

A role for maternal IgG in protecting infants from allergen-specific IgE sensitization



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Key words: Atopy, allergic sensitization, fetal immune development, maternal IgG, ontogeny of the immune system

In both mice and human subjects, the ability to respond to specific antigens develops in a controlled programmed fashion in the fetus and child.¹ This reflects programmed development of the diversity of the antibody and T-cell receptor repertoires, as well as maturation of ancillary cell systems and organs. Full immune reactivity is typically achieved by 2 years of age, when the lymphocyte component of the spleen becomes fully mature.

The ability to switch from IgM to IgG, IgA, or IgE² begins in fetal life. However, very little class-switched immunoglobulin is produced. Instead, protection at birth and in early infancy is heavily dependent on transfer of class-switched immunoglobulin from mother to child. Transmission begins in the middle of the second trimester with active transport of IgG across the placenta. At birth, the child's serum level is typically 20% to 25% greater than that of the mother. After birth, the mother provides passive protection through breast milk, which is especially enriched for IgA but also contains IgG. During *in utero* transmission, IgG is transported directly to the bloodstream. After birth, transfer is through the gut, which is less efficient. Thus the vast majority of maternally transmitted IgG is acquired before birth.

Given a half-life of a month, by 6 months, the child will retain approximately 1/64th of maternal IgG. During this 6-month period, the child begins to produce its own class-switched immunoglobulin that is specific to the antigens it encounters. Although adult levels of IgM are achieved by 2 years of age, IgG takes 6 years, with IgG₂ lagging,³ and IgA does not achieve adult levels until puberty. Thus full production can take years to acquire.

Immunoglobulin is a product of the adaptive immune system. Unlike the innate immune system, whose recognition of antigen is encoded in the germline, the adaptive immune system must be

trained to recognize exogenous antigens by using receptors that are manufactured during B-cell and T-cell development. A large antigen load is provided by the intestinal microbiota. Here again, there is evidence of developmental programming. Individual microbial species are progressively acquired largely from the mother through close intimate contact beginning with passage through the birth canal.⁴

The atopic immune system is also influenced by this critical pattern of immune development during ontogeny. IgE sensitization to allergens develops early in childhood, first to food and then to respiratory allergens.⁵ Longitudinal studies of atopic children have shown that reactivity profiles to allergens develop early in life before the onset of symptoms, echoing findings in the ontogeny of autoimmune diseases in which self-antigen reactivity patterns can be found years before the development of symptomatic disease. Presuming a precursor-product relationship, it has been hypothesized that prevention or inhibition of the development of these reactivity profiles to either atopic or self-antigens could abrogate the development of symptomatic disease.

Maternal IgG transmitted across the placenta *in utero* or into the gut through breast milk has been shown to influence acquisition or survival of intestinal microbiota.⁶ These findings have engendered great interest in defining the mechanisms by which maternal IgG can regulate the microbiota and the immune response of the infant with the hope of developing new modalities for the prevention, amelioration, or cure of disease.⁷

In the article by Lupinek et al,⁵ the authors have taken advantage of a longitudinally studied cohort of mothers and their children recruited between September 2004 and November 2007 in Sweden. Plasma samples were collected from the mother during the third trimester, and breast milk was collected 2 months after delivery. From the children, cord blood was collected at birth, and plasma was collected at 6, 12, 24, and 60 months of age. In some cases plasma from fathers was also collected, although these studies were more limited in number. Allergen-specific IgG and IgE level in mothers were compared with those in their children at 6, 12, and 60 months after delivery. As would be expected from the persistent contribution of maternal IgG in the child, correlation of reactivity was greatest at 6 months of age.

The most provocative finding came from examination of patterns of IgG reactivity and IgE sensitization to the same allergens. It was found that when levels of individual allergen-specific maternal third-trimester IgG were greater than a given cutoff value, none of these children demonstrated IgE sensitization to that same allergen (Fig 1). Conversely, IgE sensitization to allergens that are commonly recognized by children in Scandinavia occurred only among children whose mothers had lower allergen-specific IgG antibody levels. A second finding was that children with IgE sensitization against a particular allergen also had significantly greater allergen-specific IgG levels to that same allergen. Thus

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Supported in part by National Institutes of Health grant AI134027. The author is also supported by an investigator-initiated research grant from CSL Behring.

Disclosure of potential conflict of interest: H. W. Schroeder has received support from the National Institutes of Health and an investigator-initiated research grant from CSL Behring.

Received for publication May 3, 2019; revised May 9, 2019; accepted for publication May 10, 2019.

Available online June 19, 2019.

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J Allergy Clin Immunol 2019;144:410-2.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2019.05.039>

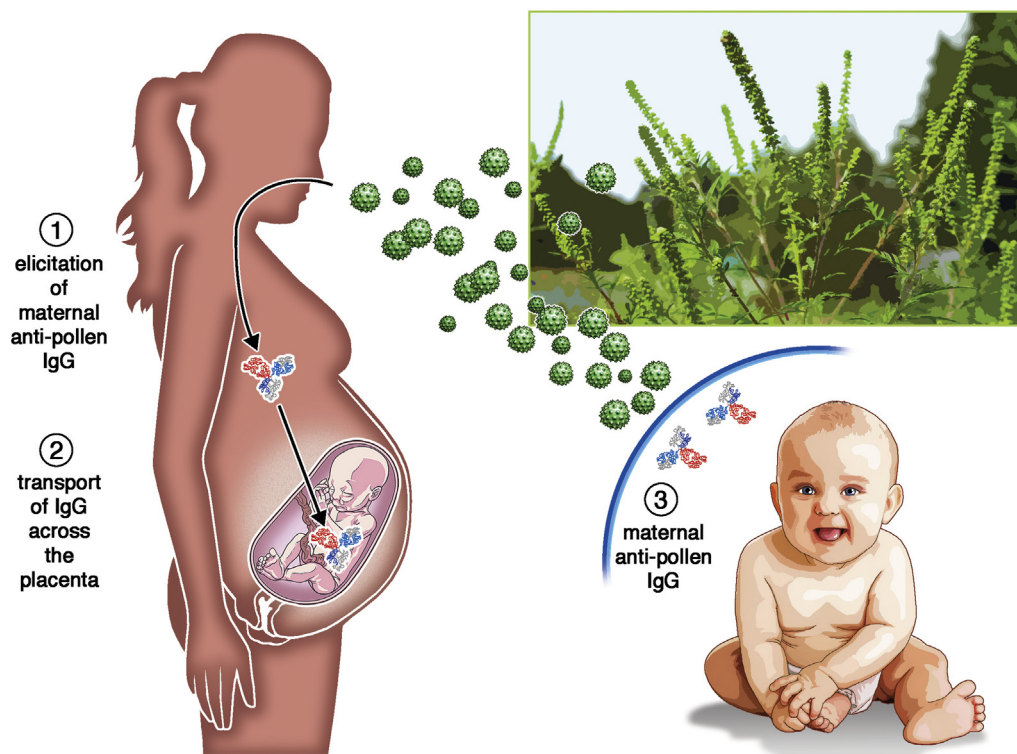


FIG 1. Maternal IgG directed against an allergen (1) is transported across the placenta to the fetus (2), potentially providing long-lasting protection to the child (3) as its immune system develops.

endogenous production by the child of IgG against the allergen did not provide the protection given by maternal allergen-specific IgG.

These findings support the view that development of allergic sensitization is time sensitive, with a critical window of susceptibility late in pregnancy, early in infancy, or both. They also suggest that it might be possible to provide prophylaxis against the development of allergies by manipulating the immune response in the infant either before or soon after birth or by providing allergen-specific IgG to the expectant mother.

The mechanism by which allergic sensitization is permitted or abrogated needs to be established to achieve this goal. Studies in mice have shown that administration of allergen-specific IgG antibodies to mice can protect against subsequent allergic sensitization to that allergen.⁸ Thus it is reasonable to hypothesize that acquisition of maternal allergen-specific IgG during a critical time period in development can provide prophylaxis against development of allergies in the infant. Possible mechanisms include direct binding and subsequent neutralization of the allergen by competition from maternal IgG; alternative patterns of Fcγ receptor activation, perhaps because of differences in glycosylation patterns between maternal and infant IgG; or even idiotypic networks with maternal IgG eliciting anti-idiotypic antibodies that subsequently inhibit B cells expressing allergen-specific immunoglobulin. However, it is also possible that maternal allergen-specific IgG is not causal but a marker for a specific immune milieu that is not conducive to the development of allergen-specific IgE.

These reports emphasize the need for further studies of development of the immune system in pregnancy and early childhood. Whether IgG subclass plays a role in neutralization needs to be determined. The role of IgA, if any, needs to be assessed. The role of maternal IgG on allergic sensitization in the context of varying levels of hygiene needs to be addressed. Sweden is an affluent country, and the role of maternal IgG might or might not be the same among subjects raised under less opportune conditions. Finally, the role of maternal IgG in manipulating the IgE or IgG response in patients with nonallergic conditions remains an open question. For example, can the presence of parasite-specific IgG in a mother affect subsequent production of parasite-specific IgE? Also, what might be the effect of maternal IgG in influencing the development of autoimmune disease? Clearly, the article by Lupinek et al⁵ has raised a number of issues that could yield a new approach to the prevention of both atopic and nonatopic diseases and thus is likely to shape the course of research in the area for many years to come.

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