
Cord blood house dust mite allergen in newborns: relationship to maternal blood levels of allergen and allergen specific IgG and IgE

Abdul Bahrainwala, MD*; Sonia Hassan, MD†; Michael Long, PhD‡; and Joseph Kaplan, MD*

Background: House dust mite allergen has previously been detected in the cord blood of some newborns but not others. The factors that affect the presence and levels in cord blood of this and possibly other allergens are unknown.

Objective: To test the hypothesis that the levels of maternal allergen and allergen specific IgG affect the presence and levels of newborn allergen.

Methods: Enzyme-linked immunosorbent assays were used to measure the levels of house dust mite allergen Der p 1 and Der p 1 specific IgG and IgE in paired blood samples from 98 mothers and full-term newborns.

Results: Der p 1 was detected in 27 mothers and 12 newborns. None of the 71 mothers who lacked Der p 1 had Der p 1-positive newborns. When present, cord blood Der p 1 levels correlated with and were approximately one third of Der p 1 levels in maternal blood. Cord blood Der p 1 levels also tended to correlate with maternal blood levels of Der p 1 specific IgG but showed little, if any, correlation with maternal blood levels of Der p 1 specific IgE.

Conclusions: When detectable, the levels of an allergen in the blood of newborns correlate with the levels of that allergen in the blood of their mothers and tend to be related to maternal levels of allergen specific IgG.

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INTRODUCTION

Although many models have been proposed for the inheritance of atopy and asthma, none have accounted for the fact that the risk of atopy and asthma is much higher in children of atopic mothers than in children of atopic fathers.¹ This pattern suggests that there is a maternal effect on the development of atopy and asthma in children beyond the transmission of genes for these conditions.

One obvious way in which mothers might directly affect the development of atopy in their infants would be by serving as a source of allergens transmitted to the infant either prenatally across the placenta and amniotic fluid or postnatally in breast milk. That some newborns are exposed to allergen before birth was originally suggested by the presence in some fetuses and newborns of allergen-presensitized lymphocytes.^{2,3} More recently, direct evidence has been obtained of the presence of house dust mite allergen in fetal amniotic fluid and umbilical cord blood in a subset of infants born to women exposed in their homes to high concentrations of house dust mite allergen (Der p 1).⁴ The mechanism(s) by which Der p 1 is transmitted from mother to fetus has not yet been established, and neither is it clear why Der p 1 is

detectable in some infants of Der p 1-exposed mothers and not others. The placenta is generally impermeable to maternal-fetal transmission of maternally derived circulating proteins and cells. However, the presence of IgG-specific placental Fc receptors permits maternal-fetal transmission of maternal IgG antibodies. Therefore, Der p 1 could conceivably cross the placenta complexed to Der p 1 specific IgG antibody in the form of soluble antigen-antibody complexes. Alternatively, given that maternal cells have been detected in the fetal circulation in approximately half of all pregnancies,^{5–8} it is possible that Der p 1 might also cross the placenta complexed with Der p 1 specific antibody adsorbed to maternal IgG Fc receptor-bearing cells. In both mechanisms, one would expect associations between the presence and levels of cord blood Der p 1 and the presence and levels of maternal blood Der p 1 and Der p 1 specific IgG antibody. To test those predictions, we investigated the relationships between the plasma levels of newborn Der p 1 and maternal Der p 1 and maternal Der p 1 specific IgG and IgE.

METHODS

Paired samples of 5 to 10 mL of heparinized maternal and umbilical cord blood were obtained at the time of delivery at Hutzel Hospital (Detroit, MI) from 98 mothers and their healthy full-term newborns. Informed consent was provided by all the participants. The mothers ranged in age from 16 to 40 years, and most were African American residents of inner-city Detroit. Selection criteria included uncomplicated full-term gestation with no history of transfusion. After centrifugation of the blood, plasma and cells were separated and stored frozen at -80°C . The concen-

* Carman and Ann Adams Department of Pediatrics, Wayne State University, Detroit, Michigan.

† Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan.

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trations of Der p 1 in the maternal and cord plasma samples was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Indoor Biotechnologies, Charlottesville, VA) according to the manufacturer's instructions. Briefly, polystyrene microtiter wells were coated with mouse monoclonal antibody 5H8 (anti-Der p 1) and then with doubling dilutions of Der p 1 to establish a standard curve or with test plasma diluted at a ratio of 1:10. Bound allergen was then detected by the addition of biotinylated 4C1, a second monoclonal antibody that recognizes a different Der p 1 epitope than recognized by 5H8, followed by peroxidase-conjugated streptavidin-peroxidase and enzyme development with a peroxidase substrate. The lower limit of detection in this assay was 0.5 ng/mL. Plasma concentrations of IgG and IgE anti-Der p 1 were measured using another commercial ELISA kit (AlaSTAT Microplate Allergen Specific Ig Assays; Diagnostic Products Corp, Los Angeles, CA). Because the lower limit of detection of allergen specific IgE was 0.5 KU/L, allergic "sensitivity" to dust mite allergen was considered to be present with IgE anti-Der p 1 levels greater than 0.5 KU/L. (Immediate skin test hypersensitivity to Der p 1 was not tested.) The relationships between the presence and levels of maternal blood Der p 1 and IgE and IgG anti-Der p 1 vs the presence and levels of detectable cord blood Der p 1 were measured using χ^2 and linear regression analyses and nonparametric log-rank tests.

RESULTS

Using a sensitive ELISA, we detected Der p 1 in plasma samples from 27 (28%) of 98 mothers and 12 (12%) of 98 newborns, with levels ranging from 0.5 to 50 ng/mL. Of the 27 Der p 1-positive mothers, 12 (44%) had Der p 1-positive newborns. In contrast, none of the 71 Der p 1-negative mothers had Der p 1-positive newborns. When the linear regression analysis was restricted to the 12 newborns in whom cord blood Der p 1 was detectable, cord blood Der p 1 levels in those newborns correlated directly with and were approximately one third of maternal blood Der p 1 levels ($r = 0.98$; $P < .001$) (Fig 1).

Allergic sensitivity to dust mite allergen, as defined by IgE anti-Der p 1 levels greater than 0.5 KU/L, was detected in 49 (50%) of 98 mothers and in none of the newborns. The relatively high proportion of mothers with dust mite allergen sensitivity was accompanied by evidence of a high prevalence of dust mite allergen exposure; IgG anti-Der p 1 was detected in 84 (86%) of 98 tested mothers. Of possible significance is the observation that compared with their mothers, a somewhat higher proportion of newborns (87/98; 89%) had detectable blood levels of IgG anti-Der p 1. This is consistent with the possibility that at least some of the cord blood Der p 1 specific IgG may have originated from the fetus itself. The presence and levels of Der p 1 in cord blood and maternal blood did not differ between Der p 1-"sensitive" and Der p 1-"insensitive" mothers. However, regression analysis restricted to

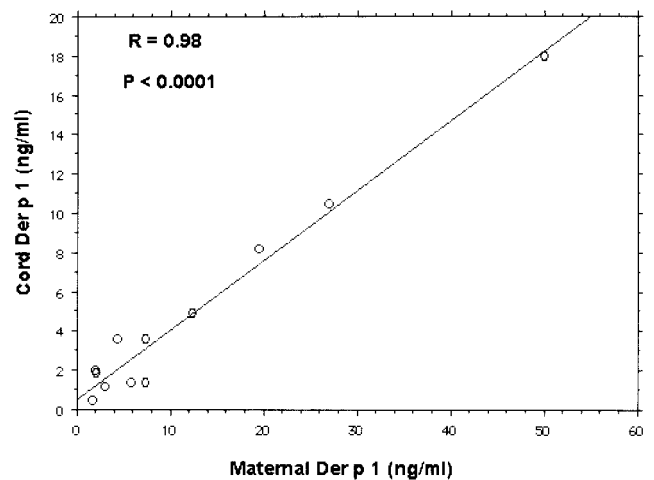


Figure 1. Direct correlation between levels of Der p 1 in mothers and their newborns ($r = 0.98$; $P < .001$).

the 12 Der p 1-positive newborns revealed that cord blood Der p 1 levels tended to positively correlate with maternal blood Der p 1 specific IgG levels ($r = 0.52$; $P = .08$) (Fig 2). In contrast, cord blood Der p 1 levels showed little, if any, relationship to maternal blood Der p 1 specific IgE levels ($r = 0.37$; $P = .23$) (Fig 2).

DISCUSSION

The only previously published study⁴ of house dust mite allergen in umbilical cord blood found that Der p 1 concentrations in the fetal circulation were usually higher than Der p 1 concentrations in the respective mothers and sometimes occurred even in the absence of detectable maternal Der p 1. In contrast, the present study found that levels of Der p 1 allergen in the umbilical cord blood of newborns correlated closely with and were invariably lower than maternal blood levels, being approximately one third of the corresponding maternal blood allergen levels. The reason for the differences in these 2 study results is unclear. However, the differences are important because our results, but not the results of the earlier study,⁴ imply that the presence of house dust mite allergen in the maternal circulation at the time of delivery is a necessary prerequisite for its presence in the blood of newborns and that newborn blood levels of allergen are greatly affected by concurrent maternal blood levels.

Our finding that Der p 1 is detectable in fewer than half of the newborns born to Der p 1-positive mothers indicates that the mere presence of maternal blood allergen does not guarantee allergen transmission and suggests that other factors play a role. One such factor may be the level of maternal blood allergen specific IgG. In the present study, approximately half of the mothers tested were sensitive to house dust mite allergen as manifested by the presence of detectable blood levels of allergen specific IgE antibodies, and an even higher proportion possessed allergen specific IgG antibody. Although the presence and level of maternal blood allergen

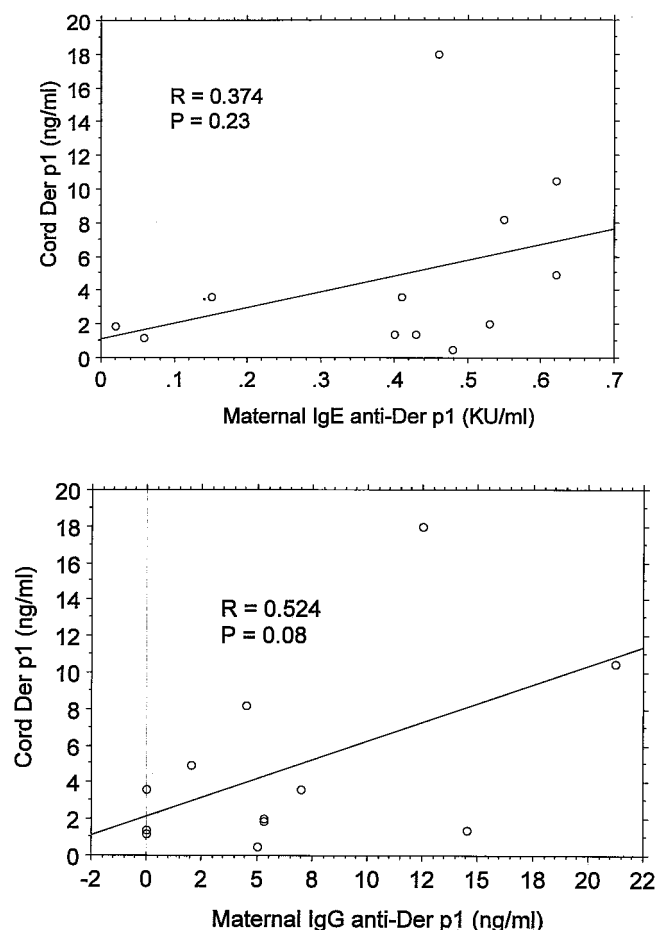


Figure 2. Relationship between levels of newborn Der p 1 and levels of maternal Der p 1 specific IgG ($r = 0.52$; $P = .08$) (top) and specific IgE ($r = 0.37$; $P = .23$) (bottom).

specific IgE antibody showed no obvious relationship to cord blood allergen levels, maternal blood allergen specific IgG antibody levels tended to correlate with newborn allergen levels. This trend is consistent with a possible role for maternal allergen specific IgG antibody in the transplacental passage of allergen from mother to fetus. Two possible mechanisms could be involved. Because maternal IgG is actively transported across the placenta via binding to IgG Fc receptor-bearing placental cells, Der p 1 in the mother's blood could be carried across the placenta in the form of Der p 1 antigen-maternal Der p 1 specific IgG antigen-antibody complexes. Alternatively, in view of the evidence that maternal nucleated cells frequently traffic into the fetus,⁵⁻⁸ these same allergen-antibody complexes could conceivably also traverse the placenta by adsorption to trafficking maternal IgG Fc receptor-bearing cells. If the latter mechanism is the primary mechanism by which maternal Der p 1 traffics into the fetus, the fact that maternal cells are detectable in approximately 50% of fetuses and newborns may explain our current finding

that even when mothers possess circulating Der p 1 and Der p 1 specific IgG, Der p 1 is found in less than 50% of their newborns. Thus, Der p 1 transport from mother to fetus, shown in the previously reported study⁴ to occur as early as 16 weeks' gestation, may require a combination of (1) Der p 1 in the maternal circulation, (2) Der p 1 specific IgG (or IgE) in the maternal circulation, and (3) IgG or IgE Fc receptor-bearing maternal cells that adsorb Der p 1 specific antigen-antibody complexes and traverse the placenta from mother to fetus.

There is a considerable body of evidence showing a relationship between the development of childhood asthma and postnatal childhood exposure to house dust mite allergen Der p 1,⁹⁻¹² including data showing a lower prevalence of asthma in children living in homes successfully treated to reduce the amounts of Der p 1.¹³ In light of this, our confirmation of the fact that allergen exposure can occur in utero by transplacental exposure to maternally derived allergen suggests that in addition to childhood avoidance of aeroallergens, prevention or avoidance of maternal aeroallergen exposure during pregnancy might further reduce the prevalence of childhood asthma.

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- Requests for reprints should be addressed to:*
Joseph Kaplan, MD
Children's Hospital of Michigan
Detroit, MI 48201
E-mail: jkaplan@med.wayne.edu
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