Relationships among prenatal aeroallergen exposure and maternal and cord blood IgE: Project ACCESS

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Background: Whereas some evidence suggests that antigen sensitization may begin prenatally, the influence of maternal allergen exposure during pregnancy has not been fully elucidated.

Objectives: We examined the relationship between prenatal maternal aeroallergen exposure and cord blood total IgE and the potential mediating/indirect effect of maternal immune response.

Methods: This study was performed in 301 mother-infant pairs enrolled in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project, a study examining the effects of prenatal and early life social and physical environmental exposures on urban asthma risk. Dust samples collected prenatally from mothers' bedrooms were analyzed for cockroach and dust mite allergens. Cord blood was analyzed for total IgE, and maternal serum collected during pregnancy for total and specific IgE. We assessed the relationship between prenatal exposure and cord blood total IgE and the potential mediation effect adjusting for maternal age, race, education, smoking status, and dust collection season; and child's sex and season of birth.

Results: In multivariate models, elevated prenatal dust mite levels (>0.2 μg/g) increased cord blood IgE concentrations by 29% ($P = .08$), and continuous dust mite concentration was associated with a significant nonlinear increase in cord blood IgE ($P = .02$). Elevated prenatal exposure to cockroach allergen (>2 U/g) was not associated with cord blood IgE, but showed a significant indirect relationship through maternal total IgE (β = 0.23; 95% CI, 0.08–0.41).

Conclusion: These results demonstrate that maternal prenatal exposure to household allergens may affect cord blood IgE, albeit the underlying mechanism may be allergen-specific. (J Allergy Clin Immunol 2009;123:1041-6.)

Key words: *Allergen, dust mite, cockroach, maternal, prenatal, cord blood, IgE, urban*

Atopy is a major risk factor for asthma development and has as its key feature the production of IgE antibodies against specific antigens.[1] It has been proposed that individuals with altered immune response at birth have an increased risk of developing allergic diseases.[2] In particular, elevated cord blood IgE has been associated with aeroallergen sensitization and the development of allergic diseases in children, particularly in those with a family history of atopy.[3-5] In addition, indoor allergen exposure is considered an important risk factor for both developing and exacerbating asthma in susceptible populations.[6] Therefore, a logical place to examine the effect of the environment on asthma development would be to investigate the effect of prenatal allergen exposure on *in utero* IgE response.[1]

Recent articles by Rowe et al[7] and Bønnelykke et al[8] have fueled the debate on the relative importance of prenatal versus postnatal exposure on allergen sensitization. One of the criticisms of attributing effect to prenatal exposure is the lack of evidence showing a quantitative relationship between maternal allergen exposure and offspring immunologic response.[7] Studies assessing the possible role of prenatal maternal antigen exposure on the neonatal immune response have primarily been experimental studies,[9-11] or human studies using surrogates of allergen exposure such as building conditions and pet ownership[12-14] or investigating cord blood cytokine or T-cell proliferation in response to antigen stimulation.[15-18] Proliferation in response to allergens does not correlate with IgE levels, and the relevance of cord blood antigen–induced proliferation as a marker of *in utero* priming and as a predictor of subsequent allergic immune response is still in question.[15,18-20]

In this study, we investigate the relation of allergen exposure during pregnancy to cord blood IgE, adjusting for important risk factors, and whether prenatal maternal total or specific IgE mediates this relationship. We hypothesize that maternal exposure to household inhalant allergens of dust mite and cockroach measured during pregnancy would be associated with elevated cord blood IgE. We further hypothesize that the influence of aeroallergen exposure on cord blood IgE may be mediated through its effect on prenatal maternal allergic responses.

METHODS

Study participants

Cross-sectional analyses were conducted in the Asthma Coalition on Community, Environment, and Social Stress (ACCESS) project, an ongoing prospective cohort of mother-child pairs originally funded to recruit 500 pregnant women and their children to study the main effects of prenatal maternal and early life stress and other environmental risk factors on urban childhood asthma risk (described in detail elsewhere[21]). Briefly, English-speaking or Spanish-speaking pregnant women who were at least 18 years of age receiving prenatal care at Brigham and Women's Hospital, Boston Medical Center, 3 urban community health centers, and their associated

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Abbreviation used
LLOD: Lower limit of detection

Women, Infants and Children programs in metropolitan Boston and surrounding suburbs were recruited in their second or third trimester between August 2002 and January 2005. Those enrolled in this phase constituted 78.1% of the women who were approached. Those women who did not want to participate in the prospective study answered a brief screener questionnaire including information on race/ethnicity and annual household income; we observed no significant differences in these covariates between those who agreed to participate and those who declined. Written informed consent was obtained, and the study was approved by the Brigham & Women's Hospital and Boston Medical Center human studies committees.

Serum IgE assays

At the time of these analyses, 301 of the 500 children (60%) had information on cord blood IgE, allergen exposure, and all potential confounders. Of these, 198 (66%) also had matching prenatal maternal total and allergen-specific IgE. Serum from mothers collected in their second or third trimester and venous placental cord blood collected at birth were analyzed by using the CAP fluorescent enzyme immunoassay (Pharmacia [now Phadia], Uppsala, Sweden). Total and allergen-specific IgE levels were determined for mothers. Specific IgE was assessed for dust mite (*Dermatophagoides pteronyssinus and Dermatophagoides farinae*) and cockroach (*Blatella germanica*). Cord blood total IgE and allergen-specific IgE levels were determined with the same system using a modified protocol reducing the lower limit of detection (LLOD) from 2.0 IU/mL to 0.2 IU/mL.[22] We compared the 198 mother-infant pairs with matching maternal IgE versus the 103 who did not have this information. Among those without maternal IgE data, mothers were more likely black, higher educated, and had higher levels of cockroach allergen.

Prenatal dust collection

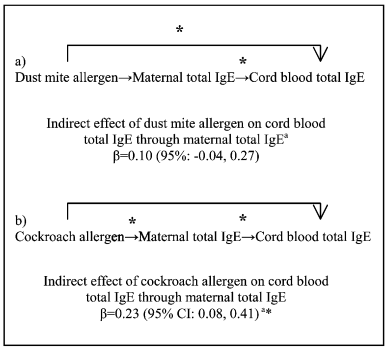
Settled dust was collected during pregnancy as a combined sample from the mother's bed and bedroom floor by using a standardized protocol.[23] Briefly, 2 m^2 of the bedroom floor was first vacuumed for 5 minutes. Then all layers of the mother's bed were vacuumed for an additional 5 minutes. Dust mite allergens (Der f 1 and Der p 1) and cockroach allergens (Bla g 1 and Bla g 2) were measured by mAb ELISA (Indoor Biotechnologies, Charlottesville, Va). The LLOD for Der f 1 and Der p 1 was 0.02 μg/g; and for Bla g 1, 0.40 U/g; and for Bla g 2, 1.0 U/g.

Statistical analysis

We first investigated the association between prenatal aeroallergen levels and cord blood total IgE and then performed mediation analysis to test whether the pathway between aeroallergen exposure and cord blood IgE occurred through maternal IgE (Fig 1).

To evaluate the effect of aeroallergen on cord blood IgE, we used Tobit regression with continuous log-transformed IgE concentrations (Tobit regression accommodates data that is truncated by detection limitation).[24]

For pathway analysis, we performed the following previously recommended series of tests: (1) association between aeroallergen levels and cord blood total IgE (as described in the first paragraph on statistical analysis); (2) association between aeroallergen levels and maternal IgE (potential intermediary); and (3) association between maternal IgE and cord blood total IgE.[25] However, we also performed a formal test (test 4) of an indirect pathway between aeroallergen exposure and cord blood IgE through maternal IgE.[26-28] For test 2, we used generalized linear models with identity link on log-transformed maternal total IgE and logistic regression with dichotomized specific IgE (>0.35 IU/mL [CAP class 1 or greater]). For test 3, we used Tobit regression, and for test 4, we used a bootstrap approach for significance testing of the indirect/mediation effect,[26,27] which is preferable here because it does not require specific assumptions, such as normality.[26-28]



[a]All models adjust for maternal age, race, education, smoking status and season of dust collection, and child's sex and season of birth.

*significant relationship ($P < .05$)

FIG 1. Summary diagram of the modeled relationships among residential allergen concentrations, maternal total IgE, and cord blood total IgE, including the indirect effects from mediation analysis using the bootstrap approach.

Composite concentrations of Der f 1 plus Der p 1 (hereafter referred to as *dust mite allergen*) and of Bla g 1 plus Bla g 2 (hereafter referred to as *cockroach allergen*) were used for analyses. Allergen exposures were dichotomized as elevated (>0.20 μg/g) versus nonelevated (≤0.20 μg/g) based on sensitivity analyses, which revealed that at cut points between 0.02 μg/g (LLOD) and 0.20 μg/g, categories of dust mite allergen showed distinguishable, significant differences in cord blood IgE. These results agree with prior research suggesting dust mite effects *in utero* and in the first 3 years of life above 0.2 μg/g.[29,30] For cockroach, no clear cut point was found when sensitivity analyses were conducted, so we used the postnatal sensitivity cut point of 2 U/g.[31] For the purposes of comparison with some existing literature on postnatal exposure, we also divided allergen exposures into 4 categories: dust mite was categorized as μg/g <0.02 (LLOD), 0.02 to 0.20, 0.21 to 2.0, and >2.0; and cockroach was categorized as U/g <0.40 (LLOD), 0.40 to 2.0, 2.1 to 8.0, and >8. We additionally ran generalized additive (nonparametric smoothing) models, which relax the assumption of linearity, by using continuous log-transformed allergen levels.[32] To minimize bias in the latter analyses, measures less than LLOD were assigned a random number less than LLOD.[24]

Spearman correlation was used to determine correlation and the rank-sum test to assess group differences (eg, those with and without maternal IgE measures). Multivariate analyses adjusted for maternal age, race, smoking status, education, and season of dust collection (spring, summer, fall, or winter) and children's sex and season of birth. Maternal allergic disease with symptoms was defined as self-report of ever having been diagnosed with asthma, eczema, or hay fever. We used graphical plotting of the Cook D and studentized residuals to identify influential points and outliers, respectively, which resulted in the removal of 2 that were both extreme influential points and outliers. Analyses were conducted by using SAS software 8.2 (SAS Institute, Cary, NC). A P value <.05 was considered significant.

RESULTS

Sample characteristics

Characteristics of the study participants are shown in Table I. The mean maternal age was 26.6 years. The population was predominately Hispanic (61.8%), and 36% of the mothers had a history of allergic disease with symptoms.

The percent of homes with dust mite allergen concentrations >0.20 μg/g was 67.6%, and with concentrations >2 μg/g, 38.1%. The percent of homes with cockroach allergen concentrations >2 U/g was 18.5%, and with concentrations >8 U/g, 8.33%.

Cord blood IgE was detected in 82.4% of the samples and maternal IgE in 98.0%; maternal total IgE was moderately