraceptives. Am Rev Respir Dis 1987;135:1039–1042.
8. Eliasson O, Densmore MJ, Scherzer HH, DeGraff AC Jr. The effect of sodium meclofenamate in premenstrual asthma: a controlled clinical trial. J Allergy Clin Immunol 1987;79:909–918.
9. Tan KS, McFarlane LC, Lipworth BJ. Loss of normal cyclical beta 2-adrenoceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. Thorax 1997;52:608–611.
10. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. Am J Respir Crit Care Med 1997;155:1273–1277.
11. Tan KS, McFarlane LC, Coutie WJ, Lipworth BJ. Effects of exogenous female sex steroid hormones on lymphoyte beta 2-adrenoceptors in normal females. Br J Clin Pharmacol 1996;41:414–416.
12. Tan KS, McFarlane LC, Lipworth BJ. Paradoxical down-regulation and desensitization of beta 2-adrenoceptors by exogenous progesterone in female asthmatics. Chest 1997;111:847–851.

13. Benyon HLC, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma. Effect of intramuscular progesterone. Lancet 1988;2:370–372.
14. Chandler MH, Schuldheisz S, Phillips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function, and beta 2-receptors. Pharmacotherapy 1997;17: 224–234.
15. Myers JR, Sherman CB. Should supplemental estrogens be used as steroid-sparing agents in asthmatic women? Chest 1994;106:318–319.
16. Collins LC, Peiris A. Bronchospasm secondary to replacement estrogen therapy. Chest 1993;104:1300–1302.
17. Lieberman D, Kopernic G, Porath A, et al. Sub-clinical worsening of bronchial asthma during estrogen replacement therapy in asthmatic post-menopausal women. Maturitas 1995;21: 153–157.
18. Lieberman D, Kopernic G, Porath A, et al. Influence of estrogen replacement therapy on airway reactivity. Respiration 1995;62:205–208.
19. Troisi RJ, Speizer FE, Willett WC, et al. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. Am J Respir Crit Care Med 1995;152:1183–1188.

John Oppenheimer, MD
Pulmonary and Allergy Associates
101 Madison Avenue
Suite 205
Morristown, NJ 07960