

Mothers of very low birth weight infants have less atopy than mothers of full-term infants

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Summary

Background Studies on the pregnancy outcome of asthmatic mothers have suggested an increased rate of preterm deliveries. In contrast, our earlier study suggests that mothers of very low birth weight (VLBW) (<1500 g) infants less frequently had atopy than did mothers of full-term infants.

Methods We inquired about symptoms of atopy and doctor-diagnosed atopy in parents of 370 infants of VLBW (<1500 g) and 544 parents of full-term infants. Odds ratios for atopic symptoms and diagnosed atopy were calculated, and groups were compared with a trend test.

Results Mothers of preterm infants of birth weight (BW) <1000 g significantly less often had physician-diagnosed allergic rhinitis (AR) ($P = 0.02$). Among all the mothers, a trend test showed that maternal AR was significantly ($P = 0.03$) higher in parallel with a higher infant BW. Fathers of infants with different BWs showed no differences in prevalence of atopic symptoms.

Conclusion We thus infer that maternal balance between T-helper type 1 (Th1) and Th2 cells, shifted towards Th2 in those with AR, may have a favourable effect on maintenance of pregnancy before gestational week 30.

Keywords allergic rhinitis, atopy, prematurity, very low birth weight infant

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Introduction

The close contact between the mother and fetus contradicts the fact that the immune system recognizes and rejects tissues with foreign antigens. The immune privilege of the fetus may be based on several mechanisms [1–3]. One of these is the ability of the placenta to function as an immune organ and direct the maternal immune response towards T-helper type 2 (Th2) reactions [4], at the same time depressing the Th1 functions central in the rejection process [5].

Indirect evidence suggests that the maternal immune balance as a whole is directed towards stronger Th2 functions, which may be advantageous for the maintenance of pregnancy [2]. Atopy should therefore be accompanied by a lower incidence of preterm termination of pregnancies. Studies, however, report a higher incidence of preterm delivery among mothers with asthma [6–9]. As would be expected, if this Th1/Th2 paradigm for the maintenance of pregnancy is valid, an autoimmune disease associated with phospholipid antibodies has been associated with recurrent pregnancy loss [10].

We recently studied whether severe prematurity (infants with very low birth weight, VLBW, <1500 g) had any effect on the appearance of atopy in these children by age 10 years. In that study, we noted that mothers of all VLBW infants tended to have less atopy than did mothers of full-term babies

[11]. In the present study, we compare the prevalence of parental atopy in a larger group of VLBW and full-term infants.

Material and methods

Parents of very low birth weight infants

In an earlier study, the prevalence of hayfever among mothers of premature babies was 23.6% and 38.5% among mothers of full-term babies, a relative risk of about 1.6. We carried out our power calculation based on this finding and estimated that with a ratio of 1.5 between premature and full-term babies, we needed 349 premature babies and 524 full-term babies to be able to detect a risk ratio of 1.4 with 80% power and α 5%.

We collected data on VLBW infants born in any of the three maternity hospitals in the Helsinki area. From November 1995 till the end of 1999, according to the registry of newborn infants, maintained at the Central Bureau of Ministry of Health in Finland, 370 VLBW infants were born. As controls, we selected 544 infants of birth weight (BW) above 3000 g, born from July 1999 till the end of year 1999, from the same hospitals using the same registry.

Separate questionnaires for both the father and the mother of each child were sent to the home address of the child, asking about symptoms suggestive of hayfever, asthma, or atopic eczema/dermatitis, and whether any doctor had diagnosed any allergic disease.

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The response rate was 56% for both groups; respondents were 213 (58%) mothers and 205 fathers of VLBW infants and 311 (56%) mothers and 305 fathers of full-term infants. Six full-term and 43 preterm infants born from multiple pregnancies were excluded from the final analysis.

Statistical methods

Odds ratios (ORs) with 95% confidence interval (CI) for allergic symptoms and doctor-verified allergies were calculated and groups were compared with a trend test. A sum for three verified allergic diseases (allergic rhinitis (AR), asthma, and atopic eczema) was formed, ranging from 0 to 3, and its correlation with BW was analysed using Spearman's rank correlation. Preterm infants were analysed in two groups: BW 1500–1000 g and <1000 g. For the trend test, three groups of mothers were formed: those with infants of BW >3000 g, 1500–1000 g, and <1000 g.

Results

A history of any allergic symptom as well as doctor-verified allergies was rarer among mothers of infants with VLBW than among mothers of term infants (Table 1). The OR for mothers of extremely low birth weight (ELBW) (<1000 g) infants to have doctor-verified rhinitis was significantly reduced (OR 0.49; 95% CI 0.4–0.89) (Table 2). When analysed with a trend test, OR of diagnosed AR in the mother was significantly higher when the infants' BW was greater ($P = 0.03$). A similar trend also existed between symptoms of AR ($P = 0.1$). No such differences were evident between symptoms and diagnoses of the fathers of these same infants (Table 2).

Among mothers of ELBW preterm infants, a significant correlation appeared between infants' BW and number of verified allergic diseases (Spearman's correlation coefficient = 0.29; $P = 0.009$).

Discussion

We found a significantly lower prevalence of AR among mothers of ELBW infants than among those with term pregnancies. Further, all mothers showed a trend towards fewer allergic symptoms along with lower infant BW. Our results contrast with earlier findings on the association between prematurity and mothers' allergic disease. In a recent review [8] on association of mothers' asthma with pregnancy, eight studies described an association between asthma and prematurity, with incidence of prematurity significantly increased in two [8]. Pregnancy in asthmatic mothers was associated with several types of complications in two studies of 2289 and 2193 mothers with asthma [9, 12]. In another study dealing with preterm infants (birth before the 37th gestational week), these mothers showed significantly more asthma than the expected or respiratory symptoms resembling asthma [7]. The atopic character of respiratory symptoms may, however, be questioned, as no difference in incidence of hayfever or levels of IgE was present [7, 13]. Of the atopic diseases, AR is most strongly associated with positive skin prick tests (SPTs) and high specific IgE levels [14], but only about half of the asthma cases can be attributed to atopy [13]. Among mothers with asthma, preterm delivery is probably more closely associated with poor control of asthma and its medication than with atopy [8].

In Finland, the proportion of VLBW infants, born usually before 30th gestational week, constitutes 15% of all preterm infants born before gestational week 37 and less than 1% of all newborns. No previous study seems to have involved such a group. The proportion of ELBW has been about half of that of VLBW infants [15]; our proportion was 43%. The risk that mothers with premature infants born prior to the 34th week have allergic symptoms showed an increase equal to that seen among the whole range of mothers of preterm infants [7]. However, infants of the present study were born earlier, on average before week 30. Even in the present group, the most significant reduction in AR was among mothers with ELBW premature infants. These data suggest that the

Table 1. Allergic symptoms and doctor-diagnosed allergies in mothers and fathers of preterm infants of very low birth weight (<1500 g, VLBW) and of full-term infants.

Type of allergy	Infants with ELBW <1000 g, <i>n</i> (%)	Infants with BW 1000–1500 g, <i>n</i> (%)	All VLBW preterm infants, <i>n</i> (%)	Full-term infants, <i>n</i> (%)
<i>Mothers</i>	(<i>n</i> = 76)	(<i>n</i> = 94)	(<i>n</i> = 170)	(<i>n</i> = 306)
History of AR	34 (45)	48 (51)	82 (48)	170 (55)
Verified AR	15 (20)	30 (32)	45 (27)	103 (34)
History of asthma	11 (15)	16 (17)	27 (16)	57 (19)
Verified asthma	9 (12)	13 (14)	22 (13)	45 (15)
History of atopic dermatitis	22 (29)	38 (41)	60 (36)	121 (39)
Verified atopic dermatitis	18 (24)	30 (33)	48 (29)	100 (33)
<i>Fathers</i>	(<i>n</i> = 76)	(<i>n</i> = 89)	(<i>n</i> = 165)	(<i>n</i> = 301)
History of AR	32 (42)	40 (45)	72 (44)	139 (46)
Verified AR	20 (26)	19 (21)	39 (24)	82 (27)
History of asthma	13 (17)	14 (16)	27 (16)	53 (18)
Verified asthma	12 (16)	9 (10)	21 (13)	41 (14)
History of atopic dermatitis	23 (30)	25 (28)	48 (29)	94 (31)
Verified atopic dermatitis	19 (25)	19 (22)	38 (23)	69 (23)

Infants of birth weight (BW) below 1000 g (extremely low birth weight, ELBW) and between 1000 and 1500 g were analysed separately.
AR, allergic rhinitis.

Table 2. Unadjusted ORs

	Mothers			Fathers		
	%	OR	95% CI	%	OR	95% CI
History of AR						
BW < 1000 g	45	0.66	0.40–1.09	42	0.85	0.51–1.42
BW 1000–1500 g	51	0.85	0.53–1.35	45	0.96	0.60–1.54
Full-term	55	1		46	1	
Test for trend (<i>P</i> -value)		0.1			0.55	
Verified AR						
BW < 1000 g	20	0.49	0.26–0.89	26	0.95	0.54–1.69
BW 1000–1500 g	32	0.92	0.56–1.51	21	0.73	0.41–1.28
Full-term	34	1		27	1	
Test for trend (<i>P</i> -value)		0.03			0.62	
History of asthma						
BW < 1000 g	15	0.74	0.37–1.49	17	0.97	0.50–1.88
BW 1000–1500 g	17	0.91	0.49–1.67	16	0.87	0.46–1.66
Full-term	19	1		18	1	
Test for trend (<i>P</i> -value)		0.40			0.82	
Verified asthma						
BW < 1000 g	12	0.78	0.36–1.67	16	1.19	0.59–2.39
BW 1000–1500 g	14	0.94	0.48–1.84	10	0.71	0.33–1.53
Full-term	15	1		14	1	
Test for trend (<i>P</i> -value)		0.54			0.87	
History of atopic dermatitis						
BW < 1000 g	29	0.63	0.37–1.09	30	0.96	0.56–1.66
BW 1000–1500 g	41	1.07	0.67–1.71	28	0.86	0.51–1.46
Full-term	39	1		31	1	
Test for trend (<i>P</i> -value)		0.17			0.76	
Verified atopic dermatitis						
BW < 1000 g	24	0.64	0.36–1.15	25	1.11	0.62–1.99
BW 1000–1500 g	33	1.00	0.61–1.65	22	0.93	0.52–1.66
Full-term	33	1		23	1	
Test for trend (<i>P</i> -value)		0.19			0.81	

OR, odds ratio; CI, confidence interval; BW, birth weight; AR, allergic rhinitis.

mother's immune balance plays a significant role in the very early termination of pregnancy.

The aetiology of prematurity is varied, and in more than half of the cases, a definitive aetiology unrelated to immune functions may be evident [16]. In the present study, we could exclude only infants from multiple pregnancies, not preterm infants delivered because of other factors unrelated to the mother's immune balance, such as hypertensive disorders or uterine malformations [16]. This problem should have reduced our chance of finding an association between the mother's immune balance and her preterm delivery. Our population-based study does, however, show a dose–response association between the mother's AR and the infant's BW among all mothers in the study, but no such association for fathers.

As our study was based on a simple questionnaire, we had no objective markers of atopy. However, self-report of AR has repeatedly been shown to be closely associated with atopy as measured with SPTs or specific IgE [14, 17]. We also had limited information on potential confounders. Most importantly, populations with low socio-economic development have been observed to have less allergic diseases [18], and mothers with low socio-economic status also have more VLBW children [19]. Therefore, we cannot exclude the possibility that the observed association between allergic

disease among mothers and BW is at least partly because of confounding by socio-economic status and factors, such as smoking, associated with that status. The participation rate in our study was also fairly low. However, this is more likely to make us unable to find statistical significance, but not to affect the observed association.

Because we observed no difference in allergic symptoms among fathers of the preterm and of full-term infants, their family environments and demographic variables provoking atopy were probably quite similar. We infer that during gestational weeks 24–30, when VLBW infants are born, the Th2 deviated immune function of the atopic mothers favours the continuation of pregnancy more effectively than does that of non-atopic mothers. This agrees with the finding that in mothers with recurrent abortions, IL-4 levels tended to be lower and TNF- α levels higher than in mothers with normal pregnancy outcome, suggesting a shift in immune balance towards Th1 [20]. A recent study on the parity of atopic mothers, however, found no change in numbers of abortion for atopic vs. non-atopic mothers [21]. In contrast to an earlier study [22], that study showed that atopic mothers had a lower number of children than did non-atopic ones [21].

In conclusion, we observed a significantly lower prevalence of atopy among mothers, but not among fathers, of ELBW (<1000 g) infants than among term infants. The immune balance of atopic mothers may thus have a favourable effect on maintenance of pregnancy, especially during early pregnancy.

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