

REVIEW ARTICLE

## Premenstrual Asthma: Emphasis on Drug Therapy Options

Amy M. Redmond, Pharm.D.,<sup>1,#</sup> Alan W. James, M.D.,<sup>2</sup>  
Shambria Haynie Nolan, Pharm.D.,<sup>1</sup> and Timothy H. Self, Pharm.D.<sup>2,\*</sup>

<sup>1</sup>UT Bowld Hospital, Memphis, Tennessee, USA

<sup>2</sup>University of Tennessee Health Science Center, Memphis, Tennessee, USA

### ABSTRACT

Premenstrual asthma is quite common, affecting up to 40% of women. Some studies suggest exacerbations of asthma requiring emergency department visits or hospitalizations are more common in the perimenstrual phase. Several drug treatment modalities for premenstrual asthma have been evaluated. Drug therapies that may be beneficial include leukotriene receptor antagonists, long acting inhaled beta<sub>2</sub> agonists, progesterone, estradiol, and gonadotropin-releasing hormone (GnRH) analogs. Further double-blind, randomized, placebo-controlled studies are required before the optimal drug therapy for premenstrual asthma is established.

*Key Words:* Premenstrual asthma; Drug therapy.

### INTRODUCTION

Premenstrual asthma was first reported over 70 years ago as a single case in one of the original descriptions of premenstrual syndrome (1). In 1938, Claude and Allemany Vall (2) further described premenstrual asthma (PMA). Because some patients experience decline in asthma control during menstruation, some authors refer to PMA as perimenstrual asthma (3).

Several groups of investigators have conducted studies aimed at determining the incidence of PMA (Table 1). The data suggest that PMA is quite common, occurring in approximately 40% of women with asthma (4). and that patients (and likely many clinicians) need heightened awareness of this potential problem (3,5–10).

In addition to asthma, several other disease states are affected by the menstrual cycle, including epilepsy, rheumatoid arthritis, irritable bowel syndrome,

<sup>#</sup>Current address: St. Francis Hospital, Memphis, Tennessee, USA.

<sup>\*</sup>Correspondence: Timothy H. Self, Pharm.D., Professor of Clinical Pharmacy, University of Tennessee Health Science Center, 26 S Dunlap St., Ste 210, Memphis, TN 38163, USA; Fax: (901) 448-6064; E-mail: tself@utmem.edu.

**Table 1.** Studies examining incidence of premenstrual asthma.\*

| Study                | Incidence of PMA |
|----------------------|------------------|
| Shames et al. (3)    | 28%              |
| Rees, L. (5)         | 32%              |
| Hanley (6)           | 35%              |
| Gibbs et al. (7)     | 40%              |
| Agarwal and Shah (9) | 23%              |
| Forbes et al. (10)   | 8%               |

\*See also Refs. (8,26,31,33,34) regarding ED visits and hospitalizations.

diabetes, migraine, depression, acne, and multiple sclerosis (11,12). Disorders showing cyclic variation associated with menstruation are easily affected by external triggers and often display relapsing courses of worsening symptoms.

### ETIOLOGY OF PREMENSTRUAL ASTHMA

Although the etiology of PMA is not established, there are plausible theories. Most investigation has obviously focused on hormonal changes during the menstrual cycle. The ratio of asthma in girls to boys increases dramatically at puberty, further suggesting a role of the menstrual cycle (13,14).

Other studies have focused on airway inflammation and reduced response to inhaled  $\beta_2$  agonists in PMA patients.

During a normal menstrual cycle, progesterone levels peak seven days before the onset of menses, followed by a rapid reduction in levels prior to menstruation (15). There are limited data suggesting both bronchodilator and anti-inflammatory effects of progesterone (16–18). Thus, one of several potentially contributing factors to PMA is the low level of progesterone. Evidence for increased airway inflammation in patients with PMA has been demonstrated by increased levels of eosinophils in sputum and increased fractionated exhaled nitric oxide (19). Studies have been conflicting regarding bronchial hyperreactivity and the effect of the menstrual cycle (8,20–22). It is pertinent to note that the menstrual cycle affects reactions to skin-prick testing with allergens and histamine (23).

In women who do not have asthma, there is increased  $\beta_2$  receptor density and responsiveness to stimulation in the luteal phase (24). However, in

women with asthma, this upregulation is lost, and one report suggests a paradoxical downregulation caused by exogenous progesterone (20,25).

In addition, patients with PMA do not have significant differences in  $\beta_2$  receptor density and responsiveness to isoproterenol during the luteal and follicular phases (26).

Since endogenous sex hormones affect PMA, it is logical to examine the possible effect of exogenous hormones on asthma. Lange et al. (27) did not find an effect of oral contraceptives in premenopausal women with asthma and only a relatively weak association with hormone replacement therapy (HRT) and asthma in postmenopausal patients. A possible relationship between HRT and asthma in postmenopausal women is controversial (27–30).

### EMERGENCY DEPARTMENT AND HOSPITALIZATION RATES ASSOCIATED WITH GENDER DIFFERENCES AND WITH PMA

After puberty, females have an increased incidence of emergency department (ED) visits and hospitalizations for asthma compared to males (31–36). Eliasson et al. (31) reported perimenstrual worsening of symptoms in 33% of 57 women with asthma. Of the women with PMA, 68% had a history of hospitalization for asthma. Among women without PMA, only 25% had a history of hospitalization due to asthma. In 1992, Skobeloff et al. (32) found a higher hospital admission rate for adult females versus males (nearly 3:1 ratio for ages 20–50), and suggested a potential role of hormonal differences. Skobeloff et al. (33) followed that study with an examination of the effect of the menstrual cycle on ED visits for asthma. In 182 women with ED visits, there was a dramatic increase in ED visits for asthma during the perimenstrual interval (46%) versus the postovulatory interval (10%). In contrast, Zimmerman et al. (34) did not find an increase in ED visits for asthma in 288 women during the perimenstrual phase (21%), but rather found more ED visits in the preovulatory phase (33%).

A 10-year analysis of patients (age range 18–50 years) admitted at least twice with asthma or status asthmaticus showed that high-risk female patients were admitted twice as often and had longer hospital stays than their male counterparts (35). In a study of the western New York state region, females over 15 years of age had admission rates for asthma twice those of males (36).

**Table 2.** Drug therapy options for PMA.\*

---

|                                            |
|--------------------------------------------|
| Progesterone IM (15,37)                    |
| Oral contraceptives (38–40)                |
| Estradiol (26)                             |
| GnRH** (45–48)                             |
| Leukotriene receptor antagonist (48,49)    |
| Long-acting inhaled $\beta_2$ agonist (50) |

---

\*Studies and cases suggestive of positive benefit.

\*\*Gonadotrophin releasing hormone.

## DRUG TREATMENT OPTIONS

Despite being treated with the standard of care, many women with PMA may still suffer frequent exacerbations resulting in diminished quality of life, unscheduled office visits, ED visits, or hospitalizations. Alternative or add-on treatment modalities have been suggested to aid in the reduction of exacerbations in these patients. Suggested therapies include progesterone, oral contraceptives, gonadotropin-releasing hormone analogues, leukotriene modifiers, sodium meclizemate, and long-acting inhaled  $\beta_2$  agonists. Further research is required to establish the optimal drug therapy for PMA (Table 2).

### Progesterone/Oral Contraceptives

Beynon et al. (15) reported three cases of successful treatment of severe PMA exacerbations with intramuscular (IM) progesterone. These women, ages 23, 33, and 48 had been unresponsive to high dose systemic corticosteroid administration premenstrually, but responded well to progesterone 100 mg IM daily (two patients) and Depo-Provera 600 mg IM twice weekly (one patient). Lam and Huang (37) also reported successful treatment of PMA with progesterone 75 mg IM daily in a 39 year-old. In potential conflict with these case reports, Tan et al. (25), as previously noted, found a paradoxical down-regulation and desensitization of  $\beta_2$  receptors by exogenous progesterone in female asthma patients. However, as Tan et al. (25) point out in their discussion, other potential beneficial effects of progesterone may outweigh the effect on  $\beta_2$  receptors.

Tan et al. (38) conducted a study comparing airway reactivity and peak flow variability in asthmatics with natural menstrual cycles and those taking oral contraceptive pills (OCP). Patients taking OCP

had cyclical airway reactivity changes and a decrease in peak expiratory flow (PEF) at nighttime. The same group of investigators also conducted a study looking at whether or not combined OCPs alter  $\beta_2$ -adrenoceptor regulation and function. Results of this study indicated that the OCPs did not alter the function or regulation of the  $B_2$ -adrenoceptors in female asthmatics (39). Case reports regarding an effect of OCP on PMA have been conflicting (40–42).

Ensom et al. (43) were unable to show a beneficial effect of estradiol in 12 women with documented PMA but otherwise mild asthma. Further trials in women with PMA and more severe asthma were suggested by the authors.

### Gonadotropin-Releasing Hormone (GnRH) Analogs

The use of long acting GnRH analogues can suppress GnRH secretion through negative feedback. Reduced GnRH leads to a inhibition of the synthesis of leuteinizing hormone and follicle-stimulating hormone, resulting in a reversible amenorrhea state (44). Three case reports described the use of GnRH analogues in women with premenstrual asthma (45–47). All three women (32, 41, and 45 years of age) had a history of long standing asthma with worsening symptoms in recent years. The women suffered frequent exacerbations requiring hospitalization occurring just prior to ovulation. After the exacerbations were linked to menstruation, the women were given GnRH analogues and amenorrhea was achieved. The severity and rate of exacerbations were decreased in all three women as measured by hospitalizations, PEF, and required prednisone dose. Due to increased risk of osteoporosis with the use of GnRH analogues, two of the women were given cyclic HRT and the third was given HRT consisting of estrogen alone. The women experienced a decline in their asthma control when challenged with the HRT. One of the women placed on cyclic HRT was able to tolerate continuous low-dose HRT consisting on estrogen and progesterone for prevention of osteoporosis and asthma was controlled with continued GnRH analogue (45). The other patient given cyclic HRT eventually underwent an ovariectomy and hysterectomy to control her asthma due to the financial burden associated with the GnRH analogue and was treated with unopposed estrogen for osteoporosis prevention (46). The patient given estrogen alone was continued on GnRH for asthma control and given a bisphosphate for osteoporosis prevention (47).

GnRH analogues prevent the cyclic release of hormones that can contribute to bronchial constriction.

GnRH analogues may be beneficial for women with frequent premenstrual asthma exacerbations, yet controlled studies are needed to confirm the benefit of GnRH analogues.

#### Leukotriene Modifiers

Nakasato et al. (48) showed that serum leukotriene ( $\text{LTC}_4$ ) levels were significantly higher in five patients with PMA experiencing an exacerbation compared with levels taken during the week representing the midpoint of their menstrual cycle. These patients were given a leukotriene receptor antagonist (pranlukast) and a clinically significant improvement in PEF and asthma severity scores were seen in all five patients (48). Similarly, Dean et al. (49) reported that 38 patients with PMA clinically improved with the addition of a leukotriene receptor antagonist (montelukast) yet these patients experienced no improvement when the dose of their inhaled corticosteroid had been increased. While further study is needed to verify the efficacy of leukotriene receptor antagonists in PMA, these initial reports are encouraging.

#### Long-Acting Inhaled $\beta_2$ Agonists

Magadle et al. (50) reported the use of salmeterol in women with PMA. The study started with 67 women with asthma who were all treated with inhaled corticosteroids and short acting inhaled  $\beta_2$ -agonists as needed. After recording PEF during three consecutive menstrual cycles, it was determined that 13 of the women experienced  $>20\%$  decrease in PEF during the premenstrual week as compared to PEF mid-cycle. The 13 patients with premenstrual exacerbations were continued on inhaled corticosteroids and given salmeterol or placebo for ten days prior to menses for two menstrual cycles. The patients were then switched to the alternative treatment for two menstrual cycles and changes in PEF prior to menses and consumption of short-acting  $\beta_2$ -agonists were compared. Seven patients had a complete response to the long-acting  $\beta_2$ -agonist resulting in decreases in PEF  $<10\%$ . There were two patients who recorded a partial response with changes in PEF  $>10\%$  yet  $<20\%$ . Four patients recorded no difference with active drug compared to placebo. The need for short-acting  $\beta_2$ -agonists decreased according to the response seen in the patient. Premenstrual asthma exacerbations were either totally or partially prevented in 70% of the women studied (50). Although the addition of long-acting  $\beta_2$ -agonists for ten days prior to menses was not completely beneficial in all 13 women, the dose of inhaled corticosteroids and rescue

inhaler use can be reduced in patients who response to this add-on therapy.

#### Sodium Meclofenamate

Eliasson et al. (51) studied the effect of sodium meclofenamate, a nonsteroidal anti-inflammatory agent used to inhibit prostaglandin synthesis, on premenstrual exacerbations in women treated for dysmenorrhea. The study was based on the involvement of prostaglandins in both asthma and dysmenorrhea and the possible association between the two. The study was a four-month placebo-controlled, double-blinded, crossover trial that involved 20 women with self-reported premenstrual worsening of asthma. Patients received 100 mg of sodium meclofenamate or placebo three times a day for 14 days for two consecutive months starting as close to day 21 of the menstrual cycle; patients were then given the treatment not already received for two consecutive months. The outcomes measured were changes in PEF, asthma medication use, and asthma and menstrual symptoms. Changes in all four measured outcomes did not reach statistical significance. The researchers concluded that the inhibiting prostaglandin synthesis did not prevent premenstrual asthma attacks (51). The same group was unable to show a benefit in an earlier double-blind, randomized, placebo-controlled trial (52).

Forbes et al. (10) investigated if women with PMA were more likely to take non-steroidal anti-inflammatory drugs (NSAIDs) to treat menstrual symptoms compared to other women with asthma. Questionnaires were mailed to women seen at one of the included practice sites who were prescribed inhaled  $\beta_2$ -agonists within the last two years. Of the 461 women with asthma who responded to the questionnaire, 38 women reported having PMA. A total of 185 of the women reported using NSAIDs with the incidence being slightly lower in the women with PMA. There was no association found between the use of aspirin or NSAIDs and the incidence of premenstrual exacerbations (10). Based on studies to date, while NSAIDs do not appear to be a contributing factor to PMA, they are not a viable treatment option in patients with PMA.

#### DISCUSSION

Although debate continues regarding the incidence and etiology of PMA, it is clear that PMA is a real problem that needs to be addressed further. Interestingly, menstruation is barely mentioned in national asthma guidelines as one of the factors that can influence asthma

severity (53). Further clinical research is needed to establish optimal management of this problem. Since our paper was first written, a very recent report has given further evidence that PMA may be associated with near-fatal asthma (54).

## CONCLUSIONS

In addition to standard long-term management of asthma (53,55), pharmacotherapies that may be of benefit in PMA include leukotriene receptor antagonists; long acting inhaled  $\beta_2$  agonists; progesterone; estradiol; and gonadotropin-releasing hormone (GnRH) analogs. Further double-blind, randomized, placebo-controlled studies are required before the optimal drug therapy for premenstrual asthma is established.

## REFERENCES

1. Frank RT. The hormonal causes of premenstrual tension. *Arch Neurol Psychiatr* 1931; 26:1053–1057.
2. Claude F, Allemany Vall R. Asthme et menstruation. *Pr Med* 1938; 38:755–759.
3. Shames RS, Heilbron DC, Janson SL, Kishiyama JL, Au DS, Adelman DC. Clinical differences among women with and without self-reported perimenstrual asthma. *Ann Allergy Asthma & Immun* 1998; 81:65–72.
4. O'Conner BJ. Premenstrual asthma still poorly understood. *Thorax* 1997; 52(7):591–592.
5. Rees L. An etiological study of premenstrual asthma. *J Psychosom Res* 1963; 7:191–197.
6. Hanley S. Asthma variation with menstruation. *Br J Dis Chest* 1981; 75:306–308.
7. Gibbs C, Coutts I, Lock R, Finnegan OC, White RJ. Premenstrual exacerbation of asthma. *Thorax* 1984; 39:833–836.
8. Pauli BD, Reid RL, Munt PW, Wigle RD, Forkert L. Influence of the menstrual cycle on airway function in asthmatic and normal subjects. *Am Rev Respir Dis* 1989; 140:358–362.
9. Agarwal AK, Shah A. Menstrual-linked asthma. *J Asthma* 1997; 34:539–545.
10. Forbes L, Jarvis D, Bumey P. Is pre-menstrual asthma related to use of aspirin or non-steroidal anti-inflammatory drugs? *Respir Med* 2000; 94:828–829.
11. Case AM, Reid RL. Effects of the menstrual cycle on medical disorders. *Arch Intern Med* 1998; 158:1405–1412.
12. Ensom MHH. Gender-based differences and menstrual cycle-related changes in specific disease: implications for pharmacotherapy. *Pharmacotherapy* 2000; 20:523–539.
13. Dawson B, Horobin G, Illsley R, Mitchell R. A survey of childhood asthma in Aberdeen. *Lancet* 1969; 1:827–830.
14. Venn A, Lewis S, Cooper M, Hill J, Britton J. Questionnaire study of effect of sex and age on the prevalence of wheeze and asthma in adolescence. *BMJ* 1998; 316:1945–1946.
15. Beynon HI, Garbett ND, Barnes PJ. Severe premenstrual exacerbations of asthma: effect of intramuscular progesterone. *Lancet* 1988; 2:370–372.
16. Foster PS, Goldie RG, Paterson JW. Effect of steroids on beta-adrenoceptor-mediated relaxation of pig bronchus. *Br J Pharmacol* 1983; 78:441–445.
17. Fox SD, Adams WC, Brookes KA, Lasley BL. Enhanced response to ozone exposure during the follicular phase of the menstrual cycle. *Environ Health Perspect* 1993; 101:242–244.
18. Kalkhoven E, Wissink S, van der Saag PT, van der Burg B. Negative interaction between RelA (p65) subunit of NF-kappaB and the progesterone receptor. *J Biol Chem* 1996; 271:6217–6224.
19. Oguzulgen K, Turktas H, Erbas K. Airway inflammation in premenstrual asthma. *J Asthma* 2002; 39:517–522.
20. 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.
21. Weinmann G, Zacur H, Fish J. Absence of changes in airway responsiveness during the menstrual cycle. *J Allergy Clin Immunol* 1987; 79:634–638.
22. Juniper EF, Klie PA, Roberts RS, Hargreave FE, Daniel EE. Airway responsiveness to methocholine during the natural menstrual cycle and the effects of oral contraceptives. *Am Rev Respir Dis* 1987; 135:1039–1042.
23. Kalogeromitros D, Katsarou A, Armenaka M, Rigopoulos D, Zapanti M, Stratigos I. Influence of the menstrual cycle on skin-prick test reactions to histamine, morphine and allergen. *Clin Exp Allergy* 1995; 25:461–466.
24. Wheeldon NM, Newnham DM, Coutie WJ, Peters JA, McDevitt DG, Lipworth BJ. Influence of sex-steroid hormones on the regulation of lymphocyte  $\beta_2$  adrenoceptors in normal females. *Br J Clin Pharmacol* 1994; 37:583–588.
25. Tan KS, McFarlane LC, Lipworth BJ. Paradoxical

- down-regulation and desensitization of  $\beta_2$  adrenoreceptors by exogenous progesterone in female asthmatics. *Chest* 1997; 111:847–851.
26. Chandler MMH, Schuldeisz S, Phillips BA, Muse KN. Premenstrual asthma: the effect of estrogen on symptoms, pulmonary function and  $\beta_2$  receptors. *Pharmacotherapy* 1997; 17:224–234.
  27. Lange P, Parner J, Prescott E, Suppli Ulrik C, Vestbo J. Exogenous female sex hormones and risk of asthma and asthma-like symptoms: a cross sectional study of the general population. *Thorax* 2001; 56:613–616.
  28. Troisi RJ, Speizer FE, Willett WC, Trichopoulos D, Rosner B. Menopause, postmenopausal estrogen preparations, and the risk of adult-onset asthma. A prospective cohort study. *Am J Respir Care Med* 1995; 152(4):1183–1188.
  29. Carlson CL, Cushman M, Enright PL, Cauley JA, Newman AB. Hormone replacement therapy is associated with higher FEV<sub>1</sub> in elderly women. *Am J Respir Crit Care Med* 2001; 163:423–428.
  30. Hepburn MJ, Dooley DP, Morris MJ. The effects of estrogen replacement therapy on airway function in postmenopausal asthmatic women. *Arch Intern Med* 2001; 161:2717–2720.
  31. Eliasson O, Scherzer HH, DeGraff AC. Morbidity in asthma in relation to the menstrual cycle. *J Allergy Clin Immunol* 1986; 77:87–94.
  32. Skobeloff EM, Spivey WH, St. Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA* 1992; 268:3437–3440.
  33. Skobeloff EM, Spivey WH, Silverman R, Eskin BA, Harchelroad F, Alessi TV. The effect of the menstrual cycle on asthma presentations in the emergency department. *Arch Intern Med* 1996; 156:1837–1840.
  34. Zimmerman JL, Woodruff PG, Clark S, Camargo CA. Relation between phase of menstrual cycle and emergency department visits for acute asthma. *Am J Respir Care Med* 2000; 162:512–515.
  35. Trawick DR, Holm C, Wirth J. Influence of gender on rates of hospitalization, hospital course, and hypercapnea in high-risk patients admitted for asthma: a 10-year retrospective study at Yale-New Haven Hospital. *Chest* 2001; 119:115–119.
  36. Lwebuga-Mukasa JS, Pszonak R. Patterns of inpatient and outpatient care for asthma in Erie and Niagara counties, western New York State. *J Asthma* 2001; 38:155–160.
  37. Lam SM, Huang SC. Premenstrual asthma: report of a case with hormonal studies. *J Microbiol Immunol Infect* 1998; 31:197–199.
  38. 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(4):1273–1277.
  39. Tan KS, McFarlane LC, Lipworth BJ.  $\beta_2$ -adrenoreceptor regulation and function in female asthmatic patients receiving the oral combined contraceptive pill. *Chest* 1998; 113:278–282.
  40. Matsuo N, Shimoda T, Matsuse H, Kohno S. A case of menstruation-associated asthma: treatment with oral contraceptives. *Chest* 1999; 116:252–253.
  41. Derimanov GS, Oppenheimer J. Exacerbation of premenstrual asthma caused by an oral contraceptive. *Ann Allergy Asthma & Immun* 1998; 81:243–246.
  42. Myers JR, Sherman CB. Should supplemental estrogens be used as steroid-sparing agents in asthmatic women? *Chest* 1994; 106:318–319.
  43. Ensom MHH, Chong G, Zhou D, Beaudin B, Shalansky S, Bai TR. Estradiol in premenstrual asthma: a double-blind, randomized, placebo-controlled crossover study. *Pharmacotherapy* 2003; 23:561–571.
  44. Lyall H, Campbell-Brown M, Walker JJ. GnRH analogue in everyday gynecology: is it possible to rationalize its use? *Acta Obstet Gynecol Scand* 1999; 78:340–345.
  45. Blumenfeld Z, Bentur L, Yoffe N, Alroy G, Rubin AH. Menstrual asthma: use of a gonadotropin-releasing hormone analogue for the treatment of cyclic aggravation of bronchial asthma. *Fertil Steril* 1994; 62:197–200.
  46. Edwards AL, Rose MS, Donovan LE, Ford GT. Premenstrual exacerbation of life-threatening asthma: effect of gonadotropin releasing hormone analogue therapy. *Can Respir J* 1996; 3(3):203–206.
  47. Murray RD, New JP, Barber PV, Shalet SM. Gonadotropin-releasing hormone analogues: a novel treatment for premenstrual asthma. *Eur Respir J* 1999; 14:966–967.
  48. Nakasato H, Ohru T, Sekizawa K, Matsui T, Yamaya M, Tamura G, Sasaki H. Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist. *J Allergy Clin Immunol* 1999; 104:585–588.
  49. Dean N, Sadat A, Nunnery S, Umesi O, Harris K. Montelukast provides superior efficacy for perimenstrual asthma exacerbations not controlled by inhaled steroids [abstract]. *Chest* 2001; 120:208S.
  50. Magadle R, Berar-Yanay N, Weiner P. Long-acting bronchodilators in premenstrual exacerbation of asthma. *Respir Med* 2001; 95:740–743.

51. Eliasson O, Densmore MJ, Scherzer HH, DeGraff AC. The effect of sodium meclofenamate in premenstrual asthma: a controlled clinical trial. *J Allergy Clin Immunol* 1987; 79(6):909–918.
52. Eliasson O, Longo M, Dore-Duffy P, Densmore MJ, DeGraff AC Jr. Serum 13-14-diOH-15- prostaglandin F<sub>2</sub>alpha and airway response to meclofenamate and metaproterenol in relation to the menstrual cycle. *J Asthma* 1986; 23:309–319.
53. Expert Panel Report 2. Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health, 1997. NIH Publication No. 97-4051.
54. Guidelines for the Diagnosis and Management of Asthma-Update on Selected Topics 2002. Bethesda, MD: National Institutes of Health, 2002. NIH Publication No. 02-5075.
55. Martinez-Moragon E, Plaza V, Serrano J, et al. Near-fatal asthma related to menstruation. *J Allergy Clin Immunol* 2004; 113:242–244.