ORIGINAL ARTICLE AIRWAY DISEASES

Birth-related factors and doctor-diagnosed wheezing and allergic sensitization in early childhood

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To cite this article: Keski-Nisula L, Karvonen A, Pfefferle PI, Renz H, Büchele G, Pekkanen J. Birth-related factors and doctor-diagnosed wheezing and allergic sensitization in early childhood. *Allergy* 2010; **65**: 1116–1125.

Keywords
allergic sensitization; asthma; children; delivery; wheezing.

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Accepted for publication 10 December 2009

DOI: 10.1111/j.1398-9995.2009.02322.x

Edited by: Hans-Uwe Simon

Abstract

Background: To investigate the associations between clinical obstetric factors during birth and doctor-diagnosed wheezing and allergic sensitization during early childhood.

Methods: We followed 410 Finnish women from late pregnancy until 18 months age of their children. All children were delivered at term. Doctor-diagnosed wheezing among children was established by questionnaires, while specific immunoglobulin E antibodies to inhalant and food allergens were measured in 388 children at 1 year of age. Data on maternal obstetric variables were recorded at the time of delivery.

Results: Children of mothers with longer duration of ruptured fetal membranes before birth had significantly higher risk of doctor-diagnosed wheezing during early childhood compared to those children with shorter period of ruptured fetal membranes (III *vs* I quartile; aOR 6.65, 95% CI 1.99–22.18; $P < 0.002$ and IV *vs* I quartile; aOR 3.88, 95% CI 1.05–14.36, $P < 0.043$). Children who were born by Cesarean delivery had significantly less allergic sensitization at the age of 1 year compared to those who were born by vaginal route (16.0% *vs* 32.2%; aOR 0.34, 95% CI 0.14–0.80; $P < 0.013$). Furthermore, allergic sensitization tended to be more common in children with longer duration of labor before birth. No other birth-related obstetric factors, such as induction, the type of fetal membrane rupture during birth or quality of amniotic fluid were associated significantly with the examined outcomes.

Conclusion: The longer duration of the ruptured fetal membranes possibly reflected the higher risk of intrapartum infection at birth, and further increased the risk of doctor-diagnosed wheezing among offspring.

Specific maternal factors and complications during pregnancy and delivery may increase the risk of asthma and wheezing among offspring (1–12). Perinatal effects have less and more diverse significance in the development of allergic sensitization and hay fever (2, 12–14). However, only a few studies have evaluated the clinical intrapartum obstetric risks besides mode of delivery in the development of asthma and allergic diseases among offspring (1, 2, 13, 15, 16). Additionally, children born by any type of Cesarean delivery have often been analyzed together even though the microbial contact with maternal vaginal microbiota is also possible via nonelective Cesarean delivery in cases with ruptured fetal membranes and prolonged labor (1, 4, 16–18). Some of the inconsistency between different studies may be explained by these variations, although the most recent studies have confirmed an association between Cesarean delivery and the risk of the later development of asthma among offspring (3, 4, 14, 19).

Kumar et al. (7) showed that maternal chorioamnionitis was associated with an increased risk of early wheezing and physician-diagnosed asthma in those born preterm, but not eczema or food allergy. Further, we demonstrated recently in another birth cohort that specific intrauterine bacterial growth relating to possible subclinical intrauterine infection at the time of Cesarean increased the risk of asthma three- to

Abbreviations
aOR, adjusted Odds ratio; CI, confidence interval; kU/l, kilo units per liter; sIgE, Specific immunoglobulin E.

sevenfold among adolescents (2). There have been some studies evaluating of the significance of prenatal maternal and early neonatal antibiotics in the developing of allergic diseases and asthma among offspring, (20, 21) but thus far we know only one study has focused on the intrapartum period. This study showed in a large population-based data that maternal antibiotics during delivery associated with both transient early wheezing and persistent wheezing among 6- to 7-year-old children (22).

It is apparent that young children with wheezing have strong correlation between both lung function and immune responses in early life and the subsequent risk of persistent wheezing and later asthma (23, 24). As the significance of birth-related variables may also vary between the different ages of the study population, we wanted to evaluate whether there was any association between birth-related obstetric factors and the prevalence of doctor-diagnosed wheezing and specific allergic sensitization among offspring in early childhood.

Patients and methods

Our study population consisted of the Finnish participants in an ongoing international birth cohort study (PASTURE; Protection against allergy study in rural environments), which is evaluating the association between a farming environment and the development of allergic diseases among offspring. This cohort has been prospectively followed up from the third trimester of pregnancy and is reported on in more detail in earlier reports (25). The second half of the cohort (the extended cohort) consisted of pregnant women with estimated delivery at Kuopio University Hospital between May 2004 and May 2005, with no selection by the occupation or area of living; however, subjects living in apartments were excluded as to make the building stock comparable between the two parts of the cohort. Otherwise, the inclusion and exclusion criteria as well as study protocol were the same. In this study, we excluded five children who were delivered with <37 gestational weeks. All the children in the study were born between September 2002 and May 2005 with gestational ages between 37–42 weeks. No differences were detected between the Cesarean delivery rates between the Finnish PASTURE cohort and the extended cohort (13.1% *vs* 11.8%).

Midwives collected intrapartum information during delivery using standardized questionnaires. Information on clinical factors included gestational age, prostaglandin induction before delivery, the duration of labor and ruptured membranes before birth, the type of fetal membrane rupture during vaginal delivery (spontaneous or artificial), the use of oxytocin during labor, the quality of amniotic fluid at delivery (clear or meconish) and the mode of delivery (spontaneous, assisted vaginal, elective Cesarean or nonelective Cesarean). Neonatal data included birth weight and 1- and 5-min Apgar scores. Maternal and paternal allergic disease was defined as the mother or father being recorded as having doctor-diagnosed asthma, hay fever or allergic eczema at any time in life in the questionnaire data gathered during and after pregnancy. Similarly, information of older biological siblings was collected on asthma, hay fever, allergic eczema and respiratory symptoms and diseases, such as recurrent obstructive or asthmatic (wheezy) bronchitis.

Venous blood samples at the age of 12 months from the offspring were analyzed for specific immunoglobulin E (sIgE) to 19 common allergens, by using the Allergy Screen Test Panel for Atopy (Mediwiss Analytic, Moers, Germany) (26). The 13 inhaled allergens tested were two house dust mites (*Dermatophagoides pteronyssinus* and *D. farinae*), seven pollens (alder, birch, European hazel, grass pollen mixture, rye, mugwort and plantain), cat, horse and dog dander and the mold *Alternaria alternata*. The six food allergens were hen's egg, cow's milk, peanut, hazelnut, carrot and wheat. Allergic sensitization was defined as sIgE concentration of equal to or greater than 0.35 kU/l.

The first questionnaire was administered during the third trimester of pregnancy, and follow-up data were collected from the mothers by self-administered questionnaires when the children were 2, 12 and 18 months old. In the Finnish PASTURE cohort, however, the 2-month data were obtained by interviews. Questionnaires were based on the International Study of Asthma and Allergies in Childhood's standardized Questionnaire (27) and the details of the questionnaires have been described elsewhere (28). In brief, information was collected on respiratory symptoms and diseases, such as parent-reported doctor-diagnosed obstructive or asthmatic (wheezy) bronchitis was asked using the question: 'Has your child had an obstructive or asthmatic bronchitis diagnosed by a doctor?'. Doctor-diagnosed asthma was inquired on by a corresponding question. Because of the small number of children with doctor-diagnosed asthma at <18 months, doctor-diagnosed obstructive or asthmatic bronchitis and asthma were combined into 'doctor-diagnosed wheezing'. The questionnaire at the age of 12 months covered the period 2–12 months; the questionnaire at the age of 18 months covered the period 12–18 months. The present analysis includes 410 mother–children pairs with available data from questionnaires concerning doctor-diagnosed wheezing ($n = 405$) or data on sIgE- levels at the age of 1 year ($n = 388$) and also data on birth-related factors.

Comparisons of the proportions between doctor-diagnosed wheezing and allergic sensitization and proportions of clinical outcomes in the univariate analysis were performed with the chi-square test or Fisher exact test and for the continuous variables with the Mann–Whitney *U*-test. Logistic regression analysis was used to investigate the relationships between doctor-diagnosed wheezing and the allergic sensitization and the adjusted effects of various predictors including the clinical variables. In logistic analyses, we tested the following potential confounders: gender (female/male), maternal age at delivery ($\leq$28, 29–33 *vs* >33 years), maternal parity (0, 1 *vs* $\geq$2), maternal weight gain during pregnancy (<12, 12–16 *vs* >16 kg), maternal smoking during pregnancy (earlier smoker but not during pregnancy, smoker also during pregnancy, including all mothers who smoked at least the first weeks of pregnancy *vs* never smoked), paternal smoking during first year (no *vs* yes), maternal education (basic, middle *vs* academic), living on a farm during pregnancy (no *vs* yes),

parental allergic diseases (including either maternal or paternal allergic diseases: no *vs* yes), gestational age (37–39 *vs* 40–42 gestational weeks), birth weight in tertiles (≤3480, 3481–3820, *vs* >3821 grams), Apgar scores at 5 min (≤7 *vs* >7), neonatal antibiotic administration during the first postnatal week (no *vs* yes), breastfeeding during the first 2 months (total, partial *vs* no), day care attendance during 1st year (no *vs* yes), presence of dogs or cats in the home during 1st year (no *vs* yes) and the cohort (PASTURE *vs* extended). In the final logistic models, variables were entered simultaneously and were treated as categorical variables. The type of cohort, farming, parental allergy, parity, maternal smoking during pregnancy, birth weight, gender, breast feeding and day care attendance were included in all analysis. Further, other variables were included in the regression analysis if they were significant at a *P*-value of <0.10 in the univariate analysis or satisfied a change-in-estimate criterion (≥10% change in the odds ratio of specific examined variable). In addition, the mode of delivery (all vaginal and nonelective Cesarean *vs* elective Cesarean) was included in the final analysis when evaluating prostaglandin and oxytocin induction, as the mode of delivery has a strong association with these factors. If in any case the proportion of missing values exceeded 5%, the remaining data were included in the analysis as a separate group. The cut-off level of significance was 0.05.

Results

Within the first 18 months, 43 of 405 (10.6%) children had had doctor-diagnosed wheezing [obstructive or asthmatic bronchitis in 9.9% (40/405) and asthma in 2.2% (9/405), respectively]. The prevalence of allergic sensitization against any examined allergen was 30.2% (117/388), and the prevalences of allergic sensitization against any inhalant and against any food allergens were 21.4% (83/388) and 16.2% (63/388), respectively. In total, 99 children of 117 (84.6%) were allergic to one to two specific allergens and 18 (15.4%) were allergic to three or more than three different allergens. The highest allergic sensitizations were against cat (17.8%, 69/388) and cow's milk (11.1%, 43/388).

Table 1 shows the clinical characteristics of the study population in relation to cohorts. As expected, there were significant differences in many maternal and environmental factors between two cohorts. Thus, the type of cohort was included as a confounder in all following multivariate analysis.

Table 2 shows associations between maternal and neonatal clinical factors and the prevalence of doctor-diagnosed wheezing and allergic sensitization among offspring in the univariate analysis. Higher maternal parity and maternal hay fever, lower Apgar scores and administration of neonatal antibiotics during first postnatal week increased significantly the risk of doctor-diagnosed wheezing. Similar associations were not detected between allergic sensitization and these factors. Only day care attendance was associated with the higher risk of allergic sensitization. However, there were only seven children (1.7%) among the total study population who attended day care during the first year.

In crude and adjusted analyses, the duration of ruptured membranes before birth was associated significantly with the doctor-diagnosed wheezing (III *vs* I quartile; aOR 6.65, 95% CI 1.99–22.18; $P < 0.002$ and IV *vs* I quartile; aOR 3.88, 95% CI 1.05–14.36, $P < 0.043$) (Table 3). No significant differences were detected in the crude or adjusted analysis between other intrapartum clinical variables and the prevalence of doctor-diagnosed wheezing among offspring (Table 3).

Table 4 shows that there was a significantly less allergic sensitization detected among children who were born by Cesarean section compared with children who were born vaginally even after adjustments (16.0% *vs* 32.2%, aOR 0.34, 95% CI 0.14–0.80; $P < 0.013$). Furthermore, the risk of allergic sensitization tended to be increased with the longer duration of labor before birth (III *vs* I quartile; aOR 1.95, 95% CI 0.98–3.88; $P < 0.056$ and IV *vs* I quartile; aOR 1.89, 95% CI 0.89–4.01, $P < 0.097$)(Table 4). No significant associations were detected between specific inhalant or food allergic sensitization and intrapartum clinical factors (Table 5).

To control the interaction between the mode of delivery and duration of ruptured membranes before birth, we analyzed separately those children who were delivered spontaneously by vaginal route ($N = 333$). Among this selected population, the association between the duration of ruptured membranes and doctor-diagnosed wheezing among offspring was stronger than in total study population (III *vs* I quartile; aOR 9.78, 95% CI 1.99–48.14; $P < 0.005$ and IV *vs* I quartile; aOR 4.93, 95% CI 0.88–27.44, $P < 0.08$). In addition, as the duration of ruptured membranes correlates significantly also with maternal parity, we secondly selected women with one or more earlier deliveries ($N = 267$) in the multivariate analysis excluding nulliparous mothers. In this separate population, similar significant association was detected between duration of ruptured membranes and doctor-diagnosed wheezing among offspring (III *vs* I quartile; aOR 5.75, 95% CI 1.58–20.94; $P < 0.008$ and IV *vs* I quartile; aOR 3.84, 95% CI 0.89–16.54, $P < 0.07$).

We further evaluated the joint association of the parental allergy and the duration of ruptured fetal membranes with the prevalence of doctor-diagnosed wheezing. While the numbers were low in terms of statistical testing, an increased risk of doctor-diagnosed wheezing was detected among both children of allergic and nonallergic parents with longer duration of ruptured membranes before delivery (aORs 4.16, 13.14 and 6.52 for allergic parents and 6.30, 4.29 and 9.83 for nonallergic parents in comparison with duration of ruptured membranes between II, III and IV *vs* I quartiles). In contrast, children of allergic parents delivered by Cesarean had significantly lower risk of allergic sensitization compared to those born vaginally (aOR 0.18, 95% CI 0.046–0.68; $P < 0.012$). Birth by Cesarean delivery was not associated with decreased risk of allergic sensitization in children of nonallergic parents (aORs 0.68 (95% CI 0.21–2.26; $P = 0.530$).

Discussion

The present results show that the duration of ruptured membranes before birth was significantly associated with the

Table 1 Basic characteristics of study population in relation to different cohorts

	Finnish PASTURE	Extended cohort	*P*-value
Maternal age at delivery	32.1 (4.8)	30.1 (4.9)	0.0001
Maternal parity	1.3 (1.0)	0.9 (1.0)	0.0001
Nulliparous	45 (21.8)	94 (46.1)	0.0001
Maternal weight gain during pregnancy, kg	13.9 (5.3)	14.4 (5.5)	0.183
Maternal smoking during pregnancy	30 (14.6)	36 (17.6)	0.396
Maternal asthma	12 (5.8)	14 (6.9)	0.666
Maternal hay fever	47 (22.8)	45 (22.1)	0.854
Maternal allergic eczema	25 (12.1)	55 (27.0)	0.0001
Maternal education			
Basic	77 (37.4)	60 (29.4)	0.087
Academic	32 (15.5)	49 (24.0)	0.031
Paternal asthma	11 (5.3)	14 (6.9)	0.519
Paternal hay fever	26 (12.6)	43 (21.1)	0.022
Paternal allergic eczema	22 (10.7)	30 (14.7)	0.221
Paternal current smoking	59 (28.6)	54 (26.5)	0.623
Older siblings with asthma, hay fever, allergic eczema or recurrent wheezing*	81 (50.3)	58 (52.7)	0.696
Area of residence during pregnancy			
Countryside	129 (62.6)	55 (27.0)	
Village or town	77 (37.4)	149 (73.0)	0.0001
Living on a farm during pregnancy	108 (52.4)	14 (6.9)	0.0001
Male gender	101 (49.0)	105 (51.5)	0.621
Birth weight, g	3672 (477)	3661 (463)	0.974
Gestational age, weeks	39.6 (1.1)	39.7 (1.1)	0.284
Apgar scores, 5 min	9.0 (0.5)	9.0 (0.5)	0.319
Antibiotics during 1st neonatal week	17 (8.3)	17 (8.3)	0.940
Breast feeding at the age of 2 months			
No	15 (7.3)	22 (10.8)	
Partial	44 (21.4)	69 (33.8)	
Total	147 (71.4)	113 (55.4)	0.004
Maternal smoking after pregnancy	26 (12.6)	41 (20.1)	0.041
Presence of dogs or cats in the home during 1st year	142 (68.9)	88 (43.1)	0.0001
Day care attendance during 1st year	4 (1.9)	3 (1.5)	0.713
Doctor-diagnosed wheezing† <18 months	21/201 (10.4)	22/204 (10.8)	0.912
Atopic sensitization at 1 year	49/192 (25.5)	68/196 (34.7)	0.049
Total	206 (100)	204 (100)	

Data are presented as mean (SD) or number (%).

P-values are determined by Mann–Whitney *U*-test or chi-square or Fisher's test.

*Including only families with equal to or more than two children.

†Including doctor-diagnosed obstructive or asthmatic bronchitis and/or asthma.

risk of doctor-diagnosed wheezing among offspring. Surprisingly, the risk was significantly increased with as short a duration as 3 h of ruptured fetal membranes before birth, which is quite a short period in terms of normal vaginal delivery and a very banal finding in the everyday labor ward. Other birth-related variables such as duration of labor or induction had less effect as regards the development of doctor-diagnosed wheezing at early childhood.

Adjustment for neonatal antibiotic administration did not reduce the observed association between longer duration of ruptured fetal membranes and increased risk of wheezing. There are several potential explanations for the finding. First, if the risk associated with the duration of ruptured membranes is explained by the possible intrauterine infection, newborns with congenitally acquired low grade infection or pathogenic microbial colonization may be free of infective symptoms and therefore are not administered antibiotics right after birth. This is especially true for term and near-term newborns. Secondly, it is possible that the longer duration of ruptured fetal membranes could be a surrogate for some other unrecognized maternal or birth-related risk factor. However, we did include into the final logistic

Table 2 Basic characteristics of study population in relation to wheezing and allergic sensitization

	Doctor-diagnosed wheezing* < 18 months			Allergic sensitization at 1 year		
	No	Yes	*P*-value	No	Yes	*P*-value
Maternal age at delivery	30.9 (4.9)	32.0 (4.7)	0.228	31.1 (4.9)	31.2 (5.1)	0.617
Maternal parity	1.0 (1.0)	1.6 (1.0)	0.0001	1.1 (1.0)	1.1 (1.0)	0.973
Nulliparous	131 (36.2)	7 (16.3)	0.009	91 (33.6)	42 (35.9)	0.659
Maternal weight gain during pregnancy, kg	14.2 (5.5)	14.2 (4.5)	0.863	14.0 (5.7)	14.7 (5.0)	0.264
Maternal smoking during pregnancy	58 (16.0)	7 (16.3)	0.965	41 (15.1)	22 (18.8)	0.368
Maternal asthma	22 (6.1)	4 (9.3)	0.415	20 (7.4)	5 (4.3)	0.253
Maternal hay fever	77 (21.3)	15 (34.9)	0.044	65 (24.0)	21 (17.9)	0.189
Maternal allergic ezcema	71 (19.6)	9 (20.9)	0.838	56 (20.7)	21 (17.9)	0.538
Maternal education						
Basic *vs* other	117 (32.3)	18 (41.9)	0.210	86 (31.7)	47 (40.2)	0.108
Academic *vs* other	73 (20.2)	7 (16.3)	0.545	55 (20.3)	19 (16.2)	0.351
Paternal asthma	22 (6.1)	3 (7.0)	0.739	12 (4.4)	11 (9.4)	0.057
Paternal hay fever	62 (17.1)	7 (16.3)	0.889	41 (15.1)	24 (20.5)	0.193
Paternal allergic ezcema	48 (13.3)	4 (9.3)	0.631	39 (14.4)	11 (9.4)	0.178
Paternal current smoking	103 (28.5)	10 (23.3)	0.473	76 (28.0)	31 (26.5)	0.754
Older siblings with asthma, hay fever, allergic ezcema or recurrent wheezing†	114 (49.4)	23 (63.9)	0.105	98 (54.4)	36 (48.0)	0.348
Area of residence during pregnancy						
Countryside	162 (44.8)	20 (46.5)		119 (43.9)	55 (47.0)	
Village or town	200 (55.2)	23 (53.5)	0.826	152 (56.1)	62 (53.0)	0.573
Living on a farm during pregnancy	110 (30.4)	10 (23.3)	0.333	79 (29.2)	36 (30.8)	0.749
Male	177 (48.9)	27 (62.8)	0.085	129 (47.6)	64 (54.7)	0.199
Birth weight, g	3648 (460)	3834 (531)	0.041	3648 (473)	3742 (475)	0.060
Gestational age, weeks	39.6 (1.1)	39.4 (1.0)	0.242	39.6 (1.1)	39.7 (1.1)	0.178
Apgar scores, 5 min	9.0 (0.4)	8.8 (0.8)	0.027	9.0 (0.6)	9.0 (0.3)	0.488
Antibiotics during 1st neonatal week	26 (7.2)	8 (18.6)	0.011	20 (7.4)	11 (9.4)	0.500
Breast feeding at the age of 2 months						
No	30 (8.3)	6 (14.0)		27 (10.0)	10 (8.5)	
Partial	97 (26.8)	14 (32.6)		69 (25.5)	36 (30.8)	
Total	235 (64.9)	23 (53.5)	0.267	175 (64.6)	71 (60.7)	0.544
Maternal smoking after pregnancy	60 (16.6)	7 (16.3)	0.961	44 (16.2)	21 (17.9)	0.678
Presence of dogs or cats in the home during lst year	207 (57.2)	19 (44.2)	0.105	153 (56.5)	62 (53.0)	0.528
Day care attendance during 1st year	7 (1.9)	0 (0)	1.00	1 (0.4)	5 (4.3)	0.011
Total	362 (100)	43 (100)		271 (100)	117 (100)	

Data are presented as mean (SD) or number (%).

P-values are determined by Mann–Whitney *U*-test or chi-square or Fisher's test.

*Including doctor-diagnosed obstructive or asthmatic bronchitis and/or asthma.

†Including only families with equal to or more than two children.

multivariate analysis many other confounders such as maternal parity and parental allergy, gender, birth weight, gestational age and neonatal Apgar scores in addition to the neonatal administration of antibiotics. Entering of all these variables together into the analysis, the detected association between the duration of ruptured fetal membranes and doctor-diagnosed wheezing was even stronger.

The information on maternal microbiota before birth might better elaborate on the infectious and inflammatory mechanisms that link the duration of ruptured fetal membranes to doctor-diagnosed wheezing. Unfortunately, we did not record microbiologic information in this study. To the best of our knowledge, there are no earlier studies on the significance of the maternal vaginal microbiota at the time of birth or its possible long-term effects on the development of wheezing or asthma among offspring, especially in those children who are exposed to the maternal flora during delivery. However, we recently showed that specific intrauterine bacteria that commonly originate from vaginal microflora at the time of Cesarean delivery were associated with a higher risk of asthma among adolescent offspring (2). Further, Benn et al. (29) evaluated the relevance of maternal vaginal microflora in early pregnancy and its association with the development of wheezing and asthma among offspring at early ages. They showed that maternal vaginal colonization with *Ureaplasma urealyticum* during early pregnancy was

Table 3 Intrapartal estimates and the prevalence of doctor-diagnosed wheezing among offspring within the first 18 months

Variable	Doctor-diagnosed wheezing* *n*/*N* (%)	Crude OR (95%CI)	Adjusted OR† (95%CI)
Type of delivery			
Spontaneous vaginal delivery	37/333 (11.1)	1	1
Assisted vaginal delivery	2/22 (9.1)	0.80 (0.18–3.56)	1.04 (0.19–5.66)
Elective Cesarean operation	2/29 (6.9)	0.59 (0.14–2.59)	0.39 (0.07–2.08)
Nonelective Cesarean operation	2/21 (9.5)	0.84 (0.19–3.76)	0.86 (0.17–4.33)
		P = 0.901	*P = 0. 742*
Type of delivery			
Vaginal delivery	39/355 (11.0)	1	1
Cesarean operation	4/50 (8.0)	0.71 (0.24–2.06)	0.60(0.18–1.95)
		P = 0.523	*P = 0.598*
Type of ruptured fetal membrane during delivery‡			
Spontaneously ruptured membranes	19/164 (11.6)	1	1
Artifical ruptured membranes	20/182 (11.0)	0.94 (0.48–1.84)	0.77 (0.37–1.62)
Not known	1/30 (3.3)	0.26 (0.03–2.04)	0.30 (0.04–2.45)
		P = 0.443	*P = 0.471*
Duration of ruptured membranes			
I quartile (<45 min)	4/101 (4.0)	1	1
II quartile (45–155 min)	12/107 (11.2)	3.06 (0.95–9.83)	3.24 (0.96–10.91)
III quartile (156–343 min)	18/97 (18.6)	5.53 (1.80–16.99)	6.65 (1.99–22.18)
IV quartile (>344 min)	9/100 (9.0)	2.40 (0.71–8.06)	3.88 (1.05–14.36)
		P = 0.016	*P = 0.020*
Duration of labor			
I quartile (< 208 min)	11/102 (10.8)	1	1
II quartile (208–356 min)	12/102 (11.8)	1.10 (0.46–2.63)	1.75 (0.66–4.66)
III quartile (356–590 min)	13/102 (12.7)	1.21 (0.51–2.84)	2.19 (0.80–6.00)
IV quartile (> 590 min)	7/99 (7.1)	0.63 (0.23–1.70)	1.61 (0.47–5.54)
		P = 0.593	*P = 0.479*
Any use of oxytocin (augmentation or induction) during delivery			
No	17/178 (9.6)	1	1
Oxytocin	26/227 (11.5)	1.23 (0.64–2.34)	1.29 (0.61–2.73)
		P = 0.538	*P = 0.504*
Any use of prostaglandin (induction) before delivery			
No	34/353 (9.6)	1	1
Prostaglandin	9/52 (17.3)	1.96 (0.88–4.37)	1.37 (0.53–3.54)
		P = 0.099	*P = 0.512*
Quality of amniotic fluid			
Normal	39/350 (11.1)	1	1
Meconium-stained	4/55 (7.3)	0.63 (0.21–1.83)	0.45 (0.14–1.42)
		P = 0.390	*P = 0.172*
Total	43/405 (10.6)		

P-value for unadjusted analysis and adjusted analysis obtained from the trend test (Wald) in logistic regression models.
*Doctor-diagnosed obstructive or asthmatic bronchitis and/or asthma in the age of 12 and/or 18 months' follow-up.
†The following variables were included in analysis (see Methods): gender, maternal age and parity at delivery, maternal smoking and weight gain during pregnancy, maternal education, living on a farm during pregnancy, gestational age, birth weight, breast feeding, parental allergy, paternal smoking, neonatal antibiotic administration after birth, Apgar scores at 5 min, presence of dogs or cats in the home during 1st year, day care attendance during 1st year and study cohort. Also in the evaluation of prostaglandin and oxytocin, the mode of delivery was included.
‡Excluded those delivered by elective Cesarean operation.

associated with infant wheezing, while specific vaginal growth of staphylococci was associated with asthma during the fifth year of life. The transmission of maternal vaginal microbiota to the fetus is rare at elective Cesarean deliveries, which are commonly performed before the onset of labor and with intact membranes. Thus, in children born by elective Cesarean deliveries, maternal vaginal microbiota might have less significance in the development of wheezing and asthma among offspring. Indeed, the lowest prevalence of doctor-diagnosed wheezing in the present study was among those children who were delivered by elective Cesarean. Certainly, we need more long-term follow-up prospective cohort studies to test this interesting hypothesis of the association between maternal vaginal microbiota, intrapartum subclinical

Table 4 Intrapartal estimates and allergic sensitization among offspring at the age of 1 year

Variable	Allergic sensitization* *n*/*N* (%)	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Type of delivery			
Spontaneous vaginal delivery	102/316 (32.3)	1	1
Assisted vaginal delivery	7/22 (31.8)	0.98 (0.39–2.48)	0.91 (0.34–2.44)
Elective Cesarean operation	4/29 (13.8)	0.34 (0.11–0.99)	0.36 (0.12–1.09)
Nonelective Cesarean operation	4/21 (19.0)	0.49 (0.16–1.51)	0.30 (0.08–1.13)
		P = 0.154	*P = 0.103*
Type of delivery			
Vaginal delivery	109/338 (32.2)	1	1
Cesarean operation	8/50 (16.0)	0.40 (0.18–0.88)	0.34 (0.14–0.80)
		P = 0.023	*P = 0.013*
Type of ruptured fetal membrane during delivery‡			
Spontaneously ruptured membranes	47/155 (30.3)	1	1
Artifical ruptured membranes	55/177 (31.1)	1.04 (0.65–1.65)	1.05 (0.64–1.73)
Not known	11/27 (40.7)	1.58 (0.68–3.66)	1.92 (0.79–4.67)
		P = 0.557	*P = 0.350*
Duration of ruptured membranes			
I quartile (< 45 min)	21/96 (21.9)	1	1
II quartile (45–155 min)	37/102 (36.3)	2.03 (1.08–3.82)	1.73 (0.90–3.33)
III quartile (156–343 min)	29/95 (30.5)	1.57 (0.82–3.01)	1.42 (0.71–2.85)
IV quartile (> 344 min)	30/95 (31.6)	1.65 (0.86–3.16)	1.43 (0.70–2.90)
		P = 0.175	*P = 0.440*
Duration of labor			
I quartile (< 208 min)	23/101 (22.8)	1	1
II quartile (208–356 min)	28/97 (28.9)	1.38 (0.73–2.61)	1.66 (0.85–3.25)
III quartile (356–590 min)	33/94 (35.1)	1.84 (0.98–3.44)	1.95 (0.98–3.88)
IV quartile (> 590 min)	33/96 (34.4)	1.78 (0.95–3.33)	1.89 (0.89–4.01)
		P = 0.208	*P = 0.235*
Any use of oxytocin (augmentation or induction) during delivery			
No	46/168 (27.4)	1	1
Oxytocin	71/220 (32.3)	1.26 (0.81–1.97)	1.17 (0.72–1.90)
		P = 0.299	*P = 0.525*
Any use of prostaglandin (induction) before delivery			
No	97/336 (28.9)	1	1
Prostaglandin	20/52 (38.5)	1.54 (0.84–2.82)	1.47 (0.77–2.81)
		P = 0.163	*P = 0.248*
Quality of amniotic fluid			
Normal	96/334 (28.7)	1	1
Meconium-stained	21/54 (38.9)	1.58 (0.87–2.86)	1.63 (0.87–3.07)
P-value		*0.134*	*0.130*
Total	117/388 (30.2)		

P-value for unadjusted analysis and adjusted analysis obtained from the trend test (Wald) in logistic regression models.

*Measured by specific IgE levels ≥ 0.35 kU/l

†The following variables were included in analysis (see Methods): gender, maternal age and parity at delivery, maternal smoking and weight gain during pregnancy, maternal education, living on a farm during pregnancy, gestational age, birth weight, breast feeding, parental allergy, paternal smoking, neonatal antibiotic administration after birth, Apgar scores at 5 min, presence of dogs or cats in the home during 1st year, day care attendance during 1st year and study cohort. Also in the evaluation of prostaglandin and oxytocin, the mode of delivery was included.

‡Excluded those delivered by elective Cesarean operation.

infections and the risk of wheezing or asthma later among offspring.

Surprisingly, in the present study, children who were delivered by the vaginal route had the significantly highest prevalence of allergic sensitization. The risk of allergic sensitization tended to be increased also with the longer duration of labor before birth in contrast to our own earlier results (13), but in line with Vonk et al. (1). Present results contradict the hygiene hypothesis theory and run counter to some of those earlier studies showing an increased risk of allergic sensitization in children born by Cesarean (14, 17, 30–32). However, in our study, number of children who were

Table 5 Intrapartal estimates and the prevalence of allergic sensitization against inhalalant and food allergens among offspring at the age of 1 year

Variable	Inhalalant allergic sensitization* *n/N* (%)	Adjusted† OR (95%CI)	Food allergic sensitization* *n/N* (%)	Adjusted† OR (95%CI)
Type of delivery				
Spontaneous vaginal delivery	71/316 (22.5)	1	53/316 (16.8)	1
Assisted vaginal delivery	5/22 (22.7)	0.93 (0.30–2.85)	4/22 (18.2)	0.99 (0.30–3.30)
Elective Cesarean operation	4/29 (13.8)	0.69 (0.22–2.18)	4/29 (13.8)	0.91 (0.29–2.90)
Nonelective Cesarean operation	3/21 (14.3)	0.47 (0.12–1.76)	2/21 (9.5)	0.40 (0.08–2.09)
		P = 0.651		*P = 0.753*
Type of delivery				
Vaginal delivery	76/338 (22.5)	1	57/338 (16.9)	1
Cesarean operation	7/50 (14.0)	0.57 (0.24–1.35)	6/50 (12.0)	0.67 (0.25–1.75)
		P = 0.201		*P = 0.409*
Type of ruptured fetal membrane during delivery‡				
Spontaneously ruptured membranes	31/155 (20.0)	1	25/155 (16.1)	1
Artifical ruptured membranes	40/177 (22.6)	1.06 (0.61–1.84)	26/177 (14.7)	1.12 (0.59–2.13)
Not known	8/27 (29.6)	1.80 (0.69–4.73)	8/27 (29.6)	3.26 (1.14–9.26)
		P = 0.479		*P = 0.082*
Duration of ruptured membranes				
I quartile (<45 min)	18/96 (18.8)	1	11/96 (11.5)	1
II quartile (45–155 min)	22/102 (21.6)	0.98 (0.47–2.05)	24/102 (23.5)	2.05 (0.90–4.69)
III quartile (156–343 min)	21/95 (22.1)	1.06 (0.50–2.25)	14/95 (14.7)	1.32 (0.53–3.30)
IV quartile (> 344 min)	22/95 (23.2)	1.15 (0.54–2.48)	14/95 (14.7)	1.13 (0.44–2.87)
		P = 0.975		*P = 0.278*
Duration of labor				
I quartile (< 208 min)	16/101 (15.8)	1	15/101 (14.9)	1
II quartile (208–356 min)	22/97 (22.7)	1.68 (0.80–3.52)	15/97 (15.5)	1.19 (0.52–2.74)
III quartile (356–590 min)	22/94 (23.4)	1.76 (0.81–3.79)	14/94 (14.9)	0.97 (0.41–2.30)
IV quartile (> 590 min)	23/96 (24.0)	1.83 (0.79–4.25)	19/96 (19.8)	1.33 (0.53–3.30)
		P = 0.416		*P = 0.873*
Any use of oxytocin (augmentation or induction) during delivery				
No	33/168 (19.6)	1	26/168 (15.5)	1
Oxytocin	50/220 (22.7)	1.18 (0.69–2.01)	37/220 (16.8)	1.09 (0.59–2.03)
		P = 0.554		*P = 0.777*
Any use of prostaglandin (induction) before delivery				
No	68/336 (20.2)	1	54/336 (16.1)	1
Prostaglandin	15/52 (28.8)	1.47 (0.73–2.95)	9/52 (17.3)	1.12 (0.49–2.60)
		P = 0.280		*P = 0. 785*
Quality of amniotic fluid				
Normal	67/334 (20.1)	1	54/334 (16.2)	1
Meconium-stained	16/54 (29.6)	1.64 (0.83–3.23)	9/54 (16.7)	0.98 (0.43–2.24)
		P = 0.153		*P = 0.958*
Total	83/388 (21.4)		63/388 (16.2)	

P-value for unadjusted analysis and adjusted analysis obtained from the trend test (Wald) in logistic regression models.
*Measured by specific IgE levels ≥ 0.35 kU/l.
†The following variables were included in analysis (see Methods): gender, maternal age and parity at delivery, maternal smoking and weight gain during pregnancy, maternal education, living on a farm during pregnancy, gestational age, birth weight, breast feeding, parental allergy, paternal smoking, neonatal antibiotic administration after birth, Apgar scores at 5 min, presence of dogs or cats in the home during 1st year, day care attendance during 1st year and study cohort. Also in the evaluation of prostaglandin and oxytocin, the mode of delivery was included.
‡Excluded those delivered by elective Cesarean operation.

delivered by Cesarean was low, and therefore, our results as regards those delivered by Cesarean may yield less reliable conclusions.

Some limitations to this approach should be acknowledged. First, the follow-up period was relatively short, extending to the first 18 months in our cohort, and the doctor-diagnosed

wheezing was based solely on questionnaire data. Rowe et al. (33) suggested earlier that specific IgE levels at 1 year were not representative of later sensitization but might be transient physiological finding during early childhood. It is thus possible that our results mirror rather the effects of intrapartum factors on the immunologic maturation and not solely later sensitization and risk of allergic diseases. However, our study is still ongoing and we will follow this cohort further with objective measurements of asthma and with allergic sensitization as these children grow up.

Secondly, the number of infants delivered by Cesarean was also somewhat lower than in the general population in our area (the Cesarean section rate for general obstetric practice in our hospital area during the study period was 17.0–18.6%) (34). This may hamper the evaluation of the association between the mode of delivery and different allergic outcomes and may cause some selection bias. It is thus possible that excluding women who were living in blocks of flats lowered the Cesarean delivery rate as these women are more likely to be younger and nulliparous and have a higher probability of having a nonelective Cesarean following trial by labor.

In conclusion, we found a significant association between the duration of ruptured fetal membranes before birth and doctor-diagnosed wheezing in early childhood among offspring. This can be explained by the fact that as the duration of rupture of membranes increases, the probability of ascending infections culminating in clinical and subclinical chorioamnionitis and neonatal infections proportionately increases. According to this hypothesis, our result agrees well with earlier results of the higher risk of wheezing and asthma among children whose mothers had chorioamnionitis or pathogenic intrauterine microbial invasion at the time of birth and a related higher risk of congenital infection (2, 7). Further, the prevalence of allergic sensitization was least among children born by Cesarean delivery. However, the number of children delivered by Cesarean was low, and thus these results should be observed with caution.

Financial disclosure

None.

Conflicts of interest

None.

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