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Original article

Prenatal factors and occurrence of rhinitis and eczema among offspring

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Background: It has recently been suggested that an atopic phenotype may already be programmed *in utero*. We examine here the association between prenatal factors and the subsequent development of allergic rhinitis and eczema among offspring.

Methods: The analyses were based on 8088 children in a population-based prospective birth cohort started in northern Finland in 1985–6.

Results: The prevalences of allergic rhinitis and allergic eczema by the age of 7 years among 8088 children were 3.3% and 6.7%, respectively. The results indicate that low parity, febrile infections in pregnancy, and the use of contraceptives before pregnancy increased the risk of allergic disorders among children. Bleeding in the first trimester and a greater weight gain during pregnancy appeared to be risk factors for rhinitis only. Children whose mothers experienced infections in the first trimester had ORs of 2.65 (95% CI 1.50–4.69) for rhinitis and 1.63 (95% CI 1.00–2.69) for eczema after adjustment for potential confounders.

Conclusions: Obstetric complications and infection in pregnancy may increase the risk of allergic disorders among the offspring.

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The causes of childhood asthma and other atopic diseases are largely unexplained (1), and it is becoming increasingly apparent that the atopic phenotype frequently begins early in life, even before birth (2). This is supported by findings that the effect of the maternal line on childhood atopic diseases is greater than that of the paternal line (3, 4), and that cord-blood T-cell proliferation responses are enhanced after stimulation with specific allergens at birth in babies

Table 1. Occurrence of allergic rhinitis and eczema among children in 1985–6 northern Finland birth cohort at age 7 years by categories of prenatal factors

Factors	Total no.	Allergic rhinitis			Allergic eczema		
		Cases	Prevalence %	P*	Cases	Prevalence %	P*
Maternal age, years							
≤20	584	19	3.3	0.437	48	8.2	0.010
21–30	5171	178	3.4		366	7.1	
≥31	2333	67	2.9		127	5.4	
Social class							
I+II	2698	79	2.9	0.212	167	6.2	0.061
III+IV	4709	167	3.5		339	7.2	
Farmers	512	16	3.1		30	5.9	
Antenatal visits							
≤9 times	1076	20	1.9	0.006	71	6.6	0.004
10–16 times	6085	209	3.4		391	6.4	
≥17 times	700	31	4.4		68	9.7	
Parity							
0	2767	120	4.3	0.000	213	7.7	0.003
1	2698	73	2.7		175	6.5	
2–3	1963	63	3.2		127	6.5	
≥4	647	7	1.1		24	3.7	
Bleeding in first trimester							
Yes	478	24	5.0	0.026	29	6.1	0.558
No	7324	231	3.2		495	6.8	
Febrile infections							
First trimester	181	14	7.7	0.009	19	10.5	0.058
Second trimester	388	15	3.9		36	9.3	
Third trimester	653	24	3.7		44	6.7	
Any two	174	7	4.0		12	6.9	
No	6692	204	3.0		430	6.4	
Vaginitis							
Yes	1772	68	3.8	0.124	120	6.8	0.874
No	6316	196	3.1		421	6.7	
Maternal weight, in quartiles							
First (lowest)	2144	76	3.5	0.888	153	7.1	0.584
Second	1635	51	3.1		108	6.6	
Third	2240	72	3.2		154	6.9	
Fourth (highest)	1938	63	3.3		118	6.1	
Maternal weight gain, in quartiles							
First (lowest)	1898	45	2.4	0.015	118	6.2	0.410
Second	1907	64	3.4		117	6.1	
Third	1900	58	3.1		133	7.0	
Fourth (highest)	1902	80	4.2		138	7.3	
Maternal smoking†							
0	6403	206	3.2	0.993	431	6.7	0.874
1–10	749	25	3.3		51	6.8	
≥11	783	27	3.4		49	6.3	

Table 1 (continued)

Contraceptive use							
No	4179	117	2.8	0.112	257	6.3	0.133
Pills	1585	58	3.7		127	8.0	
IUD	1207	50	4.1		82	6.8	
Other measures	1056	34	3.2		72	6.8	
Maternal history of allergic diseases							
Yes	120	12	10.0	0.000	20	16.7	0.000
No	7968	252	3.2		521	6.5	
Birth weight, in quartiles							
First (lowest)	2026	58	2.9	0.113	134	6.6	0.526
Second	1991	61	3.1		123	6.2	
Third	2031	83	4.1		149	7.3	
Fourth (highest)	2040	62	3.0		135	6.6	
*For global homogeneity.							
†Average number of cigarettes smoked daily after month 2 of pregnancy.							

who subsequently develop symptoms related to those allergens (5–7). These observations suggest that the atopic phenotype is probably already programmed before birth (8). However, there have been few epidemiologic studies to date that have evaluated the impact of perinatal factors on the risk of childhood atopic disorders. Our aim here was to examine the association of obstetric complications and infections in pregnancy with the subsequent development of allergic rhinitis and eczema by the age of 7 years, using a population-based prospective birth cohort collected in northern Finland in 1985–6.

Material and methods

Population and design

The population was derived from a birth cohort designed to include all pregnancies in northern Finland with expected birth dates from 1 July 1985 to 30 June 1986 (9). The women were enrolled at the 24th week of gestation when visiting the maternity health center. The cohort consists of 9479 births, accounting for 99% of all births in the area concerned. These included 47 stillbirths, 75 infants who died before the age of 7 years, and 31 who could not be traced at age 7, leaving 9326 children eligible for the follow-up in 1993. The current analyses were limited to 8088 children (87%, out of 9326) for whom complete information was available on pregnancy, birth, and follow-up.

Outcome definition

Data on the development of allergic rhinitis and eczema by the age of 7 were collected with a structured, self-administered questionnaire filled in by the parents, mostly the mothers, in 1993. The original question was, “Have your children had the following long-term illnesses?”, which was followed by the list of the diseases, including allergic rhinitis and allergic eczema.

The information on pregnancy-related conditions was obtained with a structured, self-administered questionnaire distributed to each mother at the last antenatal visit before delivery. In the case of a few mothers who failed to fill in the questionnaire before birth, the information was collected at the midwife’s first home visit, usually 2 weeks after delivery. Information concerning maternal febrile infections during pregnancy was obtained by asking, “Did you have any fever due to infectious diseases during this pregnancy?” If the answer was yes, the gestational week in which the fever occurred was ascertained. Information on maternal vaginitis was obtained by asking, “Have you been treated for vaginitis during this pregnancy?” No information was available on the timing of this vaginitis, however. Bleeding in pregnancy was assessed by asking, “Have you had any bleeding during this pregnancy?” If the answer was yes, the gestational week during which bleeding had taken place was ascertained. As very few mothers indicated they had had bleeding after 13 gestational weeks, only bleeding in the first trimester was analyzed. Maternal weight gain during the pregnancy was determined by calculating the weight at the

Table 2. Crude and adjusted effects of prenatal factors on development of allergic rhinitis among offspring in 1985–6 northern Finland birth cohort

Factors	Numbers*	Crude OR (95% CI)	Adjusted OR† (95% CI)
Antenatal visits			
≤ 9 times	992	1.00	1.00
10–16 times	5801	1.87 (1.18–2.98)	1.67 (1.03–2.72)
≥ 17 times	660	2.45 (1.38–4.33)	2.32 (1.19–4.54)
Parity			
0	2560	4.14 (1.92–8.92)	3.42 (1.55–7.55)
1	2505	2.54 (1.17–5.55)	2.73 (1.22–6.13)
2–3	1791	3.03 (1.38–6.65)	3.19 (1.43–7.09)
≥ 4	579	1.00	1.00
Bleeding in first trimester			
Yes	452	1.62 (1.05–2.50)	1.65 (1.09–2.55)
No	7001	1.00	1.00
Febrile infections			
First trimester	162	2.67 (1.52–4.68)	2.65 (1.50–4.69)
Second trimester	359	1.28 (0.75–2.18)	1.23 (0.72–2.11)
Third trimester	610	1.21 (0.79–1.87)	1.16 (0.75–1.79)
Any two trimesters	160	1.33 (0.62–2.88)	1.22 (0.56–2.67)
No	6161	1.00	1.00
Maternal weight gain, in quartiles			
First	1860	1.00	1.00
Second	1869	1.43 (0.97–2.10)	1.39 (0.94–2.07)
Third	1872	1.30 (0.87–1.92)	1.24 (0.82–1.86)
Fourth	1852	1.81 (1.23–2.62)	1.54 (1.04–2.30)
Contraceptive use before pregnancy			
No	3849	1.00	1.00
Pills	1488	1.30 (0.94–1.78)	1.04 (0.74–1.47)
IUD	1119	1.47 (1.05–2.07)	1.51 (1.07–2.14)
Other measures	997	1.13 (0.77–1.67)	1.09 (0.73–1.60)
*Numbers in final model.			
†Odds ratios adjusted for other factors in table as well as sex, birth weight, season of birth, maternal social class, smoking in pregnancy, and history of atopic disorders.			

last antenatal visit minus the weight before pregnancy and the weight of the neonate and placental weight.

Maternal demographic data and information on social background, lifestyle, and disease history before pregnancy were collected at enrollment in the cohort, and data on the birth, including birth weight and gestational age, were collected from the delivery records of the hospitals. The gestational age used in the analyses was calculated as the interval between the first day of the last menstrual period and the day of delivery. Missing information or uncertain gestational length based on the menstrual period was supplemented with ultrasonic measurements.

The determinants and potential covariates were classified in the following way: maternal age as ≤ 20, 21–30, and ≥ 31; times of antenatal visits as ≤ 9, 10–16, and ≥ 17; parity (reflecting the number of older siblings) as 0, 1, 2–3, and ≥ 4; maternal weight gain during pregnancy, birth weight, and gestational age in quartiles; social class as I + II (professionals with the highest education and other white-collar workers), III + IV (skilled workers and unskilled workers), and farmers; education as ≤ 12 years vs > 12 years of schooling; maternal smoking in pregnancy as 0, 1–10, and ≥ 11 cigarettes on average if the mother smoked after the second month of the pregnancy; season of birth as March–

Table 3. Crude and adjusted effects of prenatal factors on development of allergic eczema among offspring in 1985–6 northern Finland birth cohort

Factors	Numbers*	Crude OR (95% CI)	Adjusted OR† (95% CI)
Maternal age, years			
≤20	565	1.56 (1.10–2.20)	1.15 (0.72–1.84)
21–30	4953	1.32 (1.07–1.63)	1.20 (0.95–1.51)
≥31	2205	1.00	1.00
Antenatal visits			
≤9 times	1054	1.00	1.00
10–16 times	5986	0.97 (0.75–1.26)	0.91 (0.69–1.20)
≥17 times	683	1.52 (1.08–2.15)	1.20 (0.80–1.81)
Parity			
0	2654	2.16 (1.41–3.33)	2.31 (1.46–3.65)
1	2593	1.80 (1.16–2.78)	1.66 (1.06–2.62)
2–3	1858	1.80 (1.15–2.80)	1.61 (1.02–2.54)
≥4	618	1.00	1.00
Febrile infections			
First trimester	173	1.71 (1.05–2.77)	1.63 (1.00–2.69)
Second trimester	371	1.49 (1.04–2.13)	1.50 (1.05–2.14)
Third trimester	627	1.05 (0.76–1.45)	1.07 (0.77–1.48)
Any two trimesters	169	1.08 (0.60–1.95)	1.07 (0.59–1.94)
No	6383	1.00	1.00
Contraceptive use before pregnancy			
No	3999	1.00	1.00
Pills	1534	1.30 (1.05–1.63)	1.22 (0.97–1.54)
IUD	1168	1.09 (0.84–1.41)	1.15 (0.88–1.50)
Other measures	1022	1.10 (0.84–1.44)	1.08 (0.82–1.42)

*Numbers in final model.
†Odds ratios adjusted for other factors in table as well as sex, birth weight, season of birth, maternal social class, education, smoking in pregnancy, and history of atopic disorders.

May, June–August, September–November, and December–February; and history of maternal allergic diseases as yes if the mother had had asthma or some other allergic diseases diagnosed by a doctor.

Statistical analyses

The differences in the prevalences of allergic rhinitis and allergic eczema among the categories of each determinant were examined with Pearson's chi-square test. Logistic regression analysis was used to estimate the independent effects of maternal infections and other determinants operating through pregnancy on the development of the relevant diseases after adjustment for other potential confounding variables: sex, birth weight, season of birth, maternal social class, smoking in pregnancy, and history of atopic disorders. The variables that were shown to be

associated with allergic disorders in previous publications were taken into account as potential confounders in multiple regression analyses.

Results

The prevalences of allergic rhinitis and allergic eczema by the age of 7 years in this geographically defined population of 8088 children were 3.3% and 6.7%, respectively. Both diseases were more common in the children of mothers who had had more antenatal visits during pregnancy, were of low parity, and had experienced febrile infections in early pregnancy (Table 1). In addition, rhinitis was more prevalent in the children whose mothers had reported bleeding in the first trimester and had had a larger weight gain, whereas allergic eczema was more prevalent in children with young

mothers (Table 1). There was a linear trend in the risk of allergic rhinitis and eczema among the children corresponding to the timing of maternal febrile infections during pregnancy (Table 1); i.e., the earlier the mother contracted a febrile infection during pregnancy, the higher the risk the children would have done so also ($P=0.003$ for rhinitis and 0.008 for eczema).

Adjusting for sex, birth weight, season of birth, maternal social class, smoking in pregnancy, and maternal history of atopic disorders had little difference in the observed associations between prenatal factors and childhood rhinitis and eczema (results not shown). The results remained unchanged, except for maternal age, when mutual adjustments were also made for other prenatal factors (Tables 2 and 3). The significant effects of low maternal age on the risk of allergic eczema in the child disappeared after mutual adjustment (Table 3). The change in the effect was observed when parity was included in the logistic model, as the younger mothers had fewer children.

The children whose mothers experienced infections in the first trimester had a higher risk of rhinitis (Table 2) and eczema (Table 3) than those whose mothers had no infections during pregnancy. This was observed after adjusting for all the other covariates involved in the analysis.

The use of contraceptives before the pregnancy seemed to be related to the risk of allergic diseases in the children in the multiple analyses. As compared with not using any contraceptives, the use of an IUD contributed to an OR of 1.51 for rhinitis (Table 2), and the use of pills to an OR of 1.22 for eczema (Table 3).

Discussion

The results indicate that factors operating throughout pregnancy are associated with the subsequent development of childhood allergic disorders. There was a linear trend in the timing of maternal febrile infections during pregnancy and the risk of allergic disorders among children; i.e., the earlier the infections occurred, the higher the risk the children would run. These observations were made after adjusting for potential confounders.

Making more antenatal visits seems to be a risk factor for childhood allergic disorders. This may be due to the fact that mothers who experience complications during pregnancy may need to see a doctor more frequently than mothers without complications. This is suggested by the finding that when variables reflecting pregnancy complications, i.e.,

febrile infections and bleeding in pregnancy, are entered into the multivariate models, the effect of antenatal visits is substantially reduced. This is more obviously the case for eczema, whereas a strong effect on rhinitis remains after adjusting for these variables.

Parity actually represents the number of older siblings. Our results are consistent with those of many other studies (10–13); i.e., that having more older siblings appears to be a protective factor as far as childhood allergic disorders such as rhinitis are concerned. This has been explained by the hypothesis that possessing more older siblings increases the opportunities for contracting infections and that infections occurring in early life, perhaps specifically at the time of first exposure to the relevant allergen, may inhibit the proliferation of Th2 cell clones and thereby prevent allergy (14). The number of siblings and family size may also be imprecise surrogate measures for other unknown exposures which vary with family structure (15). For example, it is also likely that mothers having more children are less frequently exposed to any contraceptive method, and that women tend to have more obstetric complications in connection with their first delivery. Hence, other exposures which vary with the number of siblings and size of the family deserve further investigation (15, 16).

Our data suggest that maternal febrile infections during pregnancy constitute an independent risk factor for childhood allergic disorders. Such infections are believed to have substantial effects on the fetus (17), and children may develop health problems related to these effects in infancy, childhood, or even adulthood (18). The effects of maternal infections on the fetus may be due to the direct actions of toxins or organisms, or they may be indirect and a consequence of interference with placental or uterine function (17). The adverse outcome for the fetus may be anatomical, through disturbed fetal growth, or immunologic, through modification of future immunologic development (17), which may predispose the fetus to a higher likelihood of developing allergic disorders in later life.

A further question is what is the critical period in pregnancy for the development of immune competence in the fetus. It has been shown that maternal food allergen avoidance in the third trimester cannot prevent infant allergy (19). Our results imply that this may have occurred too late, as the most critical time for fetal sensitization may be in the first trimester. Lymphocytes can already be observed in the thymus as early as at 8–9 weeks of gestation, and the synthesis of immunoglobulins, including IgE, starts before 12 weeks (20, 21).

The current analyses suggest that mothers who reported having used contraceptives before the pregnancy were more likely to deliver a child with later allergic disorders. More obvious connections were observed between the use of pills and eczema and between an IUD and rhinitis. The effect of contraceptive pills with respect to eczema was reduced after multiple adjustment, as the mothers concerned also reported more febrile infections (data not shown). It is thus difficult for us to do anything more to distinguish between the effects of contraceptives and febrile infections on eczema. On the other hand, the role of oral contraceptives in increasing the occurrence of atopics in the younger generations has been questioned recently (22). A previous study has also indicated that IgE levels in the cord blood were significantly increased among neonates whose mothers had taken progesterone during pregnancy (23). Furthermore, it has been shown (24, 25) that wheezing and asthma are more common in boys than in girls during childhood, but that this pattern is reversed at puberty. The authors speculate that hormonal changes occurring in early puberty could play a role in the changing prevalence. The role of female hormones in the occurrence of allergic disorders is a topic worth investigating further.

The main advantage of the current investigation is its prospective nature, being derived from a large population-based cohort, with all the exposure information collected during pregnancy and at birth. The figures for the occurrence of rhinitis and eczema by the age of 7 years, 3.3% and 6.7%,

respectively, are lower than those obtained in the ISAAC study (26), possibly due to the question used, which may have elicited only reports of more severe allergic disorders diagnosed by a doctor. The main limitation of the present study is probably that the information on history of maternal allergic diseases was probably incompletely recorded. The observed result is therefore liable to residual confounding by maternal atopic heritage. However, this was not a major problem, as adjusting the models for maternal allergic disorders had practically no effect on the observed odds ratios for the prenatal exposures under study. That may be due to the fact that maternal history of allergic disorders was associated only with the outcomes under study, and not with exposures (data not shown). In addition, we were not able to do a further analysis to separate the roles of prenatal risk factors and risk factors after birth in the childhood atopic disorders by the age of 7 because of the lack of information on risk factors after birth. This needs to be taken into account when interpreting the present results.

In conclusion, we found that more antenatal visits, low parity, febrile infections during pregnancy, and the use of contraceptives before the pregnancy increased the risk of the child developing allergic rhinitis or eczema in later life. Bleeding in the first trimester and a greater weight gain during pregnancy appeared to be associated with rhinitis only. Our results suggest that obstetric complications and infection in pregnancy may increase the risk of allergic disorders among the offspring.

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