

EDITORIAL

Hormones not hygiene? Birth order and atopy

Two features of the world-wide increase in atopic sensitization are striking – the huge increase in the prevalence of atopic sensitization and as a result, how common atopic sensitization has now become. In some populations up to 50% of subjects have evidence of atopic sensitization [1]. The inheritance of both atopic sensitization and serum total IgE are complex, but there is clearly a familial component. As IgE is pivotal to the host defence against intestinal parasites, it has been assumed that variations within the familial tendency to atopic sensitization and serum IgE might represent a selection advantage against intestinal parasites.

An alternative postulate is that atopic sensitization confers reproductive advantages within the mother. Pregnant women have a propensity towards humoral immunity and suppression of cell-mediated immunity, and suppression of Th1 function is essential to a successful pregnancy [2, 3]. The foeto-placental unit skews towards a Th2 pattern of immunity by locally secreting cytokines in the uterine epithelium and trophoblast [4]. This shift is also responsible for the exacerbation of symptoms in conditions where humoral immunity is the major mechanism, such as systemic lupus erythematosus [5]. Similarly, conditions such as rheumatoid arthritis can go in to a remission due to diminished cell-mediated immunity [6].

In this issue of *Clinical and Experimental Allergy*, Westergaard and colleagues report their findings on the rate of allergic rhinitis in a large cohort of Danish women and relate this to reproductive history [7]. They utilized the Danish national birth cohort study to investigate self-reported and physician-diagnosed allergy – specifically allergic rhinitis and/or hayfever. They related the history of reported allergic rhinitis to the mothers' reproductive history: the number of previous pregnancies, the number of previous spontaneous abortions, the waiting time to the current pregnancy and the age of menarche. The authors estimate that approximately half of all Danish women gave information to the birth cohort study, and they had information from 31 749 women over a 2.5-year period. The authors can be criticised for confining their analysis to patient-reported allergic rhinitis, and there are no objective measures of atopy, details on other atopic diseases or need for medication relevant to atopic diseases. Nevertheless the authors report three findings of note. Firstly, the rate of allergic rhinitis was lower if the woman had been pregnant before (either live birth or incomplete pregnancy). Secondly, women who reported allergic rhinitis were less likely to have taken over a year to conceive than those who did not have allergic rhinitis, and that allergic rhinitis was not associated with the risk of spontaneous abortion. Thirdly, those with allergic rhinitis had a younger age of menarche.

The findings that women in their second or greater pregnancy (and not necessarily live birth) have a decreased rate of allergic rhinitis has two possible explanations – either that atopy decreases the rate of conception/birth; or that pregnancy decreases atopic sensitization in the mother, although the two possibilities are not mutually exclusive. However Westergaard

and colleagues also demonstrate a statistically significant inverse trend between waiting time in months to conception and allergic rhinitis, suggesting that an atopic disease increases the chance of conception/birth. Although these two observations appear contradictory, a more plausible explanation is that atopy *per se* increases the chance of conception, but with increasing pregnancy the rate of atopic sensitization decreases.

The relationship between atopy and birth order affect described by Strachan [8] has in the past been ascribed to postnatal effects, and has become a central plank in the hygiene hypothesis. However, more recent observations suggest that the birth order effect may reflect *in utero* effects. The decreased rate of allergic rhinitis in mothers who have previously been pregnant reported by Westergaard accords with the previous findings of Sunyer, who demonstrated a decreased risk of atopic sensitization as determined by skin prick testing with increasing birth order [9]. Cord blood serum total IgE has consistently been demonstrated to be a significant risk factor for the development of later atopy [10–13], and Karmaus and colleagues have demonstrated that cord total blood IgE decreases with birth order [14], while Devereux and colleagues have reported decreasing T helper cell proliferative responses of cord blood mononuclear cells with increasing birth order [15]. Thus, we are observing an effect whereby increasing birth order decreases both the rate of atopic sensitization in the mother, and the risk of atopic sensitization in the child [16].

Age at menarche is a reflection of the individual's endogenous oestrogen status [17]. Early age of menarche is associated with increased oestrogen levels at the onset of puberty, and this effect lasts into adulthood and is reflected in an increased risk of breast cancer [18]. Increased oestrogen levels have significant effects on the immune system – a skewing of the T helper response towards the Th2-type response [19], a significant inhibition of T cell transmigration [20], and enhanced histamine release [21]. In a murine model low-dose exposure to oestrogen results in thymic atrophy [22]. In humans, *in utero* exposure to the oestrogen diethylstilbestrol results in long lasting alterations in T cell-mediated immunity [23]. Thus, the earlier age of menarche in those women reporting allergic rhinitis is consistent with increased oestrogen levels having an effect on the development of atopy.

The findings of Westergaard and colleagues suggest that earlier age of menarche (as a consequence of higher oestrogen levels) is associated with an increased risk of allergic rhinitis in adulthood, although this could be an epi-phenomenon as birth order may independently affect age of menarche [24]. In contrast, Xu and colleagues reported an inverse relation between age of menarche in over 11 000 Finnish mothers and atopic sensitization in the offspring at age 31 years [25]. Although a mother's age of menarche significantly influences the daughter's age of menarche, Xu did not find an association between the child's age of menarche and risk of atopic sensitization at age 31 years. Interestingly, in the study reported by Xu, there had been a significant decrease in age of menarche in the offspring

compared to the mother's (14.1 years vs. 12.9 years) over approximately a 33-year period. Although it would be attractive to speculate that this decrease in age of menarche could have contributed to the observed increase in atopic disease, it does not accord with world-wide trends, where there is an extremely strong consensus that there has been little, if any, change in age of menarche over the last 40 years [26, 27].

The findings of Westergaard and colleagues are consistent with a number of current hypotheses – that atopy confers a small but significant biological advantage on the rate of conception, but does not affect the rate of conception leading through to live births, which is influenced by other factors. Hormonal factors, most noticeably oestrogenic effects, have an effect on the immune system promoting a shift from the Th1 to Th2 phenotype, and this relationship is reflected in the inverse relationship between age of menarche and risk of allergic rhinitis in early adulthood. Finally, the decreased risk of allergic rhinitis in those mothers who have had a previous pregnancy accords with the increasing in evidence that each subsequent pregnancy has a profound and long-lasting effect on the rate of atopy, both in the mother and the child [16]. Although an overall picture on the causes of the increase in atopic sensitization remains unclear, the findings of Westergaard and colleagues are useful pieces that give structure to the jigsaw.

References

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