

Relationship between extremely low total serum IgE levels and rhinosinusitis

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Background: The few studies examining clinical manifestations in adults with serum IgE levels less than 2.0 IU/mL provide conflicting information.

Objective: To examine self-reported respiratory disease in women with total serum IgE levels less than 2.0 IU/mL to further elucidate previous reports of an association between IgE deficiency and chronic rhinosinusitis.

Methods: In a geographically based cohort of 626 pregnant women, total serum IgE levels were measured using a standard assay with a lower limit of detection of 2.0 IU/mL. Sera with IgE levels less than 2.0 IU/mL were assayed again using a low IgE protocol with a detection limit of 0.02 IU/mL.

Results: Twenty-one individuals (3.4%) were found to have IgE levels less than 2.0 IU/mL. On repeated assay, 20 of these individuals with available clinical data were found to have detectable IgE levels ranging from 0.5 to 2.1 IU/mL (geometric mean, 1.2 IU/mL). None of these individuals with low IgE levels had physician-diagnosed sinusitis compared with 19.3% (113/585) of those with IgE levels of 2.0 IU/mL or greater ($P = .03$). Physician-diagnosed asthma was also less prevalent (1/19, 5.3%) in the low IgE group compared with 20.6% in those with higher IgE levels, but this was not significant ($P = .14$). The low IgE group reported a higher prevalence of hay fever symptoms than the remaining cohort (31.6% vs 24.4%; $P = .43$) but had less physician-diagnosed hay fever (5.3% vs 15.8%; $P = .34$).

Conclusions: Low serum IgE levels were relatively common in these pregnant women. In contrast to previous studies, a low IgE level was not associated with chronic rhinosinusitis.

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INTRODUCTION

Serum IgE concentrations are commonly measured in allergy practice. Most of the literature concerning serum IgE concentrations focuses on patients with elevated serum IgE levels due to the higher risk of atopic disease. Still, a review of the literature finds anecdotal evidence and a few case reports of increased chronic rhinosinusitis and chronic lung disease in patients with IgE levels below the limits of detection of most commercial assays. Studies of disease risk in individuals with very low serum IgE levels are limited in number and scope. Although the term *IgE deficiency* has been used in several studies, the term has not been formally defined. Most authors have used the term to indicate values below the detection limits of whatever assay they happened to use for patient samples. To our knowledge, there have been no population-based studies of either the prevalence of “undetectable” IgE

in adults or the possible relationships between undetectable serum IgE concentrations and clinically apparent illness.

Cain et al¹ proposed that selective IgE deficiency leads to chronic sinopulmonary infections because of the protective role of IgE on the respiratory mucosa. This study¹ was limited to 27 patients with various immunologic disturbances, including hypogammaglobulinemia. Isolated IgE deficiency, which was defined as no reaction to intradermal injections of guinea pig anti-human IgE with normal serum levels of IgM, IgG, and IgA, was found in only 1 patient who had sinus disease. In contrast, Levy and Chen² reported a case of a healthy 28-year-old woman with IgE levels that were undetectable using this same intradermal anti-IgE method. Another study³ found that 1 of 7 IgE-deficient patients (IgE level <7.0 IU/mL) had a history of sinusitis, and this patient had the highest IgE of the 7. Schoettler et al⁴ evaluated the sera of 23 family members of nonidentical adult twins with a history of chronic bronchitis and fibrotic lung disease. They found that 12 of the 14 symptomatic family members had IgE deficiency (defined in this study as <5.0 IU/mL) inherited in an autosomal-dominant manner, whereas the 9 asymptomatic family members all had IgE levels greater than 10.0 IU/mL.⁴ In a more recent study, Smith et al⁵ found that nearly 5% of patients seen in a Johnson City, TN, allergy-immunology clinic had IgE deficiency (IgE level <2.5 IU/mL), with normal levels of all other immunoglobulins. This group found that patients with IgE levels less than 2.5 IU/mL had increased rates of intrinsic asthma and autoimmune disease.⁵

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These previous studies of low serum IgE concentrations used IgE assays that are not as sensitive as those currently available and included only patients seeking specialty care, introducing a strong possibility of selection bias.

The objective of this study was to examine the clinical history of respiratory illness in subjects with serum IgE concentrations less than 2.0 IU/mL in a geographically based population using a more sensitive assay with a lower detection limit of 0.02 IU/mL. Another objective was to estimate the prevalence of serum IgE levels less than 2.0 IU/mL in a healthy adult population.

METHODS

We examined disease patterns in a geographically based cohort of 626 pregnant women from southeastern Michigan to elucidate the association between IgE levels less than 2.0 IU/mL and chronic rhinosinusitis. These women were recruited as part of a prospective study of environmental influences on the development of allergy in children after birth. Concentrations of IgE were measured in all the study participants using a standard assay (Pharmacia UniCap; Pharmacia Diagnostics, Kalamazoo, MI) during pregnancy. The lower limit of assay detection is 2.0 IU/mL. Serum samples with IgE levels less than 2.0 IU/mL were assayed again using the low IgE UniCap protocol with a lower limit of detection of 0.02 IU/mL. Each participant completed a questionnaire regarding physician-diagnosed asthma, sinusitis, and rhinitis. The questionnaire also asks about hay fever, nasal allergies, and rhinitis symptoms without regard to a physician's diagnosis. Data were analyzed using the Fisher exact test for a 2×2 contingency table. Confidence intervals were determined using an exact binomial calculation.

RESULTS

Twenty-one (3.4%) of the 626 women were found to have serum IgE levels below the detection level of the standard assay (<2.0 IU/mL) during pregnancy with a 95% confidence interval of 2.0% to 4.9%. Nineteen individuals had clinical data available for statistical analysis and sufficient serum for repeated IgE assay. These subjects were found to have detectable serum IgE concentrations ranging from 0.5 to 2.1 IU/mL (geometric mean, 1.2 IU/mL). In addition, of 8 women who also had 1-month postpartum samples, 6 continued to have low IgE levels (range, 1.1–2.9 IU/mL), whereas the remaining 2 had significant increases in total IgE levels (12.7 and 231.0 IU/mL). None of the 19 participants with IgE

levels less than 2.0 IU/mL reported physician-diagnosed sinusitis compared with 19.3% (113/585) of those with IgE levels of 2.0 IU/mL or greater ($P = .03$) (Table 1). Physician-diagnosed asthma was also less prevalent in the low IgE group (1 of 19 patients) compared with the higher IgE group (121 of 587 patients); however, these results were not significant ($P = .14$). Hay fever symptoms were reported more frequently in the low IgE group than in the rest of the cohort (31.6% vs 24.4%; $P = .43$), but physician-diagnosed hay fever was less common in the low IgE group, although this finding was not significant (5.3% vs 15.8%; $P = .34$) (Table 1).

DISCUSSION

These data indicate that low serum IgE concentrations, defined as those less than 2.0 IU/mL, are not associated with a significantly increased prevalence of chronic rhinosinusitis or other physician-diagnosed respiratory disorders. Contrary to the hypothesis that IgE is important for the immune protection of the nose and sinuses, we found that women with low serum IgE levels tended to have less sinusitis and rhinitis than those with higher serum IgE concentrations. Women with low IgE levels also tended to have less asthma. Previous studies have reported that individuals with serum IgE levels less than 2.0 IU/mL have an increased prevalence of chronic rhinosinusitis and other airway diseases, in addition to autoimmune diseases, but these studies have potentially significant flaws. The most important concern about previous studies is selection bias because participants were already seeking medical care for respiratory disorders. Older IgE assays were also less sensitive and precise than currently available assays. The present study involves a generally healthy, geographically based cohort of pregnant women living in southeastern Michigan. This study is limited in that it does not include men, but many studies have shown that males, on average, have higher serum IgE levels as early as 2 years of age.⁶ The inclusion of only pregnant women may introduce additional bias because women with chronic illnesses may be less likely to become pregnant. We could not find any studies suggesting that pregnancy alters serum IgE concentrations or concentrations of allergen specific IgE. The retrospective nature of this study and the study population did not allow for objective evaluation of the studied diseases, for example using computed tomography to confirm clinically diagnosed sinusitis. The questionnaire asked whether the woman has ever been diagnosed as having sinusitis, asthma, or hay fever

Table 1. Patient Characteristics by IgE Level

Characteristics	Patients, No./total No. (%)		P value
	IgE <2.0 IU/mL	IgE ≥2.0 IU/mL	
Hay fever symptoms	6/19 (31.6)	143/585 (24.4)	.43
Physician-diagnosed hay fever	1/19 (5.3)	92/581 (15.8)	.34
Physician-diagnosed sinusitis	0/19	113/585 (19.3)	.03
Physician-diagnosed asthma	1/19 (5.3)	121/587 (20.6)	.14

by a physician. This may introduce recall bias, but there is no reason to believe that the low IgE group would be more or less likely to recall illnesses than participants with IgE levels of 2.0 IU/mL or greater. In the 2 women whose IgE levels seemed to change, we suspect that the one whose IgE level was later 231 IU/mL represents a labeling error of the samples. The second change from less than 2.0 to 12.7 IU/mL may be related to changes in blood volume during and after pregnancy.

In summary, this study shows that low serum IgE levels are not associated with an increased prevalence of chronic rhinosinusitis or asthma in adult women. On the contrary, our results are consistent with the many studies showing less allergic rhinitis and asthma in individuals with lower concentrations of total serum IgE.⁷

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