

Reproductive history and allergic rhinitis among 31145 Danish women

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Summary

Background and objective A successful pregnancy is associated with a strong skewing of the immune system towards a Th2-type immune response. Because such a deviation is also the hallmark of allergic disease, it was investigated whether allergic rhinitis in women was associated with an increased likelihood of becoming pregnant and having a successful outcome of pregnancies.

Material and methods Information on allergic rhinitis and reproductive history was obtained for 31145 pregnant women who participated in a national birth cohort study in Denmark during September 1997 to March 2000, and for whom complete information on siblings and place of residence and birth was available via the Civil Registration System. Data were analysed using logistic regression.

Results Women who had previously been pregnant (OR = 0.91, 95% CI 0.85–0.98) or who had given birth previously (OR = 0.91, 95% CI 0.85–0.98) were less likely to report allergic rhinitis than others. The number of previous spontaneous abortions, gestational week of the first spontaneous abortion and fertility treatment were not associated with allergic rhinitis. Women who had waited less than a year to become pregnant more often had allergic rhinitis (OR = 1.18, 95% CI 1.06–1.32, $P = 0.002$) than women who had waited for more than a year. Early age at menarche was associated with an increased likelihood of allergic rhinitis ($P_{trend} = 0.003$).

Conclusions Our findings did not support the hypothesis that an atopic genotype overall should be associated with an increased likelihood of successful outcome of pregnancies, but it might be associated with a decreased waiting time to pregnancy.

Keywords allergic rhinitis, allergy, epidemiology, fertility, menarche, parity, pregnancy, reproductive history, spontaneous abortion, Th2

Submitted 29 October 2001; revised 27 February 2002; accepted 12 March 2002

Introduction

Several studies support that pregnancy is associated with a strong skewing of the immune system away from a Th1-type and towards a Th2-type response at the maternal–fetal interface. A general Th2-skewing of the immune system during pregnancy has also been proposed [1–8]. Such a skewing is thought to be essential both for implantation of the embryo and maintenance of pregnancy by preventing rejection of the antigenically foreign fetus by a cell-mediated Th1-type immune response from the mother. As immune responses of atopic individuals are characterized by propensity toward Th2 responses to environmental allergens [9, 10], it has been proposed that such individuals may be more likely to have successful outcomes of pregnancies [11, 12]. This was suggested by Nilsson et al. based on a study of mothers to 3667 children and their siblings which found mothers with a history of atopic disease to have more children than mothers without atopic disease [11]. However, little attention has been given to this topic since then.

Thus, to address this hypothesis, we used data on reproductive history and allergic rhinitis collected in a large national birth cohort study of pregnant women as well as data from the Danish Civil Registration System. In particular, we wished to study whether women with allergic rhinitis differed from other women with respect to number of spontaneous abortions and gestational week of their first spontaneous abortion, but also with respect to number of previous pregnancies, births, waiting time to current pregnancy and fertility treatment. Furthermore, the possible association between early age at menarche and allergy [13] was addressed.

Materials and methods

Study population

'Better Health for Mother and Child' is an ongoing national birth cohort study conducted in Denmark with the main focus on studying the importance of exposures *in utero* and during the first years of life for later development of disease. Pregnant women are invited to participate in this study when they visit their general practitioner for the first time during their pregnancy. The first of four telephone interviews is conducted around 12–16th week of pregnancy. In this interview the

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women are asked a large variety of questions including questions on reproductive history, occupation and allergy.

Overall, 39 154 women participating in Better Health for Mother and Child for the first time had completed their first telephone interview between 29 September 1997 and 14 March 2000. Among these women, complete information on date of birth and vital status of their mothers and all their siblings, as well as on the women's place of residence and place of birth, could be obtained from the Civil Registration System as long as their mothers were born in Denmark on or after 1 April 1935 [14]. The study was restricted to the 31 749 women who fulfilled this criterion. In addition, women were excluded if they were born abroad or had missing information on place of birth or place of residence ($n = 520$), or did not know whether they had had allergy ($n = 84$), leaving 31 145 women in the study.

Identification of cases with allergic rhinitis

In the first telephone interview, all women had been asked if they had ever had allergy and, if so, whether it had been diagnosed by a doctor. Women who answered affirmative to these two questions had further been asked what kind of allergy they had. Women who reported allergic rhinitis and/or hayfever were considered as cases with allergic rhinitis.

Statistical analyses

Odds ratios (ORs) for allergic rhinitis were estimated using logistic regression models. The ORs were adjusted for the woman's age at time of interview (< 20 , 20–24, 25–29, 30–34, ≥ 35 years), their mother's age at time of their own birth (< 20 , 20–24, 25–29, 30–34, ≥ 35 years), number of prior births (four categories) and age at menarche (nine categories). Furthermore, all ORs were adjusted for number of younger (four categories) and older (four categories) siblings at age 10 years, occupation (six categories) [15], and degree of urbanization of birthplace (five categories) and of place of residence (five categories) that were all significantly associated with allergic rhinitis. Degree of urbanization was categorized as capital, suburb of capital, provincial city with more than 100 000 inhabitants, provincial town with more than 10 000 inhabitants, or rural area. Maximum likelihood estimation was performed using the GENMOD procedure in the SAS 6.12 statistical software package [16]. *P*-values were based on likelihood ratio tests and 95% confidence intervals (CI) were based on Wald's tests. Trends were estimated as the slope when the categorical variables of interest were treated as continuous variables.

Results

The 31 145 women in the study were between 15 and 43 years of age and the average age was 29 years (SD 3.9 years). A total of 4202 (13.5%) women reported allergic rhinitis. Among these, 74.4% reported being allergic to pollen, 26.1% to animal dander, 19.9% to house dust mites, and overall, 89.5% were allergic to at least one of these three groups of allergens.

Table 1 shows the ORs of reporting allergic rhinitis according to the studied reproductive factors. Women who had been pregnant before (OR = 0.91, 95% CI 0.85–0.98) and women who had given birth previously (OR = 0.91, 95% CI 0.85–0.98) were less likely to have allergic rhinitis than women who had not been pregnant or given birth previously (Table 1).

The analyses of spontaneous abortions were restricted to women who had been pregnant before. There was no association between ever having experienced a spontaneous abortion or the number of previous spontaneous abortions and having allergic rhinitis (Table 1). Among women who had had at least one spontaneous abortion, we found no association between the week of pregnancy of their first spontaneous abortion and allergic rhinitis (Table 1).

All women were asked if they had planned to become pregnant, and if so for how long they had tried to become pregnant before they succeeded (waiting time to pregnancy). Women who had waited for less than a year to become pregnant more often reported allergic rhinitis (OR = 1.18, 95% CI 1.06–1.32) than women who had waited for more than a year (Table 1). The association was not modified by age or prior births (data not shown).

Women who had waited more than 6 months to become pregnant had been asked whether they had had any kind of fertility treatment in connection with the current pregnancy. There was no significant association between having received fertility treatment in connection with current pregnancy and having allergic rhinitis (Table 1).

There was a significant association between age at menarche and allergic rhinitis ($P = 0.02$; Table 1). Women who had had their menarche before the age of 12 years were 1.25 (95% CI 1.09–1.43) times more likely to have allergic rhinitis than women who had had their menarche at age 14 years, and there was a significant trend of increasing likelihood of allergic rhinitis with decreasing age at menarche ($P_{trend} = 0.003$). Additional adjustment for body mass index (BMI) before pregnancy had little effect on the association, as it did on the other risk estimates presented in Table 1 (data not shown).

Discussion

In general, our results did not support that women with allergic rhinitis should be more likely to have successful outcomes of pregnancies than other women. Women with and without allergic rhinitis were equally likely to have had spontaneous abortions and women with allergic rhinitis did not abort at a later gestational week than other women experiencing a spontaneous abortion for the first time.

In addition to the above, women with allergic rhinitis were less likely to have been pregnant before and to have born children previously than women without allergic rhinitis. This finding, however, could also reflect differences in socioeconomic factors [17] rather than being a measure of underlying fertility. We did not have information on social class in childhood but were, on the other hand, able to adjust for current occupation. In agreement with our study, a very recent investigation by Sunyer et al. of 1487 mothers reported an inverse association between atopy as well as allergic rhinitis and number of offspring; the association was present also after adjustment for social class, age and smoking [18]. They suggested that the association might be explained by atopy decreasing in woman with number of pregnancies through an effect on the immune system.

Women with allergic rhinitis, however, had waited for a significantly shorter time to become pregnant than women not reporting allergic rhinitis. This could in theory be explained if

Table 1. The percentage of women and the odds ratio (OR) of reporting allergic rhinitis according to reproductive factors among 31 145 pregnant women

	Overall No. women	Allergic rhinitis (%)	OR (95% CI)
Pregnant before*			
No	10 786	14.08	1 (reference)
Yes	20 359	13.18	0.91 (0.85–0.98) <i>P</i> = 0.02
Number of prior births*			
0	14 573	13.98	1 (reference)
1	11 964	13.11	0.91 (0.85–0.98)
2	3809	13.07	0.92 (0.82–1.03)
3+	799	12.27	0.89 (0.71–1.11) <i>P</i> = 0.10 (<i>P</i> _{trend} = 0.04)
0	14 573	13.98	1 (reference)
1+	16 572	13.06	0.91 (0.85–0.98) <i>P</i> = 0.01
Number of previous spontaneous abortions (among women who had been pregnant before)†, ‡			
0	14 604	13.10	1 (reference)
1	4423	13.41	1.00 (0.91–1.11)
2	969	13.83	1.05 (0.87–1.27)
3+	349	11.75	0.86 (0.62–1.20) <i>P</i> = 0.77
0	14 604	13.10	1 (reference)
1+	5741	13.38	1.00 (0.91–1.10) <i>P</i> = 0.95
Gestational week of first spontaneous abortion (among women who previously had experienced a spontaneous abortion)†, ‡			
4–11	4772	13.45	1 (reference)
12–15	694	13.83	1.04 (0.82–1.31)
≥ 16	231	12.12	0.92 (0.61–1.38) <i>P</i> = 0.86
Waiting time in months to current pregnancy (among women who had planned their pregnancy)†			
0	6798	13.84	1.19 (1.05–1.35)
1–2	6213	13.99	1.21 (1.07–1.38)
3–5	5452	13.57	1.15 (1.02–1.31)
6–12	4118	13.50	1.17 (1.02–1.33)
> 12	3821	12.14	1 (reference) <i>P</i> = 0.03
≤ 12	22 581	13.75	1.18 (1.06–1.32)
> 12	3821	12.14	1 (reference) <i>P</i> = 0.002
Fertility treatment in connection with current pregnancy (among women who had waited more than 6 months to become pregnant)†, §			
Yes	1753	14.20	1 (reference)
No	6179	12.48	0.89 (0.76–1.05) <i>P</i> = 0.17
Age at menarche (years)¶			
≤ 10	418	15.31	1.23 (0.93–1.62)
11	1877	15.77	1.26 (1.09–1.45)
12	4927	14.09	1.10 (0.99–1.23)
13	9185	13.75	1.08 (0.99–1.18)
14	7164	12.76	1 (reference)
15	3032	12.17	0.94 (0.83–1.07)
16	1239	13.88	1.10 (0.93–1.32)
≥ 17	576	13.54	1.08 (0.84–1.38)
Missing**	2727	12.91	– <i>P</i> = 0.02 (<i>P</i> _{trend} = 0.003)

CI, confidence interval; *P*, test for homogeneity; *P*_{trend}, test for trend. *Adjusted for age, maternal age at the woman's birth, number of older and younger siblings at age 10 years, occupation, degree of urbanization of place of birth and place of residence, and age at menarche. †Adjusted for age, maternal age at the woman's birth, number of older and younger siblings at age 10 years, degree of urbanization of place of birth and place of residence, occupation, number of prior births, and age at menarche. ‡Fourteen women who did not know whether or not they had had any spontaneous abortions were excluded from the analysis. §Seven women with missing information on fertility treatment were excluded from the analysis. ¶Adjusted for age, maternal age at time of the woman's birth, number of older and younger siblings at age 10 years, occupation, degree of urbanization of place of birth and place of residence, and number of prior births. **This category represents women who did not remember their age at menarche but instead answered that it had been early (*n* = 152), late (*n* = 221), neither early nor late (*n* = 872), which grade they were in in school (*n* = 1136), or that they did not remember (*n* = 346).

women via their atopic predisposition were able to mount a more rapid switch from a Th1- to a Th2-type response very early in pregnancy. It is likely that a deviation of the immune response towards Th2 is of importance before implantation of the embryo and may be necessary not only for maintaining a successful pregnancy but also for early embryo development [19] and for implantation to take place [4]. This is supported among others by the findings that production of leukaemia inhibitory factor is mainly a property of Th2-like cells and that leukaemia inhibitory factor seems to be essential for implantation of the embryo [4].

The inverse association between waiting time to pregnancy and allergic rhinitis might, however, have appeared even more convincing, had there been a clearer trend of decreasing allergic rhinitis with increasing waiting time to pregnancy, and not mainly a difference below and above 1 year of waiting time. However, in our analyses, we used the original pre-fixed categories for waiting time to pregnancy that had been used in the interview and it was not possible to subdivide further the category of waiting time to pregnancy above a year.

Overall, it has been estimated that approximately one-half of pregnant women in Denmark are invited to participate in the national birth cohort study as not all general practitioners have wished to be involved in the recruitment. Among women who are invited to participate, approximately two-thirds do so (unpublished data). The possibility remains that some selection bias could have occurred; however, we have no reason to believe that this should have influenced the findings in this study.

We found a significant association between age at menarche and allergic rhinitis with early age at menarche being associated with more allergic rhinitis. The cross-sectional nature of the data, however, makes causal interpretations difficult. A recent study by Xu et al. of 5188 subjects also found an increasing prevalence of atopy with decreasing age at menarche although the trend was not statistically significant in their study [13]. Young age at menarche has been associated with distinct endocrinological features such as higher oestrogen levels and lower sex-hormone-binding globulin levels [20–22]. Sex-hormones have immunomodulating propensities and oestradiol has, for example, been suggested to be able to suppress cell-mediated immunity in part by deviating the immune response from a Th1-type to a Th2-type response [23]. Age at menarche is also associated with obesity, which again has been associated with oestrogen levels [24]. However, although we did not have information on BMI at age of menarche, adjustment for BMI before pregnancy had no effect on the association between age at menarche and allergic rhinitis. Age at menarche is also correlated with maternal age at menarche [13], which in theory could account for the association with allergic rhinitis. Xu et al. reported early maternal age at menarche to be associated with a higher risk of atopy, an association they suggested might be due to differences in the maternal oestrogen environment which could programme the immune system of the fetus in a manner that could affect its atopic status later in life [13]. The concordance between studies on an association between early menarche and allergy and, in particular, our finding of a linear trend surely strengthens the credibility of such an association. However, we need a better understanding of the underlying mechanism behind the association.

In conclusion, our findings did not support the hypothesis that an atopic genotype overall should be associated with an

increased likelihood of successful outcomes of pregnancies. The finding that allergic rhinitis was associated with a shorter waiting time to pregnancy is, however, in line with the hypothesis that a more rapid deviation from Th1-type to Th2-type immune response might occur in atopic women early in pregnancy, but the finding stands alone and needs to be confirmed in other studies. The mechanism behind the association between early menarche and allergic rhinitis is unexplained.

Acknowledgements

The study was supported by the Danish National Research Foundation (grant no. 5-04-202) and the Danish Medical Research Council (grant no. 9700560).

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