

EDITORIAL

Does pregnancy prevent atopy?

The world-wide increase in the prevalence of asthma, eczema, hayfever and atopy remains unexplained. In the absence of significant changes in the gene pool, interest has concentrated on changes in environmental factors. Amongst the most attractive explanations is the so called 'hygiene hypothesis', which proposes that exposure to infection early in life protects against the development of atopy, and that the increase in atopy and allergic diseases results from decreased exposure to infection in more affluent and cleaner societies [1]. There are three tenets to the hygiene hypothesis: the protective role of siblings against the development of atopy and allergic diseases; the protective role of early life infection against the development of atopy and allergic diseases; and the prenatal and postnatal development of immune function [2].

The hygiene hypothesis developed from the original, and at the time unexplained, observation by Strachan of an inverse relationship between family size and both hayfever and eczema in two British birth cohorts [3]. He speculated that the observations could be explained if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally. Subsequent studies have confirmed the inverse relationship between atopic diseases and family size, and extended the plausibility by demonstrating the same relationships with birth order [4–6]. The relationship is strongest for reported hayfever and eczema and for objective measures such as skin prick tests and circulating levels of allergen-specific IgE [4–10]. In contrast, reports on the relationship between family size or birth order and asthma are inconsistent [11]. This is probably due to differing wheezing phenotypes in childhood being lumped together under the collective umbrella of asthma.

There are curiosities to the inverse relation between the size of sibship and the risk of atopy that do not fully support the hygiene hypothesis. The protective effect seems confined to the size of sibship as opposed to close contact with other young children, particularly for those outside the home. Although there is some evidence for an additional protective effect from sharing a bedroom as a child, independent of family size [10], a number of large studies examining attendance at preschool nurseries have demonstrated no protective effect [5,10,12,13]. Also, although the size of families has decreased significantly in developed countries, the size of decrease does not appear sufficient to

explain the magnitude of increase in reported prevalence in atopy and allergic diseases [11,14].

The evidence for a protective role for infection early in life is not as clear. Cross-sectional studies relying on parental recall of the burden of early childhood infection fail to show any strong evidence of protection [15]. Exposure to a variety of infectious agents or immunizations early in life have been proposed to protect against the development of atopy and allergic diseases including measles, mycobacteria (including tuberculosis), pertussis and hepatitis A [reviewed in 1]. There is contradictory evidence against each putative agent with the exception of hepatitis A infection [16]. Differences in the intestinal microflora of infants in Sweden and Estonia have been proposed as a factor in the marked differences in the rate of atopy and allergic disease between the two countries [17], and it is possible that the widespread use of antibiotics in affluent countries could also influence the rate of atopy by altering the intestinal microflora [18].

The hygiene hypothesis gained biological plausibility with greater understanding of the patterns of immune responses *in utero* and infancy [2]. Fetal and cord blood cells respond to either non-specific mitogens or specific allergens with a predominantly Th2-type cytokine response [19]. The transition from the default fetal Th2 response to a Th1 response may be delayed in atopic subjects [20]. It is proposed that exposure to infectious agents postnatally is a prerequisite for the switch from a Th2 to a Th1 response [2], and, in the absence of infective agents, the default Th2 response persists.

In this current issue of Clinical and Experimental Allergy, Sunyer and colleagues report the relationship between maternal atopy and the number of offspring in nearly 1500 mothers in three centres in Spain and the UK [21]. Atopy was assessed by skin prick test measurement to seven common allergens performed during the first trimester, during the third trimester or 6 months post-delivery dependent on centre. Only 61% of fathers were tested. There were demographic differences between the three centres, with more first-time mothers in Menorca. The number of mothers with more than two offspring is small, and the number of fathers in the same position is even smaller. Despite these deficiencies the authors demonstrate an inverse relationship between maternal atopy and the number of offspring. The relationship was independent of maternal age, social class, smoking, or self-reported asthma

or hayfever in the mother. In contrast there was no relationship with paternal atopy.

The findings of Sunyer and colleagues of a decreased risk atopy with increasing number of offspring are not supported by previous investigators [6,22,23], who found either no increased risk or a protective effect from pregnancy. However, previous investigators have relied on self-reported allergic diseases and not on the more objective skin prick measurement used by Sunyer. Four possibilities warrant consideration. Firstly, that skin prick test results change during pregnancy – the findings were strongest in Ashford and Barcelona where the testing was performed in the first and third trimester, respectively, while the relationship was ill-defined in Menorca where testing was performed post-delivery. Secondly, that atopy decreases fertility, although this would be at odds with trends in atopy and fertility in the developed world. Thirdly, that pregnancies in atopic mothers have a worse outcome. Although asthmatic mothers have an increased risk of perinatal complications, the magnitude, even in poorly controlled asthmatics, is not sufficient to markedly affect the number of births [24]. The most likely cause is that successive pregnancies decrease atopy in the mother (and possibly the child). If Sunyer and colleagues findings are borne out, this offers an elegant explanation to Strachan's original observation.

It has long been recognized that the offspring of atopic parents are at an increased risk of developing atopy, and that there is a dose response with greater risk if both parents are atopic. The pattern of inheritance for atopy remains unclear, but there are a number of reports that the offspring is more likely to be atopic if the mother rather than the father is atopic [25]. If Sunyer and colleagues findings are reproducible, there is a complex relationship between the mother and fetus that decreases the mother's atopy. Thus the fetus is more likely to be atopic if the mother (rather than the father) is atopic, and with increasing number of offspring the mother's atopy decreases, and so does the risk of atopy in subsequent offspring. This implies that the effects of the feto-maternal relationship last long after the child is born.

What mechanisms could explain these findings? To maintain pregnancy the maternal host has to deactivate the usual immunological responses to non-host molecules. The placental trophoblast produces high levels of Th1 inhibitory and Th2 promoting cytokines and hormones, notably interleukin 4 (IL-4), IL-10, progesterone and prostaglandin E₂. It is proposed that the Th2 bias of the feto-maternal unit protects the fetus by directing the immune response away from Th1-driven cell-mediated immunity [2]. Systemic levels of both Th1- and Th2-type cytokines decrease in the mother during pregnancy, and rise in the post-partum period [26]. It is possible that this cytokine rebound resets

the immune axis in favour of a Th1 bias. There is circumstantial supportive evidence as both autoimmune thyroiditis and rheumatoid arthritis, where Th1-type responses may dominate, both increase in the post-partum period [27].

An alternative explanation is feto-maternal cell trafficking and the possibility of microchimerism. Microchimerism indicates that a body contains low levels of non-host cells derived from a different individual. It has been known for over a century that fetal blood cells enter the maternal bloodstream early in pregnancy. Using polymerase chain reaction techniques it has become clear that these fetal cells can persist in the maternal circulation for decades after completion of pregnancy. The persistence of these fetal cells as a microchimera is implicated in the pathogenesis of many autoimmune disorders [28], most noticeably scleroderma [29], but also possibly primary biliary cirrhosis, lupus, thyroid disease, rheumatoid arthritis and Sjögren's syndrome [30]. The passage of cells in the feto-maternal unit is a two way process, and maternal DNA can also be detected decades later in the offspring [31], and again has been implicated in the pathogenesis of autoimmune disease. Could feto-maternal cell trafficking and persistent microchimerism explain the decrease in atopy in both the mother and the offspring in successive pregnancies through an as yet uncharacterized mechanism?

The final possibility is through changes in maternal nutrition with increasing parity. It is known that fetal growth is determined by many different factors including maternal nutrition, and that indices of fetal growth correlate with the risk of atopy later in life [32]. If the findings of Sunyer and colleagues are replicated, the plausibility of the hygiene hypothesis would be dented without one of the central tenets. The challenge must be to determine which one of the many factor(s) of our affluent society contribute to the increase in atopy.

References

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