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Allergy immunotherapy: target for primary prevention of atopy?

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As allergists, much of what we do on a day-to-day basis encompasses secondary and tertiary prevention strategies. We diagnose allergic conditions, identify causes and triggers of the patients' symptoms, and then recommend avoidance strategies and immunotherapy for specific allergens (secondary prevention) and prescribe a pharmacotherapy to decrease their symptoms (tertiary prevention). Although our methods of treatment continue to improve, our goal should be not only to improve our ability to modify morbidity but also to prevent the disease before any morbidity is suffered—a concept Benjamin Franklin eloquently elucidated nearly 300 years ago when discussing fire prevention strategies with his statement, “An ounce of prevention is worth a pound of cure.”

To date, excellent research has been performed in the field of primary prevention of allergy, and these studies have helped identify possible targets for allergy prevention and identify associations for the development of allergy. Much of the recent research in this field has examined strategies to prevent cutaneous and food allergies, such as vitamin D supplementation,¹ the use of probiotics or prebiotics,² the use of hydrolyzed formulas,³ maternal dietary restrictions,⁴ and breastfeeding.⁵ Despite these efforts, few convincing data suggest any specific strategy is beneficial, and thus recent guidelines for food allergy published by the National Institute of Allergy and Infectious Disease and the European Academy of Allergy and Clinical Immunology offer very few recommendations and have no strong supportive evidence.^{6,7}

For respiratory allergies, the data are not any more encouraging. In the 2010 update to the Allergic Rhinitis and Its Impact on Asthma guidelines, authors had varying recommendations for the primary prevention of respiratory allergy; however, all had “low-quality evidence” or “very low-quality evidence” to support these recommendations.⁸

What is evident from analysis of multiple studies to date is that programming an immune response away from an atopic diathesis

is not as simple as exposing neonates or infants to a single agent or removing an offending one. Rather, the intricate interaction of genetic and environmental factors that lead to allergic sensitization make any approach to primary prevention of atopy a daunting task.

One issue that complicates matters is the timing of exposure. An increasing body of evidence suggests that prenatal exposures already help shape future atopic status.⁹ Thus, one may already be “behind the eight ball” if starting prevention strategies during infancy. There is clearly some evidence that exposures in utero can increase one's likelihood of developing atopic disease.¹⁰ Unfortunately, avoidance is only half of the whole. Is there any intervention we can offer to pregnant mothers beyond avoidance to decrease atopy in offspring? On the proactive side, there are intriguing data suggesting that maternal exposures during pregnancy, such as exposure to farm animals, may lead to decreased allergic sensitization in offspring.¹¹ These studies report that maternal farm exposure can lead to interferon γ (IFN- γ) and tumor necrosis factor α in cord blood, higher numbers of T-regulatory cells and Foxp3 expression in cord blood, decreases in interleukin-5 on stimulation of cord blood mononuclear cells, and lower seasonal allergen IgE in cord blood.^{12–14}

This aspect of the hygiene hypothesis has provided us with an amazing glimpse into mechanisms of development of allergic sensitization. One can quickly see though that it lacks in practical application for most patients. One attempt to take this concept to clinical use, examining treatment with oral introduction of bacterial lysates, did not have a clinical effect in the prevention of atopic dermatitis when compared with placebo.¹⁵

The search therefore continues for an attractive, practical intervention strategy for primary prevention of allergies. One intriguing candidate that has not been thoroughly examined is allergen specific immunotherapy. Immunotherapy is known to produce immunomodulatory effects similar to those seen from farm animal exposure discussed above.¹⁶ There are, in fact, data from murine models that suggest that immunotherapy, when given to mothers, can influence the atopic state of offspring. For example, pups born to mothers that were tolerized to ovalbumin immediately before conception were protected from the development of an

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asthma phenotype in an ova sensitization and challenge model.¹⁷ Interestingly, this protection was abolished in neonatal Fc receptor knockout mice, suggesting that the protective effect required the placental transfer of allergen-specific IgG.

Encouragingly, this concept may have some validity in humans as well. For example, Flicker et al¹⁸ found IgG antibodies with defined allergen specificities in cord blood from a mother who received allergen immunotherapy but could not detect any allergen-specific IgE in cord blood (despite finding allergen-specific IgE in mother's serum). This lends credence to the fact that mother can pass allergen-specific IgG to her offspring but not allergen-specific IgE. Perhaps more interesting is the fact that IgG4 specific to the 2 allergens to which mother received immunotherapy (birch and grass) was detectable in the cord blood (in addition to various other allergen-specific IgG1 antibodies). What actual role that specific IgG antibodies play in influencing the atopic repertoire in the fetus is unknown, but at least one long-term study found that high levels of cord blood IgG antibodies to certain allergens (cat and birch but not to the food allergens) are associated with less atopic symptoms in children during the first 8 years after birth.¹⁹

Another mechanism for the hypothesized effect, beyond placental transfer of "protective" immunoglobulin, is epigenetic modifications. This finding is supported in another murine asthma model in which mothers were exposed to specific bacteria during pregnancy. Prenatal administration of the bacteria protected the offspring from the development of an asthmatic phenotype. The effect was IFN- γ dependent, and the protected offspring had protection against loss of histone acetylation in the IFN- γ promoter. Furthermore, the clinical protection was lost with pharmacologic inhibition of the histone acetylation.²⁰ Finally, immunotherapy increases both T-regulatory cell number and function.¹⁶ This protective effect is also seen in cord blood from gestations in which mothers had farm exposures and is proposed to play a causative role in the protection from atopy that farm exposure may confer.¹³

Despite these supportive murine models of the effect of maternal immunotherapy on offspring and the conceptual benefit it may confer, few to no human data support or refute this concept. We recently conducted a survey study to attempt to shed some light on this topic. Of 277 children analyzed in this study, those born to women who received immunotherapy during pregnancy had an 8% lower incidence of any self-reported allergic disease (asthma, food allergies, eczema, and/or rhinitis) than those children born to mothers with allergic rhinitis who did not receive immunotherapy. This effect persisted after controlling for the reported confounders (breastfeeding, paternal allergic status, and older siblings). This study, reported in abstract form at the American College of Allergy, Asthma, and Immunology 2013 Annual Meeting, clearly had several weaknesses (eg, selection bias and poor response rate, recall bias, lack of skin testing in offspring, and self-reported nature of the child's diagnosis) and is not meant to serve as definitive evidence of a positive effect but at least adds some credence and support to pursuing this hypothesis further.

Given the possible implications to clinical care of patients if this effect is true, we believe that a prospective study is clearly in order. The logistics of such a study would be difficult because of the limited number of potential patients. There are perhaps 2 ways to conduct the study. The first would simply be a multicenter study, requiring approximately 10 sites to recruit approximately 25 patients apiece to have a 10% reduction in disease in the offspring with 80% power ($\alpha = .05$). The second method would be to set up an anonymous, online survey to which any allergist could refer a pregnant patient receiving immunotherapy. This method would allow for rapid and robust capture of potential patients but would limit the uniformity of the immunotherapy received (doses and allergens) and perhaps decrease retention rates.

Any positive outcomes from the study would suggest that we may need to be more proactive in offering women of childbearing age immunotherapy for their respiratory allergies. Clearly, the risk-benefit ratio of such a practice would have to be taken into account and tailored to each case. In women who have a high risk of having atopic children, such as those whose children have a dual-parental history of atopy or multiple allergic family members, the risk-benefit ratio could suggest starting immunotherapy before conception if planning on future children. While initiating (and advancing) immunotherapy during pregnancy clearly carry a risk, which arguably outweighs the proposed benefit here, the risk of continuing immunotherapy during pregnancy at stable doses would arguably give way to the proposed benefit in this case.

In the end, if immunotherapy in women could add a level of protection from atopy for their offspring, it would add depth to what allergists could offer their patients and would have clear potential to improve lives and reduce long-term health-related costs.

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