ORIGINAL ARTICLE

Umbilical Artery pH Values at Birth and Risk of Asthma at 5 to 6 Years of Age

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Abstract

Background: Intrapartum factors may have a role in the development of asthma and allergic diseases among offspring.
Objective: To investigate the association between umbilical arterial pH values at birth and asthma, allergic rhinitis, and atopic eczema in children.
Methods: We performed a case-control study of 222 asthmatic children and 183 control children aged 5 to 6 years with umbilical artery pH values recorded at birth. Associations were evaluated using logistic regression analysis.
Results: Asthmatic children had significantly lower umbilical artery pH values at birth than nonasthmatics, even after adjusting. Children who were born with pH values of 7.20-7.25 had a 2.62-fold (95% confidence interval [CI], 1.31-5.23) higher risk of asthma and children who were born with umbilical arterial pH values ≤7.19 had a 3.22-fold (95% CI, 1.51-6.87) higher risk of asthma than children who were born with umbilical arterial pH values of 7.26-7.30. In contrast, children who were born with umbilical arterial pH values ≥7.30 had a 0.41-fold lower risk of atopic eczema than children who were born with umbilical arterial pH values of 7.26-7.30. No such association was detected between umbilical artery pH values and allergic rhinitis.
Conclusions: Stressful events at birth may play an important role in the development of asthma during early childhood. In contrast, higher umbilical arterial pH values were associated with a decreased risk of parent-reported atopic eczema at 5-6 years.

Key words: Asthma. Birth. Allergic rhinitis. Atopic eczema. pH. Umbilical cord.

Resumen

Antecedentes: Los factores durante el parto pueden tener importancia en el desarrollo de asma y enfermedades alérgicas en la descendencia.
Objetivos: Investigar la asociación entre los valores de pH arterial umbilical en el nacimiento y el asma, la rinitis alérgica y el eccema atópico en niños.
Métodos: Se llevó a cabo un estudio de casos y controles con 222 niños asmáticos y 183 niños controles de entre 5 y 6 años de edad, cuyos valores de pH arterial umbilical se registraron en el nacimiento. Las asociaciones se evaluaron utilizando un análisis de regresión logística.
Resultados: Los niños asmáticos tenían valores de pH arterial umbilical significativamente más bajos en el nacimiento que los no asmáticos, incluso después del ajuste. Los niños que nacieron con valores de pH de 7,20 a 7,25 presentaron 2,62 veces más riesgo (intervalo de confianza [IC] del 95%: 1,31-5,23) y los niños que nacieron con valores de pH ≤ 7,19 presentaron 3,22 veces más riesgo (IC del 95%: 1,51-6,87) de asma que los niños que nacieron con valores de pH arterial umbilical de 7,26 a 7,30. Por el contrario, los niños que nacieron con valores de pH arterial umbilical ≥ 7,30 presentaron 0,41 veces menos riesgo de eccema atópico que los niños que nacieron con valores de pH arterial umbilical de 7,26 a 7,30. No se detectó ninguna asociación de este tipo entre los valores de pH arterial umbilical y la rinitis alérgica.
Conclusiones: Los acontecimientos estresantes en el nacimiento pueden desempeñar un papel importante en el desarrollo de asma durante la primera infancia. Por el contrario, valores más elevados de pH arterial umbilical se asociaron a un menor riesgo de eccema atópico, según la notificación de los padres, a los 5-6 años de edad.

Palabras clave: Asma. Nacimiento. Rinitis alérgica. Eccema atópico. pH. Cordón umbilical.

Introduction

The quality of intrauterine life, which reflects maternal well-being and health, has profound effects on the initial programming of long-term health in children [1-3]. Early influences and interactions are associated with maternal and fetal stress and exposure to excess corticosteroids during pregnancy [2,4]. Such factors can permanently disturb development of the functional capacity of the fetal central nervous system and hypothalamic-pituitary-adrenal (HPA) axis [5,6] and may have the potential to increase the vulnerability of offspring to neuroendocrine, metabolic, and cardiovascular diseases [2,5,7-11].

Even uncomplicated spontaneous vaginal birth is associated with a certain degree of physiological stress in the newborn. Furthermore, birth complications, maternal chorioamnionitis, mode of delivery, and early neonatal interventions such as administration of antibiotics, oxygen, and phototherapy may affect the risk of asthma in later life [11-17]. We recently showed that in addition to birth by vacuum extraction, abnormal fetal cardiotocography traces and prolonged second stage were significant risk factors in the development of late-onset asthma among children delivered solely by the vaginal route [18]. In contrast, intrapartum factors play a less significant role in the development of allergic sensitization and allergic rhinitis among offspring [13,18-21]. To our knowledge, no studies have applied umbilical cord gas analysis to assess birth asphyxia or pH values as risk factors in the development of asthma and allergic diseases among offspring.

Postdelivery analysis of umbilical artery pH and gas after birth is the most objective method of assessing a newborn's acidosis, oxygenation, acid-base status, and well-being and is accepted practice in most maternity hospitals. Analysis of this type makes it possible to rule out a diagnosis of birth asphyxia in approximately 80% of depressed newborns at term [22,23]. In the present case-control study, we measured umbilical artery pH values at birth to investigate associations between birth asphyxia and the development of asthma, parent-reported atopic eczema, and allergic rhinitis in children aged 5 to 6 years.

Materials and Methods

This study was based on our previously reported asthma case-control studies [24,25]. The study population was selected from all Finnish children born between September 1992 and August 1993 inclusive (approximately 64 000) and for whom stored maternal sera from the first trimester of pregnancy were available. These children were linked to the register for reimbursement of asthma medication of the Social Security Institution of Finland. For a child to be eligible for special reimbursement for asthma medication, a physician (mainly a pediatrician) completes a special application form confirming that the patient fulfills the strict diagnostic criteria for asthma of the Social Insurance Institution, although, even then, many applications are turned down annually.

We randomly selected 800 children from the register for reimbursement (cases). We also selected 800 children in the same birth cohort from the Finnish National Population Register but who were not on the reimbursement register (controls).

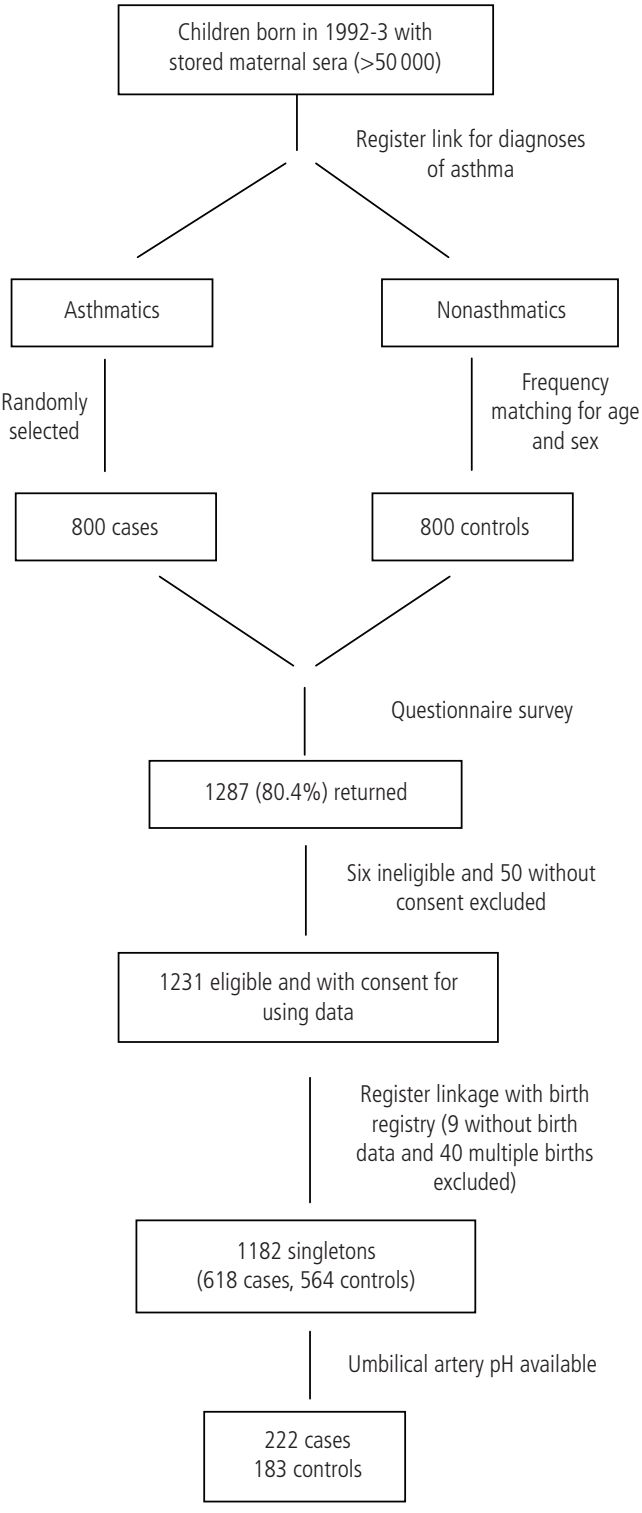

Figure. Flow diagram showing recruitment and final sample.

Cases and controls were matched for age (4 categories, every 3 months) and sex. A questionnaire was sent to the parents of the 1600 children, together with a consent form. A total of 1287 (80.4%) questionnaires were returned.

Detailed information on delivery was obtained from the Finnish Birth Registry at the Research and Development Center for Welfare and Health (STAKES). For children to be included in the study, umbilical artery pH values had to be available, although these were not routinely measured in Finland at the time of birth. Our trial sample comprised singletons with umbilical artery pH recorded at the time of birth (n=405; 34.3%) (Figure). No significant differences were detected in relation to the availability of data on pH between asthmatic cases and controls in the primary study population (222/618 [35.9%] vs 183/564 [32.4%]; *P*=.209). Umbilical arterial pH values were divided into quintiles to establish a trend, and the middle quintile was selected as a comparison group based on the normal distribution of pH values after spontaneous vaginal delivery.

The questionnaire included questions on the children's clinical history, their biological and social environments, and parental demographics. A child was considered to have asthma if he/she was on the register for reimbursement of asthma medication. A child was considered to have allergic rhinitis if parents answered yes to the question *Has your child ever had hay fever or another form of allergic rhinitis?* A child was considered to have atopic eczema if parents answered yes to the question *Has your child ever had atopic eczema (flexural rash)?* In an additional analysis, a child was considered to have recent allergic rhinitis if parents answered yes to the question *Has your child had hay fever or another form of allergic rhinitis during the last 12 months?* and recent atopic eczema if the parents answered yes to the question *Has your child had atopic eczema (flexural rash) during the last 12 months?* Results on allergic rhinitis and atopic eczema were available for 395 and 402 children, respectively. Information on asthma medication was consistent between the questionnaire and the registry. Among 222 cases, there were 2 negative answers to the question *Has your child ever had asthma?*; among 183 controls, there were no positive answers. All parents gave their written informed consent and the Ethics Committee of the National Public Health Institute of Finland approved the study protocol.

Data on parental allergy, including maternal and paternal allergic rhinitis, asthma, and atopic eczema were acquired from the questionnaires. The statistical analyses evaluated the possible risk factors for allergic diseases such as gender, current age during the study (5-6 years), maternal current smoking (no/yes), gestational age at birth (≤36, 37-39, ≥40 weeks), season of birth (March-May, June-August, September-November, December-February), maternal parity at delivery (0, ≥1), mode of delivery (vaginal/cesarean), maternal educational level (≤12, 13-15, ≥16 years), parental allergy (no/yes), and need for neonatal intensive care after birth (no/yes). Logistic regression analysis was used to investigate the relationships between the presence of allergic diseases and the adjusted effects of various predictors, including perinatal clinical variables. All variables were entered simultaneously into the logistic model and treated as categorical variables. The statistical significance of univariate relationships between the prevalence of asthma and maternal, neonatal, and current clinical factors was investigated using the χ^2 test, Fisher exact test, and Mann-Whitney test. Statistical significance was set at *P*=.05.

Table 1. Characteristics of the Study Population in Relation to Asthma Cases and Control Children[a]

	Asthma at 5-6 y		
	Yes (n=222)	No (n=183)	*P* Value
Birth weight, g	3469 (575)	3580 (536)	.034
Gestational age at birth, wk	39.1 (2.0)	39.4 (1.7)	.224
Preterm (<37 gestational wk)	18/222 (8.1%)	8/183 (4.4%)	.127
Apgar scores, 1 min	8.6 (1.4)	8.7 (0.9)	.810
Need for neonatal intensive care	15/222 (6.8%)	3/183 (1.6%)	.013
Antibiotics during first week	9/222 (4.1%)	2/183 (1.1%)	.121
Breast feeding, total duration, mo	6.5 (4.6)	6.9 (4.5)	.329
Maternal age at delivery	28.4 (4.8)	29.1 (5.4)	.271
Maternal parity	0.9 (1.3)	0.7 (1.0)	.310
First born	106/221 (48.0%)	96/183 (52.5%)	.368
Spontaneous vaginal delivery	165/222 (74.3%)	136/183 (74.3%)	.999
Elective cesarean	20/222 (9.0%)	19/183 (10.4%)	.641
Maternal asthma	40/221 (18.1%)	12/179 (6.7%)	.001
Maternal hay fever	121/221 (54.8%)	61/179 (34.1%)	.001
Maternal allergic eczema	93/217 (42.9%)	53/178 (29.8%)	.007
Parental allergy	196/222 (88.3%)	122/183 (66.7%)	.0001
Maternal education, y	13.7 (3.1)	14.3 (2.9)	.078
Maternal current smoking	59/221 (26.7%)	36/181 (19.9%)	.110
Maternal smoking during pregnancy	39/222 (17.6%)	30/183 (16.4%)	.754
Maternal current weight, kg	65.1 (12.0)	63.2 (10.2)	.129
Family income <€25 000/y	80/126 (37.0%)	68/170 (40.0%)	.552
Current age, y	5.7 (0.4)	5.7 (0.5)	.598
Current allergic rhinitis	124/216 (57.4%)	20/179 (11.2%)	.001
Current atopic eczema	143/222 (64.4%)	57/180 (31.7%)	.001

[a]Data are presented as mean (SD) or number (%).
[b]Mann-Whitney test, χ^2 test (Pearson), or Fisher exact test.

Results

In the total study population, 222 (222/405; 54.8%) children had asthma, 144 (144/395; 36.4%) had parent-reported allergic rhinitis, and 200 had atopic eczema (200/402; 49.8%). Table 1 shows the basic characteristics of the study population (cases and controls).

Table 2. Umbilical Arterial pH Values at Birth in Relation to Asthma, Allergic Rhinitis, Atopic Eczema, and Type of Delivery in 405 Children Aged 5-6 Years[a]

	No. (%)	Mean	Median	SD	Min	Max	*P* Value[c]
Asthmatic	222 (54.8)	7.27	7.28	0.9	6.93	7.45	.322^
Allergic rhinitis[a]	144 (36.5)	7.26	7.27	0.9	6.93	7.48	.109^
Atopic eczema[b]	200 (49.8)	7.27	7.28	0.8	7.00	7.48	.368
Spontaneous vaginal delivery	301 (74.3)	7.28	7.28	0.9	6.93	7.48	
Assisted vaginal delivery	24 (5.9)	7.21	7.20	0.7	7.09	7.44	.0001^^
Elective cesarean delivery	39 (9.6)	7.30	7.30	0.5	7.13	7.41	.0001^^
Nonelective cesarean delivery	41 (10.1)	7.25	7.26	0.9	6.96	7.38	.365^^
Total	405 (100)	7.27	7.28	0.8	6.93	7.48	

[a]Total N=395
[b]Total N=402
[c]*P* Values are determined ^between healthy children and those with asthma, allergic rhinitis or atopic eczema and ^^between children born by spontaneous vaginal delivery and other modes of delivery (Mann-Whitney test).

Table 3. Asthma, Parent-Reported Allergic Rhinitis, and Atopic Eczema in Children Aged 5-6 Years and Umbilical Artery pH Value at Birth

Umbilical Artery pH	Asthma		Allergic Rhinitis		Atopic Eczema	
	No. (%)	aOR[a] (95% CI)	No. (%)	aOR[a] (95% CI)	No. (%)	aOR[a] (95% CI)
≥7.34	50/92 (54.3)	1.86 (0.95-3.64)	27/89 (30.3)	0.48 (0.21-1.12)	40/91 (44.0)	0.41 (0.20-0.85)
7.30-7.33	43/77 (55.8)	1.77 (0.89-3.53)	25/75 (33.3)	0.52 (0.22-1.22)	33/76 (43.4)	0.41 (0.19-0.85
7.26-7.29	32/77 (41.6)	1	27/75	1	42/77 (54.5)	1
7.20-7.25	53/86 (61.6)	2.62 (1.31-5.23)	40/84 (47.6)	1.13 (0.49-2.62)	53/86 (61.6)	0.89 (0.42-1.86)
≤7.19	44/73 (60.3)	3.22 (1.51-6.87)	25/72 (34.7)	0.67 (0.27-1.66)	32/72 (44.4)	0.47 (0.21-1.02)
P Value[b]		.027		.148		.026

[a]Adjusted for gender, current age, maternal parity, maternal current smoking and duration of education, gestational age at birth, mode of delivery, need for neonatal intensive care unit after birth, season of birth, and parental allergy. In allergic rhinitis and atopic eczema, also cohort was included.
[b]For adjusted analysis, *P* value for trend obtained from the trend test (Wald) in logistic regression models.

Asthmatic children more frequently had a lower birth weight and more frequently needed treatment in the neonatal intensive care unit than controls. In addition, both they and their parents had more allergic diseases.

No differences were detected in median levels of umbilical artery pH between asthmatic cases and controls (7.28 vs 7.28; *P*=.322) or between children with and without parent-reported allergic rhinitis and atopic eczema (7.27 vs 7.29 [*P*=.109] and 7.28 vs 7.28 [*P*=.368], respectively) (Table 2). However, there were clear differences between mode of delivery and pH values (Table 2).

Children who were born with umbilical artery pH values of 7.20-7.25 had a 2.62-fold higher risk of asthma (95% confidence interval [CI], 1.31-5.23) and children who were born with values ≤7.19 had a 3.22-fold (95% CI, 1.51-6.87) higher risk of asthma than children who were born with umbilical artery pH values of 7.26-7.29. Children who were born with umbilical artery pH values of 7.30-7.33 and with values ≥7.34 had a 0.41-fold lower risk (95% CI, 0.19-0.85; and 95% CI, 0.20-0.85) of parent-reported atopic eczema than children who were born with umbilical artery pH values of 7.26-7.29. No similar association was detected between pH values and the prevalence of parent-reported allergic rhinitis.

Furthermore, no significant change was noted in the association between increased risk of asthma and low pH values and decreased risk of parent-reported atopic eczema and high pH values after adjusting for maternal asthma separately, maternal smoking during pregnancy, birth weight, Apgar scores, and neonatal antibiotic treatment after birth. In the multivariate analysis, asthma was also more common in children with parental allergy (odds ratio [OR], 4.58; 95% CI, 2.62-8.01; *P*<.0001) and in males (OR, 1.72; 95% CI, 1.09-2.73; *P*<.021). Parent-reported allergic rhinitis and atopic eczema were more common in children with parental allergy: allergic rhinitis, OR 6.91 (95% CI, 2.86-16.69; *P*<.0001); and atopic eczema, OR 4.68 (95% CI, 2.51-8.72; *P*<.0001). The results remained unchanged after evaluation of parent-reported allergic rhinitis and atopic eczema that had occurred during the previous 12 months.

Discussion

This is the first study to show that low umbilical artery pH values at birth are associated with a higher risk of asthma during early childhood. Our results are consistent with recent findings concerning the significance of perinatal complications in the development of wheezing or asthma during childhood [12,26-30]. In a large birth cohort study, we showed that those children with abnormal cardiotocography traces during labor (reflecting possible birth stress) had a higher risk of asthma [18]. Both the present and previous results suggest that even minor birth stress could increase the risk of asthma in some children.

Low Apgar scores may be used as a proxy measure of birth asphyxia or stress and have been associated with an increased risk of asthma among offspring in some studies (albeit with inconsistent results) [16,27,31]. To our knowledge, low Apgar scores have not been previously assessed as risk factors for allergic rhinitis or atopy. These scores are subjective, as are interpretations of cardiotocography traces during labor. Umbilical artery gas analysis is a routine approach to assessing birth asphyxia. It is readily available and is the most objective way of assessing acidosis in the newborn. In addition, mode of delivery is strongly associated with umbilical artery gas values, as we also showed in the present study. Newborns delivered spontaneously by the vaginal route generally have lower umbilical artery pH values than newborns delivered by elective cesarean section; therefore, we adjusted for the mode of delivery in our analysis. However, this did not change the significant association between low umbilical artery pH values and higher risk of asthma among offspring. Larger-scale prospective studies are needed to clarify and strengthen our results on the association between umbilical pH values and the risk of asthma and atopic eczema later in life. In contrast, no significant associations were noted between low umbilical artery pH values at birth and parent-reported allergic rhinitis.

Although there may be several explanations for these associations, most of the underlying biological mechanisms remain unclear. In animal experiments, a large body of evidence suggests that maternal prenatal stress may play an important role in programming the neuroendocrine system of offspring through the HPA axis and the immune system [8,32]. The effects on the HPA axis may differ widely depending on the nature of the stress, its timing in gestation, the genetic strain of the animal, and the sex and age of the offspring [33]. Stress during birth is not usually long lasting, and its impact on the development of asthma among offspring is questionable. Birth is a crucially important event, with a huge impact on the onset of lung function. Multiple antioxidant enzymes are regulated in the fetal lung in preparation for birth in order to decrease pulmonary vascular resistance and increase antioxidant defenses to protect against the rise in alveolar oxygen pressure associated with breathing room air. Accordingly, Giles et al [34] showed that maternal hypoxia before birth was associated with significantly decreased antioxidant enzyme values in rabbit lung tissue that affected postnatal lung function. Furthermore, Pincus-Knacksted et al [35] showed that prenatal stress rendered murine offspring more susceptible to airway hyperreactivity and induced immune responses to allergens.

Cookson et al [36] studied the association between maternal anxiety during pregnancy and development of asthma among human offspring and found a dose-dependent association between higher maternal anxiety scores during pregnancy and asthma among 7-year-old children. Furthermore, Wright et al [37] showed how maternal prenatal stress was associated with altered innate and adaptive immune responses in cord blood mononuclear cells. Recently, Priftis et al [32] reviewed the activity and responsiveness of the HPA axis in asthmatic individuals and suggested that children with a priori impaired tolerance to birth stress or in whom prenatal or intrapartum stress disturbs immunological development have an increased risk of asthma or abnormal stress responses after birth.

Maternal asthma could also be associated with a higher risk of antenatal complications, such as low Apgar scores, more frequent cesarean deliveries because of fetal distress, and higher perinatal morbidity [38-40]. However, including maternal asthma in the multivariate model did not decrease the significance detected between low pH values and asthma. Male fetuses are more likely to suffer intrapartum complications and be delivered operatively than females. This finding was also observed in the present study population (data not shown). Furthermore, boys are also at a higher risk of common morbidities, such as asthma, during early childhood [41]. However, male gender and mode of delivery did not explain the higher risk of asthma among children with low umbilical artery pH values.

Our study is subject to a series of limitations. First, we did not apply any objective measures of asthma. However, the diagnostic criteria for asthma were based on reimbursement for asthma medication and were thus very strict. In addition, a special application form had to be completed to confirm that the patient fulfils the criteria of the Social Insurance Institution for asthma. Second, these children had asthma when they were 5 to 6 years old, but we do not know whether their asthma was transient or permanent. In Finland, reimbursement for asthma medication may be transient during childhood and adolescence, lasting generally 3 to 5 years before becoming more permanent during adulthood. Third, the results concerning parent-reported atopic eczema and allergic rhinitis should be interpreted with caution. This was an asthma case-control study, and the results for atopic eczema and allergic rhinitis cannot be extrapolated to the general population.

Our preliminary findings, together with the results of previous studies, support the hypothesis that stressful events at birth may have important effects on the risk of asthma in childhood. During the study period, umbilical cord blood sampling was not routine practice in Finland, as it is nowadays, Any association detected may also be arbitrary and needs to be confirmed in future studies.

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