

T helper cell 2 immune skewing in pregnancy/early life: chemical exposure and the development of atopic disease and allergy*

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Summary

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During the last 50 years there has been a significant increase in Western societies of atopic disease and associated allergy. The balance between functional subpopulations of T helper cells (Th) determines the quality of the immune response provoked by antigen. One such subpopulation – Th2 cells – is associated with the production of IgE antibody and atopic allergy, whereas, Th1 cells antagonize IgE responses and the development of allergic disease. In seeking to provide a mechanistic basis for this increased prevalence of allergic disease, one proposal has been the 'hygiene hypothesis', which argues that in Westernized societies reduced exposure during early childhood to pathogenic microorganisms favours the development of atopic allergy. Pregnancy is normally associated with Th2 skewing, which persists for some months in the neonate before Th1/Th2 realignment occurs. In this review, we consider the immunophysiology of Th2 immune skewing during pregnancy. In particular, we explore the possibility that altered and increased patterns of exposure to certain chemicals have served to accentuate this normal Th2 skewing and therefore further promote the persistence of a Th2 bias in neonates. Furthermore, we propose that the more marked Th2 skewing observed in first pregnancy may, at least in part, explain the higher prevalence of atopic disease and allergy in the first born.

What's already known about this topic?

- Over the last 50 years there has been an epidemic of atopic disease and associated allergy, the environmental causes of which have not been established.

What does this study add?

- The physiological T helper (Th) 2 cell skewing of pregnancy and early life, and how accentuation of this Th2 skewing is associated with development of atopic disease and allergy is reviewed and highlighted.
- We postulate that certain types of exposures to chemicals can accentuate this Th2 skewing.
- We postulate an alternative explanation, which is independent of the hygiene hypothesis, for the inverse association between birth order and atopic allergy.

Epidemiological studies have shown that in Westernized countries there has been a 300–500% increase in the prevalence of atopic disease over the last 50 years.¹ The current prevalence of atopic dermatitis (AD) in children is estimated to be in the order of up to 20%.² A corresponding increase in other IgE-mediated allergies has also been documented. For example, food allergy has risen rapidly over the last few decades and now peaks at 6–8% in the first few years of life.³ The rapid increase in the prevalence of allergy has been far too rapid to have resulted from a change in the gene pool, the implication being that alterations in environmental conditions, lifestyle and/or diet must be driving an increased predisposition. The most popular explanation for this increase is the 'hygiene hypothesis', in which it is postulated that reduced exposure to infectious microorganisms during early infancy favours the development of atopic allergy.⁴ One key observation that has been used to support this hypothesis is that within families the eldest sibling is more likely to develop atopic allergy than the children that follow. The argument has been that siblings born later are afforded greater protection from allergy by contact with infected older children.⁴

We argue here that during pregnancy there is a developmentally programmed skewing to a T helper cell (Th) 2-biased immune phenotype that persists in the infant following birth.⁵ It is believed that the Th2 skewing of adaptive immune function confers important benefits, including protection of the developing embryo from the attentions of the maternal immune response.⁶ Although there is no doubt that this skewing is hormonally controlled and developmentally programmed, we consider here whether such programming is accentuated by environmental factors, and, in particular, by exposure to chemicals that have irritant and/or sensitizing properties. In addition, we explore the possibility that the firstborn child is more prone to atopic allergy, not only owing to a reduced opportunity to encounter microorganisms, but also from a more profound Th2 skewing of the immune system during the first pregnancy. The relationship and interplay between chemical exposure and encounter with microorganisms in governing the phenotype of the infant immune system are discussed.

Although it is important to acknowledge that there are other immunological and environmental factors that may impact on the characteristics and bias of the infant immune system, the scope of the present article will be restricted to the influence of chemical exposure and experience of microbial antigens (Ags) in pregnancy and early life dictating the infant immune phenotype.

A T helper cell 2 immune bias as a physiological response in pregnancy

The immunology of pregnancy is intriguing. It seems paradoxical that a fetus expressing paternal histocompatibility Ags can survive in what should apparently be the immunologically hostile environment of the mother. In immunological terms, the fetus can be considered a semiallogeneic graft.^{6,7} The phenomenon has been called 'nature's transplant'.⁸ It was

proposed originally by Medawar that fetal survival would require some form of local or systemic immunosuppression, and this view spawned considerable research activity.⁹ However, since then, a rather different picture has emerged of more subtle changes in immune function during pregnancy. It is now known that pregnancy is associated with the development of a Th2 immunological bias that is most pronounced and most important at the maternal–fetal interface.^{5,6}

Pregnancy hormones such as progesterone, leukaemic inhibitory factor, oestradiol, human chorionic gonadotrophin (HCG) and prostaglandin D2 all promote Th2 immunity (reviewed by Sykes *et al.*⁶). Piccini *et al.* studied the effect of progesterone on T cells and found that interleukin (IL)-4 and IL-5 were produced under the influence of progesterone.¹⁰ Furthermore, progesterone was able to induce the production of the Th2 cytokine from established Th1 cell lineage cells.¹⁰

Miscarriage in mice can be effected by Th1 cytokines and blocked by IL-10.^{11,12} Women with a history of recurrent serial spontaneous abortions were found to have lower levels of Th2 cytokines compared with those with a history of normal pregnancy.¹³ Moreover, higher levels of IL-12 and lower levels of IL-4 were identified in cervical secretions of preterm labour, reflecting a local Th1 dominance.¹⁴ Interestingly, a Th1 shift in 30 patients with preterm labour was observed, together with higher levels of inducible IL-2 and interferon (IFN)- γ in peripheral blood mononuclear cells.¹⁵ Women with higher IL-12 levels and a Th1 shift were found to have twice the rate of premature labour.¹⁶ Marzi *et al.* showed higher levels of IL-4 and IL-10, and reduced IL-2 and IFN- γ in serum drawn from pregnant compared with nonpregnant controls; they also found that a Th2-dominant cytokine milieu favoured normal pregnancy compared with pathological pregnancy.¹⁷ Levels of inducible IL-4 are also higher in pregnancy, whereas levels of IFN- γ and IL-2 are reduced.¹⁸

As indicated above, Th2 cytokine production and a Th2 bias at the maternal–fetal interface may be of greater significance than peripheral Th2 immunity.⁶ A Th2 chemokine, thymus and activation-regulated chemokine (CCL17), is produced by trophoblasts and endometrial gland cells, and regulates the infiltration of CC chemokine receptor 4⁺-bearing Th2 lymphocytes into the human decidua during early pregnancy.¹⁹ Trophoblast, decidua and amnion all produce Th2-type cytokines, such as IL-4, IL-10 and IL-13.^{6,20–23} This local production of Th2 cytokines inhibits Th1 cell development and Th1 cytokine production, thereby protecting the fetus and preventing rejection.²⁴ In conclusion, Th1-dominant immunity appears to endanger normal pregnancy and duration to full term, whereas, in contrast, a Th2 basis affords protection.⁶

A T helper 2 cell preference persists into neonatal life

The Th2 skewing of the immune system observed in the neonate and during early life has its origins within the fetus. A further study showed that selective Th2 responses from cord blood cells to common environmental allergens (e.g. house-dust mite

allergen and ovalbumin), characterized by IL-4 and IL-5 expression, were found in a significant number of individuals.²⁵ A distinct CD4⁺ subset expressing IL-4 has been identified in cord blood cells (but not in adult cells) with mRNA of the Th2 master transcription factor GATA binding protein (GATA) 3.²⁶

A range of effector functions is undeveloped in newborn humans.²⁷ With reference to this review, IFN- γ production is markedly reduced in neonates compared with adults, in response to both Ag presenting cell (APC)-dependent and APC-independent stimuli.^{28,29} Further differences observed in neonates compared with adults include reduced IL-12 production, hyporesponsiveness to IL-12 and hyper-responsiveness to IL-4. All of those characteristics will favour the development of preferential Th2-type immune responses.²⁷ Consistent with this, it has been found that expression of the Th2-associated chemokines CCL17 and CCL22 was highest in neonates and then decreased over the course of following 2 years.³⁰

Dendritic cells in cord blood preferentially induce Th2 differentiation in naïve T cells.³¹ The capacity to synthesize bioactive IL-12, a Th-1 polarizing cytokine, is reduced at birth, and IL-12 expression matures and increases relatively slowly during childhood.³² During early life the immune system and T-lymphocyte function matures, which is coincident with changes that serve to improve Th1 immunity.³³ It is possible that, in part, this realigning of the immune system may be influenced by the activation of Toll-like receptors (TLRs) and by other pathogen-associated molecular pattern (PAMP) signals.^{27,34} It is possible that activation of TLRs could impact on T-cell differentiation and thereby the biased Th1/Th2 balance

of the adaptive immune system via epigenetic mechanisms, including chromatin remodelling and DNA methylation.³⁵

The epigenetic control of T-cell maturation has been reviewed and summarized by Martino and Prescott.³⁶ Moreover, the potential impact of epigenetic regulation of Th1/Th2 responses to skin-sensitizing chemicals has been described recently.^{37,38} Methylation of IFNG is the main epigenetic mechanism of control of Th1 expression. Promoter regions in IFNG are hypermethylated in the naïve CD4 T cell and undergo progressive demethylation during Th1 lineage commitment. This is accompanied by silencing (DNA methylation) of IFNG in Th2 cells. Indeed, studies indicate that methylation at IFNG promoter sites are the cause of the selective attenuation of IFNG expression.³⁹ GATA-3-mediated chromatin remodelling at the Th2 cytokine locus (IL-4, IL-5, IL-13) is essential for Th2 lineage commitment. The mechanisms involve changes in permissive histone modifications following T-cell receptor signalling and concomitant silencing (DNA methylation) of IFNG. Therefore, environmental stimuli/lack of stimuli in pregnancy and early life may have the potential to affect Th1/Th2 immunity and programming by affecting these chromatin remodelling processes.

Accentuated T helper 2 cell immune skewing in pregnancy and early life, and subsequent atopic allergy

There is persuasive evidence to suggest that excess Th2 skewing in pregnancy and early life may predispose to the development of atopic allergy (Fig. 1). Kim *et al.* studied 90 mothers

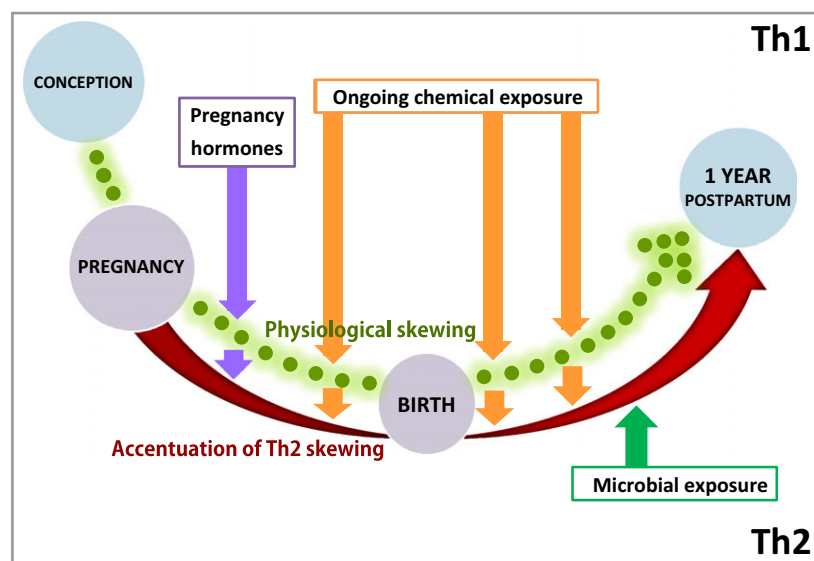


Fig 1. Physiological T helper cell (Th) 2 immune skewing in pregnancy and early life. There is a physiological shift towards a Th2 immune bias during pregnancy to prevent miscarriage and premature labour. This shift from Th1 to Th2 immune dominance is primarily driven by pregnancy hormones such as human chorionic gonadotrophin and progesterone. Th2 dominance persists in the newborn and, under normal physiological conditions, the Th1/Th2 imbalance is corrected during the first year of life. However, environmental factors during pregnancy and early life, such as persistent exposure to haptenic/irritant chemicals, have the potential to accentuate this Th2 bias, leading to permanent skewing of the immune system towards a Th2 bias and development of atopic disease and allergy. The inverse association between birth order and development of atopic disease/allergy may be explained, in part, by Th2 deviation being most marked during first pregnancies than in subsequent ones.

during pregnancy and their resulting child,⁴⁰ and compared cytokine levels during pregnancy (18 weeks of gestation), and the development of wheezing and allergic disease at 3 years of age. Maternal Th1 cytokines were decreased both during pregnancy and postpartum (6 weeks) in children who went on to develop wheezing. Individual maternal IL-4 (Th2 cytokine) levels were higher during pregnancy than postpartum in mothers whose children developed wheezing. In children with atopy the maternal IFN- γ /IL-4 (Th1/Th2 cytokine) ratio during pregnancy was decreased compared with mothers who had children in whom atopy was not observed. The conclusion drawn was that a stronger Th2 bias during pregnancy was associated with childhood wheezing and atopy at 3 years of age.⁴⁰ A separate study measured total plasma IgE levels in 458 women in the third trimester of pregnancy and compared this with childhood eczema at 2 years of age.⁴¹ Prenatal IgE levels were significantly higher among women whose children developed eczema compared with women whose children did not – indicative of a generally greater Th2 bias during pregnancy in mothers whose children developed eczema. Among pregnant mothers with rhinitis and positive prick tests there was a significant increase of Th2 cells in the cord blood of their newborn.⁴² The regulatory T cell (Treg)/Th2 ratio was also significantly decreased in the cord blood.⁴²

Children with both a reduced cord blood Th1/Th2 ratio and reduced Treg/Th2 ratio have been shown to display an increased risk of developing AD by 2 years of age.⁴² A Swedish study examined cord blood levels of Th2- and Th1-associated chemokines, and compared these with allergic sensitization by 2 years of age.³⁰ High levels of Th2-associated chemokines and reduced levels of Th1-associated chemokines correlated with sensitization. A high Th2/Th1 ratio at birth was associated with both atopic protein sensitization and eczema development.³⁰ A study from Leipzig showed that both increased IL-4 and decreased IFN- γ levels at birth were associated with the development of AD by 2 years of age.⁴³ Chang *et al.* reported that elevated total IgE levels at birth (a sign of Th2 skewing) were associated with AD by 6 months of age.⁴⁴ In another independent study it was found that active asthma from 1–5 years of age was positively associated with prior increased levels of IL-13 in the blood and inversely associated with blood levels of IFN- γ at the age of 3 months.⁴⁵ Total plasma IgE levels from 1 to 5 years were associated with increased levels of Th2 cytokines at 12 months and inversely associated with IFN- γ .⁴⁵ Further reports revealing an association between Th2 immune deviation in early life and subsequent development of atopic allergy have been summarized elsewhere.⁴⁶

Therefore, the argument is that normal pregnancy is associated with Th2 skewing of the immune system. This is most pronounced at the maternal–fetal interface and affords protection to the fetus. This Th2 bias persists in the neonate and during early development, and there is evidence that the duration and/or degree of a preferential Th2-type immune phenotype is associated with susceptibility to the development of atopic allergy. We propose that, in addition to the naturally

programmed Th2 bias associated with pregnancy, that exposure, especially during specific temporal windows, to chemical allergens and irritants may serve to accentuate and/or prolong the selective Th2 phenotype such that predisposition to atopic allergy is enhanced. The evidence supportive of this hypothesis is considered below.

Exposure to chemicals may further promote the T helper cell 2 bias in pregnancy and infancy

Maternal atopic disease

Many studies have shown that both maternal and paternal atopy is associated with atopic disease in the child, but the maternal influence appears to be the stronger association, suggesting both a genetic and epigenetic or environmental effect.⁴⁴ There is ample evidence that a Th2 bias is associated not only with the presence of atopic disease, but also with disease severity.^{47,48} For example, Leonard *et al.* showed that the IFN- γ /IL-4 (Th1 cytokine/Th2 cytokine) ratio is inversely related to atopic asthma severity scores.⁴⁷ Therefore, it is of interest that not only the presence of atopic disease in pregnant mothers, but also increased disease activity, is associated with both the development of AD and rhinitis in the subsequent child.⁴⁹ This would be consistent with a model of an accentuated and or prolonged pregnancy/early life Th2 shift predisposing to subsequent atopic disease.

Chemical exposure

We have postulated that personal exposure to chemicals through the skin, gut and airways, and, in particular, to chemical allergens (haptens) or to irritant chemicals, has contributed to the remarkable increase in prevalence in atopic allergy that has been witnessed in recent decades in Westernized countries (the ‘haptens–atopy’ hypothesis).^{50–52} Although chemical allergens cause skin sensitization and allergic contact dermatitis, and irritant chemicals cause irritant contact dermatitis, both of which are associated primarily with Th1 activity, repeated low-dose exposure via the skin to such chemicals may result in a Th2-type immunological bias.⁵¹ This is probably mediated via innate ‘danger’ signalling rather than by a direct influence on the adaptive immune system.^{51,52} Chemical allergens and irritants can produce oxidative stress leading to release of damage-associated molecular pattern molecules that, like PAMPs, are known to serve as danger signals and to be required for the elicitation of optimal adaptive immune responses.⁵³

One of the commonly employed animal models of AD involves repeated topical exposure to a chemical allergen that causes a gradual shift from Th1 dominance to Th2 dominance.^{54–56} It has also been argued that airway exposure to chemicals may induce a Th2 shift.⁵² Recent investigations have demonstrated that experimental food allergy and gut-associated Th2 skewing is promoted by low-dose oral haptens

exposure.⁵⁷ Furthermore, in a Th2-dominant immune background (e.g. patients with AD but also feasibly in physiological Th2-dominated circumstances such as pregnancy) exposure to chemical allergen, which would normally elicit a Th1 response, results in a more selective Th2-type response.⁵⁸

Of recent interest, and of considerable relevance, may be the results of recent investigations reported by Dhingra *et al.*⁵⁹ On the basis of gene expression and cellular studies it was found that fragrance chemical allergens induced responses with a clear Th2-type bias.⁵⁹

There is emerging evidence that certain chemical exposure over the critical time of maternal pregnancy and early life is associated with subsequent atopic disease. Ingestion of haptenic drugs in maternal pregnancy and early life is associated with the development of atopic disease.⁵² A large study found that five maternal occupations during pregnancy, all associated with exposure to specific airborne chemicals, significantly correlated with atopic disease at the age of 18 years in the subsequent child.⁶⁰ In another investigation of maternal occupational exposure patterns an association between exposure to biocides and the development of atopic allergy in offspring was reported.⁶¹ A report also found that maternal occupation exposure, with an increased likelihood of exposure to hapten/irritant chemicals, was associated with subsequent childhood allergy.⁶² Both pre- and postnatal exposure to domestic cleaning chemicals is associated with the development of an infant Th2 immune bias and atopic allergy (but see below regarding confounding factors; there is the possibility of an inverse co-association between the use of cleaning chemicals and domestic endotoxin levels).⁵² House painting during pregnancy has been also identified as a risk factor for the development of early infantile AD.⁶³ Wet wall paint releases several volatile chemicals, including biocides, such as methylisothiazolinone, with haptenic/irritant potential.⁶⁴

Over the last 60 years, during which time the prevalence of atopic allergy has risen, there has also been a substantial increase (among Westernized societies at least) in personal exposure to common chemicals in the form of personal care products, domestic cleaning products, drugs, processed food and the use of volatile airborne chemicals such as perfumes and bleaches. This has been reviewed elsewhere.^{50–52} However, as a single example, between 1958 and 1976 there was a 250% (in real terms) increase in the sale of toiletries, most of which occurred in Western countries experiencing a rapid growth in atopic disease.⁵¹

Therefore, the case for chemical exposure contributing to the current epidemic of atopic disease/allergy is supported by (i) immunological evidence that certain chemical exposures in a Th2-enriched milieu (pregnancy, early life) can lead to Th2-biased expression; (ii) epidemiological studies indicating that certain chemical exposures during this developmental window are associated with subsequent atopic disease/allergy in the child; and (iii) evidence of unprecedented personal exposure to common chemicals over the last 60 years that coincides with the increasing prevalence of atopic allergy.

Chemical exposure and the hygiene hypothesis: complementary effects on predisposition to atopy?

The idea that pathogenic microbial exposure might influence the development of AD originally stemmed, in part, from observations that disease risk is inversely related to sibship size.⁴ PAMPS (e.g. lipopolysaccharide) from pathogenic bacteria have the ability to stimulate TLRs, which, in some circumstances, will lead to Th1-type cytokine expression.⁶⁵ Lack of exposure to infectious microorganisms may lead to a reduction of Th1 stimulation and maturation. This appears eminently plausible; indeed, it would be surprising if pathogenic microbial exposure did not influence immunological maturation and the shape of the immune system. However, attractive as the hygiene hypothesis is, there are only limited data available to support an argument that this has been the only, or even major, influence on the increasing susceptibility to atopic allergy. A recent meta-analysis of 49 papers published between 1966 and 2010 found no convincing evidence of an association between bacterial or viral infections during early life and development of atopic disease/allergy.⁶⁶ Only an inverse association with helminth infection and the development of atopic disease/allergies was found.⁶⁶ A large prospective study for risk factors in the development of AD in children aged 3.5 years found no evidence to support the hygiene hypothesis.⁶⁷ Some studies have shown an association between certain infections (e.g. hepatitis A, measles) or bacille Calmette–Guérin (BCG) vaccination and a lower prevalence of atopy and allergies.⁶⁸ However, these findings have been inconsistent.⁶⁸ In addition, it has been highlighted recently that in ‘unhygienic’ cities there is no negative association between the allergic asthma and airborne viral infections.⁶⁹

There are several epidemiological observations that provide indirect support for the ‘hygiene hypothesis’.^{2,66} However, in some cases other alternative explanations can be entertained. For instance, high levels of exposure to domestic microbial endotoxin can be associated with protection from atopic disease/allergy, whereas lower levels are not.^{2,66} However, an alternative explanation might be that high levels of cleaning chemicals could cause both a reduction in endotoxin levels and predispose to the development of atopic disease/allergy. Similarly, the use of antibiotics in early life is associated with atopy developing.⁷⁰ Rather than this having an effect through altering gut microbes, it could be due to the haptenic effect of most antibiotics, as nonantibiotic oral haptenic drug exposure is also associated with an increased risk of atopic disease/allergy developing;⁷¹ experimental low-dose gut hapten exposure also leads to promotion of food allergy and Th2 skewing.⁵⁷ Drinking unpasteurized milk during the first 2 years of life may protect against the development of atopic diseases because of higher levels of whey protein in the milk delivering oral tolerizing signals rather than increased microbial contamination of the milk.^{66,72}

Although, in theory at least, the hygiene hypothesis provides a plausible explanation for the increased prevalence of

atopic allergy, the evidence available to support the hypothesis is commonly indirect and somewhat patchy.⁶⁶ The argument developed here is that if decreased microbial exposure in infancy acts to maintain or exaggerate a predominant Th2 phenotype driving the development of atopic allergy and atopic disease, then it may well act in concert with the immunological effect from exposure to certain types of chemicals, especially during specific developmental windows (Fig. 1). There may also be shared immunostimulatory pathways between environmental agents that can interact with the immune system, as pathogenic microbes, irritant/haptenic chemicals and some atopic proteins are all able to stimulate TLRs.^{53,65}

Is there another explanation for the inverse association between sibship size and atopic disease/allergy?

This inverse association,⁴ which has been repeatedly reported,⁷³ is considered to be a cornerstone of the hygiene hypothesis. However, the observation that birth order is a risk factor independent of sibship size would suggest prenatal factors are operative in this association.⁷⁴ If maternal Th2 skewing is greater in the first pregnancy compared with later ones then there would be no need to invoke postulated infections from older siblings to explain this inverse association. A review of relevant literature appears to suggest that this is, indeed, the case.

A Finnish study compared hormone levels between primi- and multigravid women.⁷⁵ Serum levels of HCG and progesterone were significantly and consistently higher in primigravid women. Among other immune effects, HCG modulates the Th1/Th2 balance towards a Th2 bias.⁷⁶ As mentioned previously, progesterone favours the development of Th2 cells and the production of the Th2 cytokines IL-4 and IL-5.¹⁰ Kim *et al.* found levels of the Th2 cytokine IL-4 were higher in the first pregnancy.⁴⁰ In order to explain why multigravida women are less likely to contract malaria a study from Africa measured cytokine levels during pregnancy.⁷⁷ Comparing noninfected primi-/secundigravid women with noninfected multigravid women they found levels of Th1-associated IFN- γ were sevenfold higher in multigravid women.⁷⁷ Independent studies have also found that cord blood IgE levels were significantly higher in the first pregnancy, again in favour of a more marked Th2 bias.^{78,79}

One other observation regarding pregnancy is worthy of mention. Recent attention has focused on the phenomenon that preterm birth is negatively associated with development of atopic disease/allergy, while post-term delivery is positively associated with it.^{80,81} We postulate that the most likely explanation for this is co-association. Accentuated Th2 skewing during maternal pregnancy would be associated with both later term delivery and increased risk of developing atopic disease/allergy, while the opposite would be true for defective Th2 skewing.

Concluding comments

Pregnancy is associated with a natural, developmentally programmed skewing of the immune system to a Th2 bias, which affords protection to the fetus. We hypothesize that this Th2 bias may be accentuated and/or prolonged by exposure to certain chemicals, and, in particular, to chemicals that have sensitizing or irritant properties. We argue that such accentuated or more prolonged skewing to a Th2 immunological phenotype would be associated with a predisposition to the development of atopic allergy, and that this mechanism may have contributed to the increased prevalence of atopic diseases that has been witnessed in Westernized societies during recent decades.

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