

New pregnancies and loss of allergy

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Abstract

Background Inverse associations between allergic disease and sibship have been consistently described and are frequently explained by purported lower rates of early infection among children from small families. Alternative explanations include the possibility that pregnancy itself determines maternal atopic status.

Objective To test the hypothesis that atopy defined by skin prick test (SPT) declines with increasing numbers of pregnancies.

Methods At enrolment to a birth cohort, mothers were skin prick tested to three common allergens. Seven years later these women underwent a second SPT and provided information on their reproductive histories. At both visits, information on allergic disease was also sought.

Results Twenty five (15%) women who were initially atopic were no longer so at the second visit; loss of hayfever symptoms was reported by 33 (29%) women. Women with higher numbers of intervening pregnancies were more likely to 'lose' their atopy ($P = 0.05$) and symptoms of hayfever ($P = 0.02$); this was not true for asthma. The findings could not be accounted for by maternal age.

Conclusion Successive pregnancies may in part determine a mother's atopic state. Since maternal atopy is a risk factor for childhood atopic disease, this process may affect the atopic state of successive children. These findings suggest an alternative explanation for the sibship effect in allergic disease.

Keywords allergic disease, atopy, family size, parity, pregnancy

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Introduction

There is consistent evidence that the prevalence of allergy is lower in children who have several siblings [1]. Originally suggested as a reflection of lower rates of early infection in children from small families [2], alternative explanations for this sibling effect – or part of it – need to be considered [3].

In 2001, we published data from three birth cohorts suggesting that mothers with more children were less likely to be atopic as demonstrated by skin prick test (SPT) [4]. One explanation for this observation is that women 'lose' their atopy with successive pregnancies. To test this, we re-examined mothers from one of the cohorts and related the changes in their atopic status to the number of their intervening pregnancies.

Methods

In November 1993 recruitment to a birth cohort began in Ashford, Kent. Over the next eighteen months all newly pregnant women who presented for ante-natal care to one of

three general practices were invited to take part; 658 (93%) agreed and 642 babies were born to 625 women. At recruitment all but three of the women and 542 (87%) of their partners underwent SPTs with Allergopharma (Hamburg, Germany) allergens. Information on current allergic disease (asthma and hayfever) was collected from all participants.

By January 2002, 35 women were no longer taking part in the study and two had died. Five hundred and two women were still living within a 10 mile radius of Ashford and were thus eligible for the current study. We revisited 483 (96%) to repeat their SPTs and administer a questionnaire enquiring into all pregnancies and their outcomes and again into current symptoms of asthma and hayfever. The repeat skin tests were carried out by the research nurses (C. W., P. M. or S. M.) without knowledge of the results from the original tests. Tests were performed by the same research nurse on each occasion for 95% of the participants.

Within the entire cohort, the prevalence of atopy among those tested again (34.0%) and those who were not (34.5%) did not differ ($P = 0.90$). Women were revisited a mean of seven (range 5–8) years after their initial SPT. At the second visit their mean age was 34 years (range 22–48).

We also repeated SPTs for a sample of (male) partners who were atopic at the time of enrolment ($n = 138$; 73% of those eligible). Their mean age was 38 years (range 26–49); on average they were re-tested seven (range 3–8) years after the first SPT.

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Statistical methods

A SPT was recorded as positive when its mean weal diameter was at least 3 mm greater than the response to a negative control (saline). Subjects are described as atopic if they had one or more positive SPTs to extracts of *Dermataphagoides pteronyssinus*, cat fur or grass pollen.

Among the women, changes in atopic status and current symptoms of asthma or hayfever were related to the number of their pregnancies (and live births) between the first and second SPTs using χ^2 tests and χ^2 for trend. Associations between ordered categories and continuous data were investigated using a non-parametric test for trend. Multivariate logistic regression techniques were used to investigate independence of associations found. In particular, the role of maternal age, expressed continuously, was examined. These results were expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). All analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) and Stata (Stata Corporation, College Station, TX, USA) software.

Results

One hundred and sixty four (34%) of the 483 women seen twice were atopic at their first test. Twenty five (15%) of these were not atopic at their second test. Of those 319 women who were not initially atopic, 33 (10%) were atopic at the time of their second SPT.

Symptoms of current asthma were reported by 48 (10%) women at the first interview; at the time of the second interview 16 (33%) of them no longer reported such symptoms. Conversely, ten women (2%) of the 435 who were not asthmatic at first interview reported that they were at second. Loss of hayfever symptoms was reported by 33/115 (29%) women; 24/368 (7%) reported that they had acquired such symptoms between the two surveys.

At the time of re-examination, 221 (46%) women reported that they had not been pregnant since their first SPT (Table 1). The remainder reported between one and seven intervening pregnancies. Women with more intervening pregnancies were more likely to have lost their atopic status, a trend that was statistically significant ($P = 0.05$). These women with more intervening pregnancies were also more likely to have ceased reporting current hayfever ($P = 0.02$; Table 1) but no such pattern was found with asthma. Women were most likely to lose positive tests to *D. pteronyssinus* or cat fur; although the pattern of loss with intervening pregnancies was seen for each aeroallergen separately it was clearest for grass pollens. In only one case was there a potential effect of season: a woman had a positive skin test to mixed grass pollens at the first visit (in August) and a negative test at the second (in February). Women who had lost their positive skin test to cat fur were no more likely to have stopped keeping a cat (29%) than women whose test remained positive (31%).

We considered changes in atopic status to be 'borderline' if they were defined by the skin response to the pertinent aeroallergen lying between 2 and 4 mm (diameter) at both visits. In this way, 8 (24%) of the women who were not atopic at the first visit but atopic at the second were classified as

having 'borderline changes'; similarly 6 (24%) women who lost atopy had 'borderline changes'.

We also analysed these findings by number of intervening live births. Two hundred and forty-one (50%) women reported that they had not had any further children since their first SPT. The remainder reported between one and four intervening births. A similar pattern was observed; women with more intervening births were more likely to have lost their atopic status and current hayfever, although these trends were not statistically significant ($P = 0.62$ and 0.14 , respectively).

Women with fewer intervening pregnancies were older (Table 1; $P < 0.001$) and atopic mothers were slightly older than non-atopic mothers (35.7 vs. 34.9 years; $P = 0.08$). However, loss of atopy was evenly spread across different age categories; for the 71 atopic women with no further pregnancies, 3 (12%) of those aged 34 became non-atopic. The proportions for women aged 35–37 and 38 were 16% ($n = 3$) and 8% ($n = 2$), respectively ($P = 0.66$).

Using logistic regression, maternal age was not significantly associated with loss of atopy (OR 0.95, 95% CI [0.86, 1.06], $P = 0.35$ per year). For each intervening pregnancy the crude OR was 1.65 (1.03, 2.65), $P = 0.04$; little change was observed when this association was adjusted by maternal age (OR 1.62 [1.00, 2.62], $P = 0.05$). The association between intervening pregnancies and loss of hayfever remained significant after adjusting for maternal age (crude OR 1.77 per pregnancy [1.08, 2.90], $P = 0.02$; adjusted OR 1.77 [1.08, 2.91], $P = 0.02$).

At the second skin test, 18 (13%) men were no longer atopic. At the first interview, 29 (21%) men reported current asthma and 73 (53%) reported current hayfever. By the second interview, 9 (31%) men were no longer reporting current symptoms of asthma and 16 (22%) were no longer reporting current symptoms of hayfever. The rates for new current symptoms for the men were 6% for asthma and 14% for hayfever.

Discussion

In this study, we repeated SPTs to common allergens over a gap of 7 years. We found that women who had had higher numbers of intervening pregnancies were more likely to have lost their atopic status. We also found a corresponding decrease in reported current hayfever. It has not been possible to explain these associations by maternal age. As in our original study [4], we did not observe any relationship between pregnancy and current symptoms of asthma perhaps because the prevalence of these was low.

Beyond its small size, we have considered a number of limitations of this study. At the time of their initial skin test, all the women were pregnant but just nine were so at the time of the second test. Although pregnancy may affect the response to prick testing any such effect would have been common to all studied women and we think this is unlikely to have produced any systematic bias. Skin prick testing is subject to variations in both technique and interpretation. We attempted to minimize these by maintaining the research nurses' 'blindness' between the first and second test results and by ensuring, as far as possible, that women were tested by the same nurse on each occasion. 'Atopic status' is a somewhat

Table 1. Number of intervening pregnancies and atopic status (defined by skin prick test) and hayfever

Number of intervening pregnancies	Mean age	Atopic status at first visit (1993–1995)		Change in atopic status (2002)			
		Neg	Pos	Neg/Neg <i>n</i> = 285	Neg/Pos <i>n</i> = 33	Pos/Pos <i>n</i> = 142	Pos/Neg <i>n</i> = 25
0 (<i>n</i> = 221)	36.5	150	71 (32%)	134	16 (11%)	63	8 (11%)
1 (<i>n</i> = 179)	34.6	109	70 (39%)	101	8 (7%)	60	10 (14%)
2 (<i>n</i> = 59)	33.3	43	16 (27%)	36	7 (16%)	11	5 (31%)
3+ (<i>n</i> = 23)	32.5	16	7 (30%)	14	2 (13%)	5	2 (29%)
	<i>*P</i> < 0.001			<i>*P</i> = 0.56		<i>*P</i> = 0.05	

Number of intervening pregnancies	Mean age	Current hayfever at first visit (1993–1995)		Change in current hayfever (2002)			
		Neg	Pos	Neg/Neg <i>n</i> = 344	Neg/Pos <i>n</i> = 24	Pos/Pos <i>n</i> = 82	Pos/Neg <i>n</i> = 33
0 (<i>n</i> = 221)	36.5	171	50 (23%)	158	13 (8%)	40	10 (20%)
1 (<i>n</i> = 179)	34.6	132	47 (26%)	125	7 (5%)	32	15 (32%)
2 (<i>n</i> = 59)	33.3	47	12 (20%)	44	3 (6%)	7	5 (42%)
3+ (<i>n</i> = 23)	32.5	18	5 (22%)	17	1 (6%)	2	3 (60%)
	<i>*P</i> < 0.001			<i>*P</i> = 0.58		<i>*P</i> = 0.02	

Number of intervening pregnancies	Mean age	Current asthma at first visit (1993–1995)		Change in current asthma (2002)			
		Neg	Pos	Neg/Neg <i>n</i> = 425	Neg/Pos <i>n</i> = 10	Pos/Pos <i>n</i> = 32	Pos/Neg <i>n</i> = 16
0 (<i>n</i> = 221)	36.5	201	20 (9%)	195	6 (3%)	13	7 (35%)
1 (<i>n</i> = 179)	34.6	163	16 (9%)	160	3 (2%)	12	4 (25%)
2 (<i>n</i> = 59)	33.3	51	8 (13%)	51	0	3	5 (63%)
3+ (<i>n</i> = 23)	32.5	19	4 (17%)	18	1 (5%)	4	0
	<i>*P</i> < 0.001			<i>*P</i> = 0.58		<i>*P</i> = 0.83	

*Tests for trend. Neg, negative; Pos, positive.

arbitrary categorization of what is probably a continuous trait. Naturally, then, some of the changes we observed resulted from small ('borderline') changes in mean weal size, but again these were equally distributed among women who 'gained' and women who 'lost' their atopic state. There was little evidence that the time of year in which the skin tests were performed could explain our findings; or that the changes might reflect the complex relationships between family size and domestic allergen exposures in this cohort [5]. Due to the delicate nature of the subject, we may have incomplete data on all pregnancies although only one woman declined to answer questions regarding her pregnancies. Again we doubt that any variations in the quality of these data would be related to atopic status.

These findings suggest that atopic status is in part affected by repeated pregnancies and we propose this as an appropriate explanation for our original observation that the prevalence of atopy is lower in women – but not men – with several children [4]. Others too have reported associations between pregnancy and relevant immunological or clinical measures. Cord blood mononuclear cells from women

delivering their first child were less reactive to house dust mite allergens than cells from mothers giving birth to their second or subsequent children although this may have been attributable to differences in maternal age [6]. Karmaus and colleagues have reported an inverse association between birth order and cord blood IgE and proposed that the sibling effect may have its origin *in utero* [7]. In a large population of Danish women the rate of self-reported allergic rhinitis was lower among women who had previously been pregnant [8].

The mechanisms whereby a mother's allergic status may be influenced by her obstetric history remain elusive although there seems little doubt that such an effect is plausible. Pregnancy after all involves the carriage of a more or less 'foreign' fetus and repeated pregnancies are likely to require an increasing degree of immune adjustment. Maternal immunomodulation in this way could reasonably be expected to be transmitted to the developing fetus. If our findings are reproducible in a separate (and perhaps larger) population then they may explain in part at least the sibling effect in allergic disease and thus enrich the debate over the 'hygiene hypothesis'.

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