

Letters

SEVERE ACUTE ASTHMA ASSOCIATED WITH RAW MEAT CUTTING

Symptoms related to food allergen ingestion are linked to diffusion of the responsible allergens across the digestive barrier into the entire body. In some cases, especially in occupational asthma, respiratory symptoms can be related to the penetration of food allergens into the bronchial airways. Several mechanisms may be involved: the presence of food allergens after boiling or cooking various foods or exposure to food additives or contaminants such as carmine in butcher's shops or fine volatile particles such as spices¹ or egg.² Allergy to mammal meat is rare, and allergens³⁻⁵ are strongly modified by heating and cooking, as suggested by Fiocchi et al,⁶ whose data apply to beef allergy secondary to oral ingestion. The problem differs when symptoms occur after inhalation. We report 2 cases of respiratory manifestations after the handling and cutting of raw meat.

A 26-year-old woman was admitted to the hospital on several occasions for acute severe asthma after preparing couscous and, specifically, after cutting raw beef and lamb before cooking. Pulmonary function tests revealed an obstructive pattern. At her first visit to the emergency department, she had significant urticaria and facial edema, rhinoconjunctivitis, and mostly a rapidly progressive and severe asthma attack. All these symptoms were triggered during the handling of raw lamb. Skin prick test (SPT) results were positive for *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, and horse epithelia and for several raw meats (lamb, beef, and pork). The patient reported that she could eat cooked lamb and beef without any adverse effects. Total IgE level was 814 IU/L, and specific IgE antibodies (CAP System; Pharmacia, Uppsala, Sweden) were positive for lamb and pork (15.1 and 30.6 IU/mL, respectively) and only weakly positive for beef (0.4 IU/mL). A realistic provocation test was then performed. Raw lamb was handled and cut into small pieces by a nurse in the presence of the patient, which provoked an immediate cutaneous reaction (urticaria), sudden rhinitis, and conjunctivitis with acute bronchospasm. Peak expiratory flow rate values fell rapidly from 450 to 270 L/min (38% reduction). The positive response confirmed the link between cutaneous, nose, eye, and bronchial manifestations and the preparation of raw lamb.

A 41-year-old cook in a restaurant whose job consisted exclusively of preparing and cutting raw meat had symptoms only during work time. Ten minutes after an unusual ingestion of raw meat, the patient noted rhinitis, conjunctivitis, breathlessness, localized itching, edema, and an episode of laryngeal edema with increasing dyspnea. Aeroallergen SPT results were negative for a panel of 13 food allergens. Results of SPTs with raw veal, beef, lamb, and pork were positive. Results of SPTs with beef, pork, horse, dog, and cat albumins were positive at dilutions of 10⁻⁵ g/L. Total IgE level was 515 IU/L, and specific IgE antibodies were positive for beef (class II) and pork (class I). The patient had a negative methacholine test result after a 15-day holiday, but a provocation test to methacholine performed after 3 weeks back at work showed a significant decline in forced expiratory volume in 1 second (FEV₁) (provocation concentration that caused a decrease in FEV₁ of 20%, 1 mg/mL), demonstrating bronchial hyperresponsiveness.

The exact nature of allergens dispersing during the handling of raw beef is unknown and needs identification of allergen molecules present in the environment surrounding the cutting of raw meat and inhaled by the patient. Crab-processing workers may develop respiratory manifestations as specific IgE antibodies to crab proteins. A study performed aboard crab-processing vessels in Alaska⁷ quantified crab allergen concentrations and showed that the highest amounts were measured in air samples at butchering workstations. Similar conditions were observed in our 2 clinical cases with exposure to raw meat during the cutting phase. Another example is given by fish proteins, which become nebulized simply by being exposed to the atmosphere.⁸ Using a competitive IgE immunoassay to analyze environmental samples at a fish market, Taylor et al⁹ measured levels of fish allergen ranging from 2 to 25 ng/m³.

Exposure to raw meat has the potential to induce, without any ingestion, anaphylactic symptoms and acute severe asthma. The handling and cutting of raw meat are likely to allow the release of meat aerosolized allergens into the environment, as already demonstrated in crab-exposed workers. The exact nature of the raw nebulized antigens deserves to be evaluated. The cases reported herein underline the clinical importance of the inhalation route of food allergens.

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TOLERANCE TO WATER BUFFALO MILK IN A CHILD WITH COW MILK ALLERGY

Cow milk allergy is the most common food allergy affecting toddlers, with a prevalence of 2% to 3%.¹ Alternatives to cow milk include hydrolyzed or elemental cow milk, soy milk, and rice milk. Other mammalian sources, such as goat milk and sheep milk, have shown a high degree of cross-reactivity.^{2,3} Milk from water buffalo (*Bubalus bubalis*) is a common drinking milk in many developing countries and is the main component of buffalo mozzarella eaten throughout the world. In vitro studies^{4,5} demonstrate a similar proteomic makeup and suggest antibody cross-reactivity between cow milk and water buffalo milk proteins. Similarly, 1 human study⁶ showed a high degree of skin test positivity to water buffalo milk in patients with cow milk allergy. However, the use of water buffalo milk in these patients has never been further studied. We describe the first report of a child with cow milk allergy who tolerated water buffalo milk.

The patient is a 3-year-old boy followed up for cow milk allergy. At the age of 4 months, he developed immediate vomiting after drinking 4 oz of cow milk formula. He was transitioned to a partially hydrolyzed whey-based cow milk formula without any reaction. At 11 months of age, cow milk products were reintroduced into his diet. On this occasion, he developed facial erythema and diffuse urticaria within 30 minutes of ingestion of 8 oz of cow milk.

He was referred to our allergy program at the age of 20 months and was found to have a positive skin prick test (SPT) reaction (5-mm wheal) to cow milk extract (Greer Laboratories, Lenoir, North Carolina) and a negative SPT reaction to casein extract (Adamis Pharmaceutical Corp, San Diego, California) in the presence of negative saline and positive histamine controls (6-mm wheal). His total IgE level was 1,440 U/mL, with positive allergen specific IgE levels (ImmunoCap 250, Phadia AB, Portage, Michigan) to cow milk (4.99 kU/L), casein (2.09 kU/L), and the whey proteins α -lactalbumin (2.92 kU/L) and β -lactalbumin (0.78 kU/L).

Repeated SPTs were performed at the age of 2 years, and results continued to be positive for cow milk (5-mm wheal). Per parental request, the patient underwent SPT to water buffalo milk-based yogurt (Woodstock Water Buffalo Co, Woodstock, Vermont), and the results were negative. Subsequently, he passed an open food challenge to water buffalo milk-based yogurt. During the next year, he continued to strictly avoid cow milk and cow milk-containing products. He continued to consume water buffalo milk-based yogurt and cheese on a regular basis without any reaction.

At follow-up at 3 years of age, he had a negative SPT reaction to cow milk, with a reduction in his allergen specific IgE levels to cow milk (1.34 kU/L), casein (0.71 kU/L), α -lactalbumin (0.89 kU/L), and β -lactalbumin (<0.35 kU/L). He underwent an open food challenge to cow milk. During this challenge, he developed urticaria within 15 minutes of exposure to 15 mL of whole cow milk. The failure of this challenge was indicative of the persistence of his cow milk allergy.

To our knowledge, this is the first reported case of a patient with cow milk allergy who was clinically tolerant of water buffalo milk. Previous in vitro and SPT studies^{5,6} indicate that this scenario is unexpected. However, the true rate of water buffalo milk allergy in

cow milk-allergic patients is unknown because a clinical intervention study has never been performed.

It is also interesting that this patient tolerated partially hydrolyzed whey-based cow milk formula. These formulas are not typically recommended because they have been shown to be allergenic in 45% of patients with cow milk allergy.⁷ The present patient had allergen specific IgE antibodies to the whey proteins α -lactalbumin and β -lactalbumin; however, these levels were lower than to other cow milk proteins. Therefore, it is possible that this patient is allergic to whey; however, the partial hydrolysis has allowed for tolerance.

There exists a case report of a patient with the opposite scenario in that this patient was allergic to water buffalo milk but was tolerant of cow milk.⁸ That report, combined with our patient, suggests that there are allergenic proteins in cow milk that are not contained in water buffalo milk, and vice versa. This implies that other cow milk-allergic patients may tolerate water buffalo milk. Further clinical studies are required to determine whether water buffalo milk is a suitable alternative for children with cow milk allergy.

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LICHEN PLANUS ASSOCIATED WITH OMALIZUMAB ADMINISTRATION IN AN ADULT WITH ALLERGIC ASTHMA

A 63-year-old white woman was referred to the Allergy Service of Texas Children's Hospital for evaluation of recurrent lichen planus (LP). The patient's medical history was remarkable for a long history of steroid-dependent asthma, allergic rhinitis, osteoarthritis, hypertension, and hypercholesterolemia. Her serum IgE level was 55 kU/L, and omalizumab therapy was prescribed at Food and Drug

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Administration—approved recommended dosing. Medications at first dosing of omalizumab included montelukast, albuterol, cromolyn, beclomethasone (inhalation), cetirizine, fluticasone, diclofenac, esomeprazole, lisinopril, hydrochlorothiazide, and atorvastatin. She had no known allergies to these medications and had tolerated them for months. The patient received an omalizumab injection (300 mg) for allergic asthma control and experienced a generalized pruritus that persisted for 2 to 3 days (Table 1). She did not report this to her physician.

Administration of a second omalizumab injection resulted in a generalized pruritic rash with lacy, violaceous papules on her face and back that persisted 8 weeks. A skin punch biopsy specimen showed epidermal hyperkeratosis, hypergranulosis, irregular acanthosis, and occasional necrotic keratinocytes with bandlike lymphocytic infiltrate interspersed with frequent eosinophils involving the dermoepidermal junction, findings consistent with drug-induced LP (DiLP). The use of a nonsteroidal anti-inflammatory drug (NSAID) (diclofenac) for osteoarthritis and omalizumab was discontinued. During the next 3 to 4 months her lesions gradually disappeared.

Because NSAIDs have been implicated in DiLP, diclofenac was considered the cause of DiLP and a third omalizumab injection was administered. Within several days of injection, she again developed a generalized pruritic rash with lacy, violaceous papules on her face and extremities. In addition, her oral mucosa was involved with reticulated white streaks under her tongue and buccal mucosa. Use of omalizumab was discontinued, and the patient was referred to our clinic for an allergy evaluation.

Two months after the second DiLP episode, physical examination in our clinic revealed reticulated white streaks under her tongue and buccal mucosa. No rash was observed. Laboratory tests produced normal serum chemical, renal, and liver function results. Antibodies to hepatitis A, hepatitis B, and hepatitis C viruses and hepatitis B surface antigen were negative. Because omalizumab is produced in Chinese hamster ovary cell suspension culture,¹ the results of skin prick testing performed for hamster epithelia were negative.

LP is a chronic inflammatory T-lymphocyte-mediated disease. It is characterized by pruritic, violaceous, polygonal papules and plaques with characteristic fine white lines known as Wickham striae involving skin and mucous membranes.² Most cases of LP are idiopathic. However, malignancies,³ hepatitis C infection,⁴ autoimmune diseases, vaccinations,⁵ and numerous medications^{6–8} have been implicated in its cause.

The histopathology of LP typically reveals hyperkeratosis with characteristic bandlike infiltrate of inflammatory cells at the dermo-epidermal junction, irregular acanthosis, and hydropic degeneration of the basal cell layer. Inflammatory cells of LP are primarily composed of activated T cells (CD4⁺ and CD8⁺ lymphocytes, CD45RO⁺ memory effector cells).^{9,10} Several studies support an abnormal cell-mediated immune response to an antigen stimulus produced by epidermal Langerhans cells in susceptible individuals. Activated T lymphocytes and increased cytokine production within the lesion result in increased intercellular adhesion molecule-1 expression by keratinocytes and major histocompatibility complex class II antigens and contribute to tissue destruction.¹⁰ The presence of eosinophils in the cellular infiltrate of our patient's biopsy specimen suggests DiLP.

In DiLP the offending drug acts as a hapten, binding to keratinocytes and triggering a cellular immune response.¹¹ Identification of the causative agent in DiLP can be complicated by factors such as simultaneous drug exposure or drug-drug interactions. The latent period between drug administration and appearance of LP can range from 10 days to 24 months. Lesions may clear spontaneously despite drug therapy continuation or resolve in days or months after discontinuation of drug use. Recurrences are not uncommon. Differentiation of DiLP from idiopathic LP can be difficult. However, distinction may be possible by correlating the onset of the lesion to drug administration.¹²

Reported adverse effects of omalizumab include anaphylaxis,^{13,14} rash, diarrhea, nausea, vomiting, epistaxis, menorrhagia, and injection site reactions.¹⁴ DiLP due to omalizumab has not been previously reported. Our described patient developed DiLP after 2 challenges with omalizumab, and a causal relationship is proposed. First administration of omalizumab caused generalized pruritus that lasted a few days. A second dosing of omalizumab resulted in biopsy-documented LP. A third challenge with omalizumab again resulted in LP, this time with oral mucosa involvement.

We believe that the temporal relationship of cutaneous and oral lesions after 2 doses of omalizumab confirms a causal relationship. LP-type eruptions have been described in other disorders, including graft-vs-host disease and other immunodeficiency states. The immune modulator imatinib has been reported to cause oral and cutaneous lichenoid reactions.⁸ We postulate that omalizumab may result in DiLP through its immunomodulator function (ie, alteration of host immunity).

Table 1. Omalizumab-Induced Lichen Planus Symptom and Treatment Timeline

Omalizumab dose No.	Symptoms	Treatment	Duration of symptoms
1	Pruritus	None ^a	2–3 days
2 (1 month after dose 1)	Rash ^b Pruritus	Hold omalizumab and diclofenac Prednisone (oral) Topical steroid H ₁ -blocker ^d	8 weeks
3 (7 months after dose 2)	Rash ^b Pruritus Oral mucosa involvement	Hold omalizumab Prednisone (oral) Topical steroid H ₁ -blocker ^d	>2 months ^c

^a Reaction to dose 1 was not initially reported to the prescribing physician.

^b Lacy rash and papules on the face, trunk, and extremities.

^c No further omalizumab dosing and no return of lichen planus to date.

^d Histamine₁ blocker.

Although rare, the neoplastic transformation of LP has been reported.¹⁵ In clinical trials of omalizumab, malignant neoplasms (mostly solid tumors) were observed in 20 of 4,127 omalizumab-treated patients (0.5%) compared with 5 of 2,236 control patients (0.2%). The onset of most tumors preceded treatment with omalizumab, and 60% of tumors presented within less than 6 months of treatment.^{14,16} Omalizumab therapy was discontinued in this patient to prevent further recurrences of DiLP and a theoretical risk for LP-associated malignant transformation. Our observation suggests that omalizumab should be considered as a cause of DiLP.

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MONTELUKAST-ASSOCIATED CHURG-STRAUSS VASCULITIS: ANOTHER ASSOCIATED REPORT

A 37-year-old woman presented to her allergist's office after 6 months of dry cough. Before her appointment, she was treated sporadically with inhaled corticosteroids, albuterol, and antibiotics but showed no improvement. On evaluation, aeroallergen skin prick test results were negative; a complete blood cell count was normal, with 4% eosinophils; and her chest radiograph showed only peribronchial thickening. She was empirically administered montelukast for possible cough variant asthma.

Within 1 month, her cough began to worsen, and she developed dyspnea that required 2 pulse corticosteroid treatments for relief. Inhaled salmeterol and budesonide were added. Chest computed tomography revealed a left-sided suprahilar opacity. The patient was referred to a pulmonologist for bronchoscopy. At that visit, a repeated chest radiograph showed infiltrates in the left upper lobe and lingula, and lavage fluid from the bronchoscopy showed predominant eosinophilia. Shortly thereafter, the patient developed a vesicular rash on her head and arms, fever, myalgias, hemoptysis, pleuritic chest pain, and worsening dyspnea. On examination, she had distended neck veins with bilateral infiltrates and cardiomegaly on her chest radiograph.

On admission to the hospital, her echocardiogram showed a depressed left ventricular ejection fraction of 42% with a pericardial effusion. Pericardiocentesis yielded fluid with a differential count significant for eosinophilia of 42%. She also had peripheral eosinophilia of 24%. A biopsy specimen of the hand revealed necrobiotic collagen with granulomas and an eosinophilic infiltrate (Fig 1). The patient improved with administration of intravenous inotropes, diuretics, and corticosteroids. Montelukast use was discontinued. During the next year, she was weaned off oral corticosteroids, and she now has intermittent asthma that is controlled by daily inhaled mometasone therapy. She also developed nasal polyps that were treated successfully with surgery.

Churg-Strauss vasculitis (CSV) is a small- to medium-sized vessel vasculitis associated with asthma and peripheral eosinophilia. This patient had 4 of the 6 American College of Rheumatology criteria for a CSV diagnosis (asthma, peripheral eosinophilia, pulmonary infiltrates, and extravascular eosinophils),

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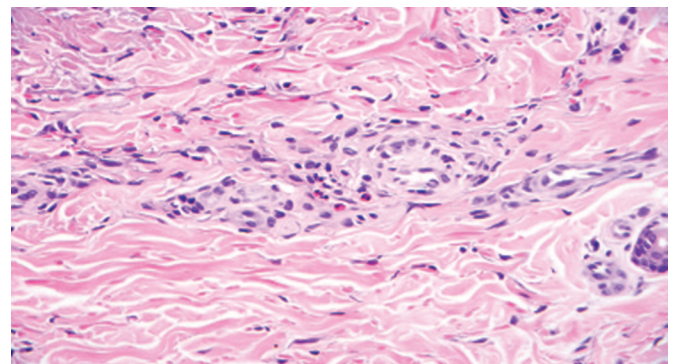


Figure 1. Perivascular eosinophils and granuloma formation in a skin biopsy sample, findings consistent with Churg-Strauss vasculitis.

and she later developed a fifth (nasal polyps). In patients with CSV, indicators of poor prognosis include cardiac and gastrointestinal involvement.¹ In a study by Guillevin et al,¹ 96 patients with CSV were followed up to evaluate outcomes. This study showed 39% mortality with myocardial disease, and most of these patients died during the acute phase of their illness. Corticosteroids are the first-line treatment for CSV, and remission rates are 80% to 90% with this therapy.

In the past decade, there seems to be an increase in the diagnosis of CSV with the introduction of leukotriene modifiers, such as montelukast. Wechsler et al² published a 6-patient case series in 2000 that concluded that the relationship is coincidental. The authors postulated that the vasculitic component of CSV is suppressed by corticosteroids and that the addition of montelukast allows for the withdrawal of corticosteroids, thus allowing the vasculitis to be "unmasked." Lofdahl et al³ showed in a double-blind, placebo-controlled trial that montelukast can allow for tapering of inhaled corticosteroids, but this may not be the case in all patients.

Other case reports have shown a diagnosis of CSV in association with montelukast while inhaled corticosteroids were not being weaned. Sabio et al⁴ described a 49-year-old patient who developed rash and duodenal necrotizing vasculitis 5 months after switching from salmeterol to montelukast. Villena et al⁵ described a patient who developed rash, eosinophilia, and bilateral pulmonary infiltrates 4 months after beginning montelukast treatment while taking inhaled corticosteroids and bronchodilators only. Solans et al⁶ described an asthmatic patient who had never received oral corticosteroids who developed CSV 4 months after initiating montelukast treatment.

In summary, this patient developed corticosteroid-dependent asthma and biopsy-proven CSV with a poor prognostic indicator of cardiac involvement after starting montelukast treatment. She survived with cessation of montelukast treatment, and currently her asthma is controlled with mometasone only. Although there is strong circumstantial evidence of a relationship in this patient, Weller et al⁷ showed in an extensive summary that no evidence exists to support the causation of CSV by leukotriene receptor antagonists. As cases continue to be reported, there should be further investigation to determine whether a true relationship exists.

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β -AGONIST USE AS AN INDICATOR OF CHANGE IN ASTHMA CONTROL DURING PREGNANCY

Asthma is a common chronic disease that affects care during pregnancy in approximately 8% of pregnant women.¹ Asthma during pregnancy has adverse effects on both mothers and infants, including increased risk for preeclampsia, pregnancy-induced hypertension, preterm delivery, and birth weight of less than 2,500 g.^{2,3} A commonly quoted generalization based on data from several small and select study populations is that the course of asthma worsens in one-third of pregnant women, improves in one-third, and remains unchanged in one-third.⁴

In a large population-based cohort, we studied 8,149 pregnant women with asthma from a larger group of 112,171 pregnant white and black women aged 15 to 44 years who were enrolled in TennCare, Tennessee's Medicaid managed care program from 1995 to 2001 and who had at least 180 days of continuous enrollment before their last menstrual period. The 112,171 eligible women represented 48% of all deliveries to women enrolled in Tennessee Medicaid and 21% of all live births in Tennessee during the study period. Data were obtained from linked Tennessee Medicaid database and vital records files, providing information on maternal demographics, *International Classification of Diseases, Ninth Revision (ICD-9)* diagnoses, and pharmacy claims. The protocol was approved by the institutional review boards of Vanderbilt University and the Tennessee Department of Health. A more complete discussion of these methods is contained in the article by Enriquez et al.⁵ Asthma control was defined by use of short-acting β -agonists. Pharmacy claims containing short-acting β -agonist dose and days of supply were available for all study participants from 25 weeks before last menstrual period until the end of pregnancy. These data were used to determine short-acting β -agonist use for each week from 20 weeks before last menstrual period through the last full week of pregnancy or 40 weeks. Women were classified as current users for each week that was within 30 days of their last dispensed prescription; otherwise, they were classified as nonusers for that week. In Figure 1 (bottom), 95% confidence bands were estimated by bootstrap simulations.⁶

Among the 8,149 pregnant asthmatic women, 77% used short-acting β -agonists during follow-up. Overall, pregnant women had an initial decrease in β -agonist use in the first trimester before experiencing peak use in the third trimester, with 31.8% experiencing worsening asthma control, 31.4% experiencing unchanged asthma control (defined as <5% variation from baseline), and 36.8% experiencing improved asthma control during pregnancy. Changes in use for black and white women are given in Figure 1 (top). Figure 1 (center) shows that asthma control improves during the first half of pregnancy and then worsens. Among pregnant white women control improves during the first half of pregnancy and then reverts to control similar to baseline (Figure 1). However, black women show

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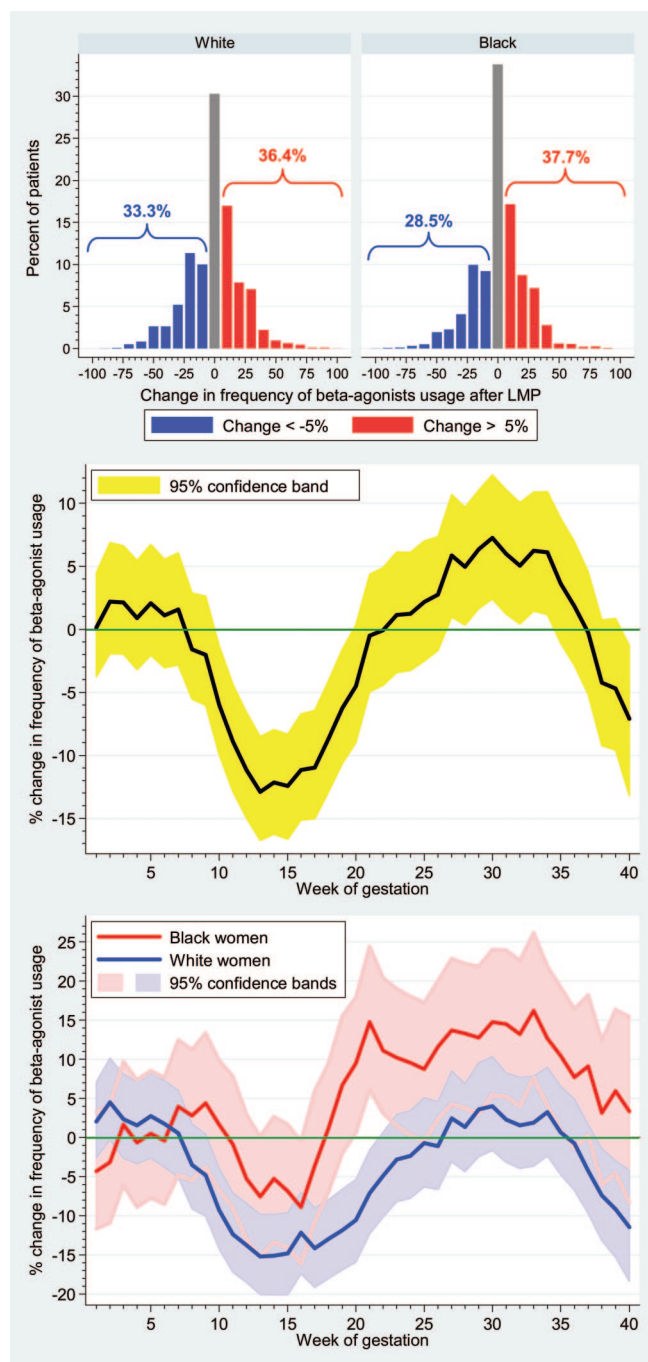


Figure 1. Effect of pregnancy on asthma control as measured by short-acting β -agonist use. Top, Proportion of white and black women whose β -agonist use increased or decreased during pregnancy. Black women had a significantly greater increase in β -agonist use than did white women ($P = .002$). Center and Bottom, Change in percentage of study participants actively using short-acting β -agonists each week compared with the average percentage using each week for the 20 weeks before their last menstrual period (baseline). Center, Data for all study subjects; the yellow band gives the 95% confidence interval. Asthma was significantly improved in weeks 10 to 19 and was significantly exacerbated in weeks 27 to 34 ($P < .05$). Bottom, Same data subdivided by race.

little change in asthma control in the first 20 weeks and then experience worsening control in the last half of their pregnancy.

The initial decrease in albuterol use early in pregnancy is consistent with previous work, from both our group and other groups, showing that despite national guidelines that recommend continuation of maintenance asthma medications,⁷ use of inhaled corticosteroids and rescue medications decreases overall during pregnancy.⁵ Alternatively, consistent with prior work,⁸ the group whose asthma improved may have experienced the improvement early in pregnancy, resulting in decreased overall use in this interval. The rebound in albuterol use early in the third trimester may be attributable to previously stopping use of controller medications or may be partly attributable to the physiologic effects of pregnancy on asthma control.⁴ Finally, the racial differences in worsening asthma control during the third trimester compared with prepregnancy seen in blacks but not whites is important and requires further study.

We present the first study of the time course and trends in asthma control during pregnancy in a large population-based cohort. This study affirms the classic adage about change in asthma severity during pregnancy, with approximately one-third of pregnant women showing improved control, one-third experiencing worsened control, and one-third remaining unchanged, as measured by change in pharmacy claims for short-acting β -agonist prescriptions. This pattern is similar for both blacks and whites; however, compared with their prepregnancy states, black women were more likely to have worsened asthma control during pregnancy than white women.

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