

Maternal Allergen Exposure as a Risk Factor for Childhood Asthma

Susan L. Prescott, MBBS, B Med Sci, PhD, FRACP

Corresponding author

Susan L Prescott, MBBS, B Med Sci, PhD, FRACP
UWA School of Paediatrics and Child Health, Princess Margaret
Hospital, PO Box D184, Perth, WA 6840, Australia.
E-mail: susanp@ichr.uwa.edu.au

Current Allergy and Asthma Reports 2006, **6**:75–80

Current Science Inc. ISSN 1529-7322

Copyright © 2006 by Current Science Inc.

The role of early allergen exposure has been a central focus in the effort to curtail the rising rates of allergic disease. Exposures in pregnancy have been of interest because the first signs of disease are often seen in early infancy. However, so far, strategies to avoid or reduce allergen exposure in pregnancy have had disappointing results in reducing disease. Although there is growing evidence that the fetus is exposed to allergens, this appears to be physiologic and not a risk factor for allergic disease. It is still not clear if this exposure has some role in the context of normal tolerance. Although infants who later develop allergic disease show some differences in neonatal allergen-specific responses, these are not consistent. Furthermore, the magnitude and frequency of responses do not correlate well with maternal allergen exposure, and it now seems likely that these responses do not reflect true immunologic “memory.” Despite this, there is accumulating evidence that a number of other exposures in pregnancy have the capacity to significantly influence immune development and alter the risk for allergic responses to allergens. This underscores the importance of further defining the events in this early period, to determine causal pathways and better strategies for prevention.

Introduction

Allergen exposure in any context can lead to the development of tolerance or sensitization, depending on a complex set of endogenous and exogenous factors. Many host and environmental factors have the capacity to influence immune responses at the time of first allergen encounter, and in the subsequent period when memory immune responses are being determined. This is also likely to hold true for allergen exposure in the antenatal period, and there is preliminary evidence that this is the case, as discussed further later.

For many years, early allergen exposure was regarded as the major factor in the development of allergic disease. Although evidence was limited, this was the basis for allergen avoidance as the first main strategy for primary allergy prevention in the genetically predisposed. The results of such measures have been fairly disappointing or even paradoxical [1•], shifting interest to other potential etiologic factors.

Early immunologic studies also focused on neonatal allergen-specific immune responses as a risk factor for allergic disease. These studies identified a number of interesting relationships. Relative impairment of neonatal Th1 responses in infants at risk for subsequent allergic disease has been a fairly consistent finding throughout this literature. Many studies have shown that atopic risk or subsequent disease are associated with stronger or more frequent lymphoproliferative responses to allergens [2,3], although this is not consistent [4,5] and the significance of these responses is not clear [6••]. It is still not clear if these responses are driven by allergen exposure or by some other process [6••]. Although neonatal allergen-specific responses are typically dominated by type 2 (Th2) cytokine production, this does not appear to be equivalent to the Th2 allergic responses seen in more mature individuals. The complexity of this situation was highlighted by observations that neonatal allergen-specific responses do not necessarily correlate with exposure [3,7] and that some responses are seen in the absence of known exposure [6••,8]. There was also speculation that allergens could reach the fetal circulation in sufficient levels to induce memory responses, particularly for allergens inhaled by the mother in low levels. In this review, new evidence supporting the theory that the fetus can be exposed to allergen in utero is examined. Also, whether this theory has a possible or significant role in conferring risk for subsequent allergic airway disease is explored. On balance, it appears that a number of complex interactions, which may begin in utero, influence evolving immune responses to allergens. Thus, although the level, pattern, and route of allergen exposure appear to play some role, it is the current view that other environmental changes are responsible for the allergy epidemic.

Evidence that Allergens Can Cross the Placenta

Although the significance of neonatal immune responses to allergens remains unclear, there is now good evidence

that allergens (particularly food allergens from the maternal diet) can reach the fetal circulation. Edelbauer et al. [9••] recently detected endogenous nutritive allergens (ovalbumin and beta-lactoglobulin) in human placentas from term and preterm pregnancies. These food allergens were also detected in cord blood samples from all preterm babies ($n = 9$) and in 50% (9/18) of the term babies, at levels of up to 16.7 ng/mL. They also reported a correlation between maternal consumption of these foods and the levels measured in cord blood. However, they noted that there was no relationship between lymphoproliferative responses to these food antigens and levels detected in the circulation. The same group previously demonstrated transfer of inhalant allergen (Bet v1) in addition to food allergens, albeit in very low doses [10]. Fel d 1 cat allergen has also been detected in cord blood, complexed with maternal IgG [11]. These observations provide evidence that food and inhalant allergens can reach the fetus; however, the role of this exposure in determining subsequent patterns of immunologic memory and disease is not clear.

The Relationship Between Maternal Allergen Exposure and Infant Immune Responses

Although there is growing evidence that the fetus is exposed to allergens, particularly from foods, the effects of this exposure are not clear. Allergen exposure (at any age) does not usually lead to sensitization. Rather, allergen exposure is essential for the development of normal tolerance processes. It could be argued that early exposure to innocuous proteins from the future environment may be physiologic rather than pathologic, particularly as this phenomenon is observed in a significant proportion of babies, regardless of atopic risk. As in the early postnatal period, in the absence of "danger" signals, this could be important for initiating tolerance. However, inherent differences in neonatal immune responses to allergens have made it difficult to interpret their significance, and these neonatal responses do not appear to be related to any classic mature memory responses [6••]. This may explain the lack of correlation between level of exposure and neonatal responses in a number of studies [3,7,12,13]. Smillie et al. [3] found no relationship between house dust mite (HDM) Der p 1 levels in maternal beds ($n = 225$) and cord blood mononuclear (MC) lymphoproliferative responses, whereas postnatal exposure appeared to have a significant effect on responses at 1 year of age. Marks et al. [7] also examined the relationship with cytokine responses and found no relationship between Der p 1 concentrations in the maternal bed ($n = 142$) and cytokine (interleukin [IL]-4, IL-5, IL-10, or interferon [IFN]- γ) responses to either phytohemagglutinin (PHA) mitogen or HDM. In contrast, another more recent (but much smaller) study found that levels of HDM from the maternal mattress in early mid-pregnancy was associated with lower numbers of

IFN- γ -producing CD4⁺ T cells, although they only studied 22 cases [14]. A further study ($n = 221$) recently showed a significant dose relationship between HDM allergen levels in maternal beds in pregnancy and neonatal IgE levels (collected 3–5 days after birth) [15]. However, the significance of neonatal IgE is not clear, and this study did not address HDM-specific responses.

On balance, the existing evidence indicates that allergen exposure has a stronger effect in the postnatal period; however, the role and importance of antenatal allergen exposure in "initiating events" is still not clear. Therefore, although there is little debate that cord blood-derived mononuclear cells can respond to allergen, the main questions in this area surround 1) the origin and significance of these responses, 2) the role of these responses in evolving tolerance or sensitization, and 3) the other events during allergen encounter that increase the risk for sensitization. At this stage it appears more likely that other factors are likely to influence the development of sensitization rather than allergen encounter per se.

The Relationship Between Maternal Allergen Exposure and the Risk for Allergic Disease

In most situations, it is difficult to examine the separate effects of antenatal and postnatal exposure on clinical outcomes. In one study, wide variations in birch pollen counts between successive years made it possible to compare cohorts that were presumed to have "low" versus "high" pollen exposure in pregnancy [16]. Although a higher level of maternal exposure to this inhalant allergen in pregnancy was associated with increased risk for birch pollen sensitization in childhood (4.5 years of age), postnatal exposure to birch pollen had a much stronger effect [16]. Maternal allergy also appeared to have a stronger effect on the risk for allergic rhinoconjunctivitis than the degree of pollen exposure in pregnancy [17]. Most studies of nonseasonal inhalant allergens (such as HDM) have not determined the separate effects of pre- and post-natal exposure. Although one small study found an association (nonstatistically significant) between HDM (Der p 1) levels in mothers' beds and the risk for atopic dermatitis in the first year of life [14], much larger multicenter birth cohorts have found no relationship between HDM levels and symptoms such as wheezing in the first 4 years of life [18]. The effects of exposure to pet allergens are more complex, and it is likely that some of the apparent protective effects of early pet exposure may be due to concurrent endotoxin exposure. As discussed further later, endotoxin exposure in pregnancy has the capacity to modify developing immune responses.

The potential role of allergen exposure can also be inferred from studies of early allergen avoidance for primary disease prevention [19••]. Food allergen (egg) avoidance in pregnancy has been shown to reduce levels of maternal ovalbumin (OVA)-specific IgG as well as the

levels of specific antibody reaching the fetus [20]. In this study ($n = 229$), women were randomized to an egg-free diet or a normal diet containing eggs. The effects on this risk for allergic disease in the infants were complex. Children with "mid-range" exposure to egg were at highest risk for atopy at 6 months, whereas low-level or high-level exposure appeared protective. A longer period of follow-up is necessary to determine the clinical significance more clearly. Currently, there is insufficient evidence to support specific allergen avoidance in pregnancy.

A number of large-scale intervention studies have focused primarily on early inhalant allergen (HDM) avoidance with disappointing [21] or even paradoxical effects [1••]. In the Manchester-based study [1••], allergen-reduction was associated with significantly better lung function (at 3 and 5 years). However rates of sensitization were actually significantly higher. In other studies, HDM avoidance beginning in the prenatal period has been associated with reduced sensitization at 3 years of age [22]. Further studies are clearly needed to clarify this. Again, although these strategies were initiated in pregnancy, it is not possible to separate antenatal and postnatal effects. Other prevention studies have used multiple interventions. Some of these have shown apparent reduction in allergic disease [23,24] and sensitization [24], others have not [21,25], although further follow-up is necessary. It remains difficult to determine the isolated benefits of specific allergen avoidance.

Other Antenatal Factors that Could Influence Infant Responses to Allergens

There is mounting evidence that other factors can influence developing responses to allergens and other antigens. Although most studies have focused on the role of early postnatal exposures, more recent studies have shown that antenatal events can also shape the subsequent patterns of allergen response and disease risk. Furthermore, with the recognition that allergens are unlikely to be primarily responsible for the allergy epidemic, "allergen exposure" must be examined in the context of other exposures.

Effects of antenatal microbial exposures on neonatal allergen responses and asthma risk

Most interest in the "hygiene hypothesis" has logically been focused on the early postnatal period when microbial encounter is most apparent. More recent studies indicate that this story may begin before birth. In an animal model, Blumer et al. [26••] demonstrated that antenatal (maternal) exposure to bacterial lipopolysaccharide (LPS) enhances neonatal Th1 IFN- γ responses and inhibited (ovalbumin) allergen sensitization in the offspring. LPS-exposed animals showed attenuated Th2 IL-5 and IL-13 responses as well as parallel reduction of allergen-specific IgE levels. Of great interest, although these animals also showed attenuation of airway eosinophil and macrophage

responses following allergen challenge, airway hyper-responsiveness was not affected. This study provides important experimental evidence that antenatal exposures to microbial products can influence postnatal responses to other environmental antigens, namely allergens. The lack of effect on airway hyperresponsiveness provides further evidence (at least in the mouse) that immune responses and airway hyperresponsiveness are governed by different pathways. This paper also supports earlier observations in humans that LPS exposure is inversely correlated with cord blood IgE levels [27] and that antenatal infection in humans can promote maturation of Th1 IFN- γ function [28]. A Boston study ($n = 498$) [29•] also recently showed that higher LPS levels detected in the home in infants 2 to 3 months of age were associated with lower risk for atopic dermatitis in the first 12 months. It is also possible that there may have been an antenatal component to this effect. Thus, it seems likely that the effects of the level of allergen exposure during this early period are likely to be heavily influenced by microbial burden.

Effects of maternal exposure to cigarette smoke and other pollutants on allergen responses and risk for allergic airway disease

Exposure to cigarette smoke remains a major risk factor for respiratory pathology in early childhood, including asthma and recurrent infections. The antenatal effects on lung development are well established [30], and, unlike other allergy avoidance strategies, there is virtually no controversy surrounding recommendation for cigarette smoke avoidance in pregnancy and childhood. Although there have been extensive studies of the effects of cigarette smoking on neonatal lung mechanics [31,32], there is very limited information about effects on developing immune responses. Cigarette smoke is a major source of free radicals and oxidative stress [33], and may influence placental cytotrophoblast proliferation and differentiation during critical early stages of development [34]. Of concern, effects have also been seen in women passively exposed to tobacco smoke [34]. These disruptions in antioxidant systems could foreseeably lead to further disruptions of local immune function in the placenta and in the fetus. Oxidative stress plays a major role in inflammation. Macrophages infiltrate inflamed tissue and release reactive oxygen species (ROS) and reactive nitrogen species (RNS), and in doing so become depleted of antioxidants, as reflected by their reduced glutathione status [35]. It has been demonstrated that change of "redox" status (reduced glutathione) of antigen-presenting cells (APC) promotes CD4 T-cell Th2 differentiation [35] and the production of IL-4 and IL-5, which contribute to allergic inflammation. Specifically, oxidative stress promotes pro-Th2 signaling by APC, by reducing IL-12 production in mice [35] and humans (which can be reversed by antioxidants [36]). Thus, the effects of modifying oxidative function provide a plausible pathway for smoking in modifying developing immune responses.

Earlier studies noted that parental smoking is associated with higher cord blood IgE levels, providing indirect evidence of an effect of maternal smoking on fetal cellular immune function [37]. More recently, Devereux et al. [38] observed that maternal smoking is associated with stronger neonatal lymphoproliferation. We recently also showed preliminary data that maternal smoking in pregnancy is associated with significantly impaired newborn Th1 IFN- γ function and higher neonatal Th2 (IL-13) responses to both house dust mite and ovalbumin allergens [39]. Although this needs to be investigated further, it indicates that maternal smoking can also influence immune function, and that this may also contribute to the increased risk for asthma and respiratory disease in these children.

Effects of maternal stress on infant immune responses

Although the links between stress and immune function are well recognized, the effects of maternal stress in pregnancy on fetal immune development are still not well understood. Maternal stress can affect hormonal stress response in the offspring [40,41], and two recent studies show preliminary evidence that stress may also affect readouts of immune function [42••,43]. The first of these studies, conducted in Taiwan, showed a significant link between maternal stress and neonatal cord blood IgE levels [43]. The second study, from Boston, showed that chronic caregiver stress measured in the early postnatal period was associated with stronger subsequent lymphoproliferative responses to house dust mite allergen and altered cytokine responses (at 2–3 years of age) [42••]. These effects were seen after adjustment for variations in the level of allergen exposure. Although this study measured caregiver stress in the early postnatal period, it appears likely that at least some of this effect (where the mother is the caregiver) could have been initiated antenatally, when disruptive effects of stress on neuroendocrine function have been noted. This remains to be investigated, but again illustrates that although maternal allergen exposure could influence patterns of immune responsiveness in her child, many other factors are likely to play a role.

Effects of maternal cellular and humoral responses

Maternal allergy appears to confer greater risk for allergic disease in offspring than paternal allergy, suggesting that there may be direct immunologic effects in addition to genetic risk. In genetically similar animals, the risk for sensitization and asthmatic phenotype is greater if the mothers were sensitized [44]. In other animal models, maternal immunization with HDM prior to conception has been shown to protect offspring from allergic sensitization [45]. Although this was associated with the generation of transplacental, allergen-specific IgG, there were also changes in the number of CD4⁺CD25⁺ T cells with presumed regulatory function [45]. The significance of this is not clear but

suggests that maternal effects on the fetus may be mediated through a number of pathways.

Recent human studies by our group [46••] suggest that variations in maternal cellular immune response to the fetus are associated with fetal immune responses and the subsequent development of allergic disease. Specifically, fetal Th1 (IFN- γ) function was directly related to HLA mismatch, and the capacity of the fetus to produce IL-13 and IL-10 was directly related to the level of these cytokines produced by the mother in response to fetal alloantigens. Allergic disease at 6 years of age was associated with significantly higher maternal responses to fetal alloantigens (including lymphoproliferation, IL-13, and IFN- γ responses). The number of previous pregnancies (gravidity) was associated with stronger maternal responses to fetal alloantigens, as measured by lymphoproliferation and IFN- γ synthesis. This provides support for the recent intriguing observations by others [47] that cord serum IgE antibody levels are reduced in higher-order offspring. Together, these observations imply that the level and pattern of immunologic reactivity at the feto-maternal interface may influence the level and pattern of evolving fetal immune responses.

Effects of other maternal exposures on allergen responses and risk for allergic disease

A number of other environmental exposures during pregnancy may potentially alter developing immune responses, including dietary nutrients with immunomodulatory properties [48]. Devereux et al. [38] were the first to note that the magnitude of neonatal responses to allergens ($n = 223$) was inversely related to maternal dietary intakes of antioxidant vitamin E during pregnancy (determined by food frequency questionnaire). We also recently noted that variations in maternal dietary omega 3 polyunsaturated fatty acids (n-3 PUFA) in pregnancy (achieved by fish oil supplementation) could also influence neonatal immune responses [49]. Infant cytokine responses were negatively correlated with n-3 PUFA levels and positively correlated with n-6 PUFA levels, and a number of these relationships were statistically significant [49]. Although this study was designed to assess immune outcomes (rather than clinical outcomes), preliminary clinical data showed a consistent trend for fewer allergic symptoms and less sensitization in the supplementation group [49]. We are now undertaking a larger study ($n = 400$) to determine the significance for allergy prevention. These observations suggest that other exposures in pregnancy have the capacity to influence developing immune responses to allergens, and possibly also the subsequent risk for allergic disease.

Conclusions

The increase in allergic disease has been associated with complex environmental changes. Although allergen exposure is important in dictating the patterns of allergic

sensitization, there is no clear evidence that changes in allergen exposure during early life are responsible for the increased propensity for allergic disease. It appears more likely that other, more significant environmental changes are responsible for the rising rates of disease during the past 40 to 50 years. It is also logical that environmental changes must be exerting effects very early in life, as allergic disease is often manifest within the first months of life. On this basis, the interest in exposures in pregnancy is clearly justified and still needs to be explored further. A number of endogenous and environmental factors during this early period appear to influence developing immune responses and the risk for subsequent disease. Further studies are needed to understand these early events with the ultimate goal of safely preventing allergic disease.

Therefore, although the level and type of allergen exposure in pregnancy do not appear to be responsible for the allergy epidemic, other conditions around the time of early allergen encounter appear to be promoting Th2 allergic responses to these common proteins, and these events are likely to begin in utero. This emphasizes the importance of better defining the events in this early period, to determine causal pathways and better strategies for prevention.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

- 1.●● Woodcock A, Lowe LA, Murray CS, et al.: **Early life environmental control: effect on symptoms, sensitization, and lung function at age 3 years.** NAC Manchester Asthma and Allergy Study Group. *Am J Respir Crit Care Med* 2004, 170:433–439.
- Children at high risk for allergic disease ($n = 251$) were prenatally randomized to stringent environmental control for HDM or no intervention. At 3 years of age children in the active group were more likely to have developed sensitization compared with control subjects (risk ratio, 1.61, 95% CI, 1.02–2.55, $P = 0.04$). However, lung function (airway resistance) was significantly better in the active group.
2. Miles EA, Warner JA, Jones AC, et al.: **Peripheral blood mononuclear cell proliferative responses in the first year of life in babies born to atopic parents.** *Clin Exp Allergy* 1996, 26:780–788.
3. Smillie FI, Elderfield AJ, Patel F, et al.: **Lymphoproliferative responses in cord blood and at one year: no evidence for the effect of in utero exposure to dust mite allergens.** *Clin Exp Allergy* 2001, 31:1194–1204.
4. Prescott S, Macaubas C, Holt B, et al.: **Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T-cell responses towards Th-2 cytokine profile.** *J Immunol* 1998, 160:4730–4737.
5. van der Velden VH, Laan MP, Baert MR, et al.: **Selective development of a strong Th2 cytokine profile in high-risk children who develop atopy: risk factors and regulatory role of IFN- γ , IL-4 and IL-10.** *Clin Exp Allergy* 2001, 31:997–1006.

- 6.●● Thornton CA, Upham JW, Wikstrom ME, et al.: **Functional maturation of CD4+CD25+CTLA4+CD45RA+ T regulatory cells in human neonatal T cell responses to environmental antigens/allergens.** *J Immunol* 2004, 173:3084–3092.

This study demonstrates that neonatal T-cell responses to allergens (and other antigens) differ markedly from those occurring in later life, with significantly high levels of apoptosis and the emergence of CD4+CD25+ (CTLA4+) cell populations with immunosuppressive properties. The findings of this suggest that neonatal responses to allergens represent a default response by recent thymic emigrants, providing an initial burst of short-lived cellular immunity in the absence of conventional T cell memory, which is then limited by parallel activation of regulatory T cells.

7. Marks GB, Zhou J, Yang HS, et al.: **Cord blood mononuclear cell cytokine responses in relation to maternal house dust mite allergen exposure.** *Clin Exp Allergy* 2002, 32:355–360.
8. Prescott SL: **The significance of immune responses to allergens in early life.** *Clin Exp Allergy* 2001, 31:1167–1169.
- 9.●● Edelbauer M, Loibichler C, Nentwich I, et al.: **Maternally delivered nutritive allergens in cord blood and in placental tissue of term and preterm neonates.** *Clin Exp Allergy* 2004, 34:189–193.

This paper documents the presence of endogenous (maternally derived) food allergens (from egg and milk) in human placentas from term and preterm pregnancies, and shows that the levels were correlated between maternal consumption of these foods.

10. Loibichler C, Pichler J, Gerstmayr M, et al.: **Materno-fetal passage of nutritive and inhalant allergens across placenta of term and pre-term deliveries perfused in vitro.** *Clin Exp Allergy* 2002, 32:1546–1551.
11. Casas R, Bjorksten B: **Detection of Fel d 1-immunoglobulin G immune complexes in cord blood and sera from allergic and non-allergic mothers.** *Pediatr Allergy Immunol* 2001, 12:59–64.
12. Miller RL, Chew GL, Bell CA, et al.: **Prenatal exposure, maternal sensitization, and sensitization in utero to indoor allergens in an inner-city cohort.** *Am J Respir Crit Care Med* 2001, 164:995–1001.
13. Chan-Yeung M, Ferguson A, Chan H, et al.: **Umbilical cord blood mononuclear cell proliferative response to house dust mite does not predict the development of allergic rhinitis and asthma.** *J Allergy Clin Immunol* 1999, 104:317–321.
14. Hagendorens MM, Ebo DG, Bridts CH, et al.: **Prenatal exposure to house dust mite allergen (Der p 1), cord blood T cell phenotype and cytokine production and atopic dermatitis during the first year of life.** *Pediatr Allergy Immunol* 2004, 15:308–315.
15. Schonberger HJ, Dompeling E, Knottnerus JA, et al.: **Prenatal exposure to mite and pet allergens and total serum IgE at birth in high-risk children.** *Pediatr Allergy Immunol* 2005, 16:27–31.
16. Kihlstrom A, Lilja G, Pershagen G, Hedlin G: **Exposure to high doses of birch pollen during pregnancy, and risk of sensitization and atopic disease in the child.** *Allergy* 2003, 58:871–877.
17. Kihlstrom A, Lilja G, Pershagen G, Hedlin G: **Maternal pollen allergy may be more important than birch pollen exposure during pregnancy for atopic airway disease in the child.** *Pediatr Allergy Immunol* 2004, 15:497–505.
18. Polk S, Sunyer J, Munoz-Ortiz L, et al.: **A prospective study of Fel d1 and Der p1 exposure in infancy and childhood wheezing.** *Am J Respir Crit Care Med* 2004, 170:273–278.
- 19.●● Arshad SH: **Primary prevention of asthma and allergy.** *J Allergy Clin Immunol* 2005, 116:3–14.

This provides a current comprehensive review of the findings and limitations of a number of cohort studies designed to assess the effects of various allergy prevention strategies.

20. Vance GH, Grimshaw KE, Briggs R, et al.: Serum ovalbumin-specific immunoglobulin G responses during pregnancy reflect maternal intake of dietary egg and relate to the development of allergy in early infancy. *Clin Exp Allergy* 2004, 34:1855–1861.
 21. Brunekreef B, Smit J, de Jongste J, et al.: The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002, 13(Suppl 15):55–60.
 22. Peat JK, Mihalshahi S, Kemp AS, et al.: Three-year outcomes of dietary fatty acid modification and house dust mite reduction in the Childhood Asthma Prevention Study. *J Allergy Clin Immunol* 2004, 114:807–813.
 23. Becker A, Watson W, Ferguson A, et al.: The Canadian asthma primary prevention study: outcomes at 2 years of age. *J Allergy Clin Immunol* 2004, 113:650–656.
 24. Arshad SH, Bateman B, Matthews SM: Primary prevention of asthma and atopy during childhood by allergen avoidance in infancy: a randomised controlled study. *Thorax* 2003, 58:489–493.
 25. Schonberger HJ, Dompeling E, Knottnerus JA, et al.: The PREVASC study: the clinical effect of a multifaceted educational intervention to prevent childhood asthma. *Eur Respir J* 2005, 25:660–670.
 26. Blumer N, Herz U, Wegmann M, Renz H: Prenatal lipopolysaccharide-exposure prevents allergic sensitization and airway inflammation, but not airway responsiveness in a murine model of experimental asthma. *Clin Exp Allergy* 2005, 35:397–402.
- This study provides important experimental evidence that antenatal exposures to microbial products can influence postnatal responses to environmental allergens. Antenatal (maternal) exposure to bacterial LPS enhances neonatal Th1 IFN- γ responses and inhibits allergen sensitization in the offspring.
27. Heinrich J, Bolte G, Holscher B, et al.: Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. *Eur Respir J* 2002, 20:617–623.
 28. Matsuoka T, Matsubara T, Katayama K, et al.: Increase of cord blood cytokine-producing T cells in intrauterine infection. *Pediatr Int* 2001, 43:453–457.
 29. Phipatanakul W, Celedon JC, Raby BA, et al.: Endotoxin exposure and eczema in the first year of life. *Pediatrics* 2004, 114:13–8.
- Higher LPS levels detected in the home at 2 to 3 months of age were associated with lower risk for atopic dermatitis in the first 12 months (OR 0.76; 95%CI, 0.61–0.96) of life.
30. Stick SM, Burton PR, Gurrin L, et al.: Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *Lancet* 1996, 348:1060–1064.
 31. Le Souef PN: Pediatric origins of adult lung diseases: tobacco-related lung diseases begin in childhood. *Thorax* 2000, 55:1063.
 32. Ronchetti R, Macri F, Ciofetta G, et al.: Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. *J Allergy Clin Immunol* 1990, 86:400–407.
 33. Bluhm AL, Weinstein J, Souza JA: Free radicals in tobacco smoke. *Nature* 1971, 229:500.
 34. Genbacev O, McMaster MT, Zdravkovic T, Fisher SJ: Disruption of oxygen-regulated responses underlies pathological changes in the placentas of women who smoke or who are passively exposed to smoke during pregnancy. *Reproduct Toxicol* 2003, 17:509–518.
 35. Murata Y, Shimamura T, Hamuro J: The polarization of T(h)1/T(h)2 balance is dependent on the intracellular thiol redox status of macrophages due to the distinctive cytokine production. *Int Immunol* 2002, 14:201–212.
 36. Utsugi M, Dobashi K, Ishizuka T, et al.: c-Jun N-terminal kinase negatively regulates lipopolysaccharide-induced IL-12 production in human macrophages: role of mitogen-activated protein kinase in glutathione redox regulation of IL-12 production. *J Immunol* 2003, 171:628–635.
 37. Magnusson C: Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986, 78:898–904.
 38. Devereux G, Barker RN, Seaton A: Antenatal determinants of neonatal immune responses to allergens. *Clin Exp Allergy* 2002, 32:43–50.
 39. Noakes PS, Holt PG, Prescott SL: Maternal smoking in pregnancy alters neonatal cytokine responses. *Allergy* 2003, 58:1053–1058.
 40. Vallee M, Mayo W, Dellu F, et al.: Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. *J Neurosci* 1997, 17:626–636.
 41. Liu D, Diorio J, Tannenbaum B, et al.: Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal response to stress. *Science* 1997, 277:1659–1662.
 42. Wright RJ, Finn P, Contreras JP, et al.: Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J Allergy Clin Immunol* 2004, 113:1051–1057.
- Chronic caregiver stress was associated with stronger subsequent lymphoproliferative responses to house dust mite allergen and altered cytokine responses (at 2–3 years of age). These effects provide preliminary evidence that a stressful environmental may affect readouts of immune function very early in life.
43. Lin YC, Wen HJ, Lee YL, Guo YL: Are maternal psychosocial factors associated with cord immunoglobulin E in addition to family atopic history and mother immunoglobulin E? *Clin Exp Allergy* 2004, 34:548–554.
 44. Barrett EG, Rudolph K, Bowen LE, Bice DE: Parental allergic status influences the risk of developing allergic sensitization and an asthmatic-like phenotype in canine offspring. *Immunology* 2003, 110:493–500.
 45. Victor JR Jr, Fusaro AE, Duarte AJ, Sato MN: Preconception maternal immunization to dust mite inhibits the type I hypersensitivity response of offspring. *J Allergy Clin Immunol* 2003, 111:269–277.
 46. Prescott SL, Taylor A, Roper J, et al.: Maternal reactivity to fetal alloantigens is related to newborn immune responses and subsequent allergic disease. *Clin Exp Allergy* 2005, 35:417–425.
- This study suggests that cellular immunologic reactivity (as a result of HLA incompatibility) at the fetal-maternal interface may influence the level and pattern of evolving fetal immune responses.
47. Karmaus W, Arshad SH, Sadeghnejad A, Twiselton R: Does maternal immunoglobulin E decrease with increasing order of live offspring? Investigation into maternal immune tolerance. *Clin Exp Allergy* 2004, 34:853–859.
 48. Devereux G, Seaton A: Diet as a risk factor for atopy and asthma. *J Allergy Clin Immunol* 2005, 115:1109–1117.
 49. Dunstan J, Mori TA, Barden A, et al.: Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomised controlled trial. *J Allergy Clin Immunol* 2003, 112:1178–1184.