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THE AUTHORS REPLY: We appreciate the comments of Scialli and Lione regarding the detection of diabetes. For the reasons they describe with regard to the possibility of insufficient documentation of chronic illnesses by physicians, our primary definition of diabetes was made on the basis of either a diagnosis of diabetes or a prescription for a hypoglycemic agent. We also performed a secondary analysis with a broader definition of diabetes that excluded women with a prescription for a hypoglycemic agent during pregnancy or a diagnosis of diabetes during the first trimester. The results were essentially unchanged. Undetected diabetes could not have directly influenced the physician's decision to prescribe an ACE inhibitor. Given this scenario, confounding is less plausible, since a confounder must be associated with both the exposure (the ACE inhibitor) and the outcome.¹

We were aware that hypertension and obesity (a possible, but not yet established, risk factor for congenital malformations²⁻⁴) were potential confounders. We thus included a control group of women who used other antihypertensive medications during the first trimester only and did not have an increased risk of congenital malformations. However, to assess the effects of hypertension that is more difficult to control, we performed two additional analyses.

The first analysis excluded women in both the ACE-inhibitor and other antihypertensive groups who filled prescriptions for drugs in two or more classes (e.g., beta-blockers and diuretics) during

the 90 days before the last menstrual period. There was a statistically increased risk of major congenital malformations among study infants born to women in the ACE-inhibitor group (risk ratio, 2.22; 95% confidence interval [CI], 1.11 to 4.44), but not to women in the other antihypertensive group (risk ratio, 0.69; 95% CI, 0.25 to 1.87).

In the second analysis, we expanded the other antihypertensive group to include women who had used antihypertensive agents during the second or third trimester, since we considered it likely that the severity of hypertension would be related to the decision to continue the use of the drug during pregnancy. Among the 951 infants born to women in this group, there was no increased risk of congenital malformations (risk ratio, 1.22; 95% CI, 0.86 to 1.72). Both analyses thus suggest that hypertension that was difficult to control did not account for the study findings.

We concur with Sealey and Itskovitz-Eldor regarding the need for studies of the use of other antihypertensive agents during pregnancy. Given the secular trend of increasing maternal age, more women who become pregnant will have hypertension, making it vital to define how best to treat this chronic illness during pregnancy.

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Omalizumab for Asthma

TO THE EDITOR: Strunk and Bloomberg (June 22 issue)¹ discuss omalizumab for the treatment of asthma associated with high serum IgE levels. We provided care for a man who received omalizumab and in whom the Churg–Strauss syndrome subsequently developed.

Our patient was a 55-year-old man with a history of asthma who presented with acute onset of numbness and tingling in his extremities. A neurologic examination was notable for hyporeflexia. The patient had a purpuric rash on both lower extremities. A pulmonary examination was

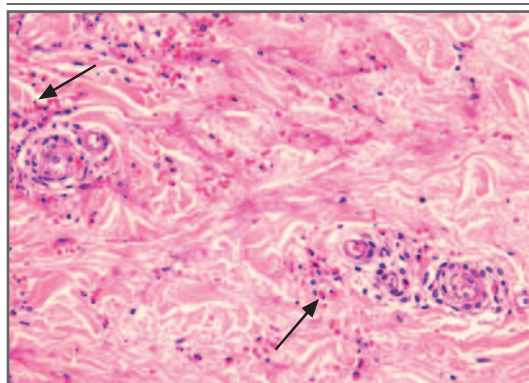


Figure 1. Photomicrograph of Skin-Biopsy Sample Showing Inflammation of Small Blood Vessels and Prominent Perivascular Infiltration with Eosinophils (Arrows) (Hematoxylin and Eosin).

unremarkable. The white-cell count was 23.1×10^3 per microliter with 47% eosinophils. Skin biopsy revealed a leukocytoclastic vasculitis with an eosinophilic infiltrate (Fig. 1). The patient was treated with intravenous methylprednisolone. His symptoms improved, treatment was changed to oral prednisone, and he was discharged several days later. Cyclophosphamide was added to outpatient therapy.

Our review of the literature yielded many articles discussing the association between leukotriene-receptor antagonists²⁻⁴ and the Churg–Strauss syndrome but none associating this disease with omalizumab. To our knowledge, this is the first description of a temporal association between the use of this drug and the development of the Churg–Strauss syndrome.

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TO THE EDITOR: The efficacy and safety of omalizumab for severe asthma have been reviewed.^{1,2} We report two unexpected consequences of omalizumab among 16 patients with allergic asthma treated for at least 6 months. The first patient had allergic asthma, aspirin intolerance, and stabilized nasal polyposis. He received 10 mg of prednisolone per day, 2000 μg of fluticasone per day, and a long-acting β_2 agonist. With omalizumab (300 mg every 2 weeks), his asthma was brought under control (regimen at 6 months: 500 μg of fluticasone per day and 100 μg of salmeterol per day), but the patient reported a recurrence of obstructive nasal polyposis.

The second patient had uncontrolled severe allergic asthma treated with 2000 μg of fluticasone per day and 200 μg of salmeterol per day. She received eight short courses of systemic corticosteroids per year. Omalizumab (250 mg every 2 weeks) was initiated in January 2006. After 3 months, her asthma was controlled. Six weeks later, she was found to have subacute adrenal insufficiency. Exhaustive questioning revealed that the patient had received two intramuscular injections of 80 mg of triamcinolone acetone, the last one in November 2005.

The possibility of paradoxical complications of successful treatment with omalizumab, induced by the rapid reduction of glucocorticoids, must be considered.

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Drs. Tonnel and Tillie-Leblond report having received consulting fees from GlaxoSmithKline, AstraZeneca, Novartis, and Boehringer Ingelheim, and consulting fees from Merck Sharp & Dohme.

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