The Burden of Childhood Asthma and Late Preterm and Early Term Births

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Objective To evaluate the association between gestational age at birth and the risk of subsequent development of asthma.

Study design We conducted a retrospective observational hospital-based birth case-control study in a university-based obstetrics and gynecology department in Finland. A total of 44 173 women delivering between 1989 and 2008 were linked with the social insurance register to identify asthma reimbursements for their offspring (n = 2661). Pregnancy factors were recorded during pregnancy. Infants were categorized as moderately preterm (≤32 weeks), late preterm (33-36 weeks), early term (37-38 weeks), term (39-40 weeks), or late term and postterm (≥41 weeks). The main outcome measure was asthma among the infants.

Results Children born moderately preterm (≤32 weeks gestation) had a significantly increased risk of asthma (aOR, 3.9; 95% CI, 3.2-4.8). The risk of asthma was also increased in those born late preterm (aOR, 1.7; 95% CI, 1.4-2.0) and early term (aOR, 1.2; 95% CI, 1.1-1.4). In contrast, delivery at 41 weeks or later seemed to decrease the risk of asthma (aOR, 0.9; 95% CI, 0.8-1.0). The burden of asthma associated with preterm birth was associated mainly with early term infants, in whom 108 extra cases of asthma were observed.

Conclusion Even though the individual risk of asthma was inversely correlated with gestational age at birth, the overall burden brought about by delivery before term was associated with late preterm and early term deliveries. Furthermore, delivery after term was protective against asthma. *(J Pediatr 2014;164:295-9)*.

Asthma in children is a common disease with significant health and societal costs. Both genetic and environmental factors have roles in its development.[1,2] Prenatal programming, immunologic changes, and immune development already determined in utero may further influence the risk.[3,4]

Several factors during pregnancy may be of importance. Maternal stress and anxiety (indicators of prenatal stress) may program the development of asthma[5] and, through the regulation of fetal endocrinology, decrease serum cortisol levels in the fetus, leading to the development of an allergic phenotype.[1] Maternal infections, such as chorioamnionitis, during pregnancy can lead to an altered cytokine milieu that may play a role in the development of asthma in offspring.[6] Maternal hypertension and diabetes are known to be related to an altered inflammatory state and are associated with wheezing in childhood.[7] Furthermore, gestational age, method of delivery, birth order, and weight have been associated with the risk of childhood asthma.[1,6,8] Neonatal respiratory morbidity at term also is associated with an increased risk of asthma in childhood.[9]

Gestational age at birth is the most significant determinant of asthma. A recent large British cohort study found a decline in health outcomes with decreasing gestational age at birth, with asthma and wheezing showing a gradient of effect with increasing prematurity.[10] These risks appeared to be strongest in early childhood and decreased later in life.[11]

The purpose of the present study was to evaluate the role of gestational age at birth in the development of childhood asthma. We conducted an observational hospital-based birth case-control study to examine the association between gestational age at birth and the risks of asthma in childhood.

Methods

The study population was derived from a clinical birth database comprising a total population of 45 030 infants born after 22 completed weeks of gestation at Kuopio University Hospital between 1989 and 2008 (**Table I**). Stillbirths (n = 193), neonatal deaths (n = 177), and cases with missing data (n = 487) were excluded. Data on 44 173 women with live-born infants were linked with data from the register for reimbursement at the Social Insurance Institution of Finland for asthma medication for their offspring aged 0-19 years. Controls were women with live-born infants without asthma. The infants were categorized as very preterm (<28 completed weeks of gestation), moderately preterm (28-32 weeks of gestation), late preterm (33-36 weeks of gestation), early term (37-38 weeks of gestation), term (39-40 weeks of gestation), late term (41 weeks of gestation), or postterm (≥42 weeks of gestation).

ART Assisted reproduction technology

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Table I. Basic characteristics of the study population in relation to asthma at any time

	Control (n = 41 512)	Asthma (n = 2661; 6%)	*P* value
Primipara, n (%)	17 075 (41.1)	1043 (39.2)	.049
Maternal disease, n (%)			
Asthma	1248 (3.0)	117 (4.4)	<.001
Chronic disease*	3878 (9.3)	278 (10.4)	.058
Diabetes mellitus	242 (0.6)	21 (0.8)	.180
Gestational diabetes mellitus	3287 (7.9)	145 (5.4)	<.001
Hypertension	809 (1.9)	78 (2.9)	.001
Epilepsy†	327 (0.9)	22 (0.9)	.994
ART‡	1864 (4.5)	183 (6.9)	<.001
Maternal age, y, mean (± 2 SD)	29.0 (5.5)	28.7 (5.3)	.004
Maternal smoking (>5 cigarettes/day), n (%)			
Before pregnancy	9202 (22.2)	576 (21.6)	.530
During pregnancy	2265 (5.5)	189 (7.1)	<.001
Prepregnancy body mass index, mean (± 2 SD)§	23.3 (4.7)	23.4 (4.5)	.236
Number of previous pregnancies, mean (± 2 SD)	1.44 (1.63)	1.50 (1.60)	.129
Number of previous deliveries, mean (± 2 SD)	1.04 (1.31)	1.06 (1.24)	.498
Marital status, n (%)			
Unmarried	15 750 (37.9)	908 (34.1)	
Married	25 762 (62.1)	1753 (65.9)	<.001
Mode of delivery, n (%)			
Vaginal	33 981 (81.9)	2053 (77.2)	
Cesarean	7531 (18.1)	608 (22.8)	<.001
Singleton, n (%)	39 992 (96.3)	2518 (94.6)	
Twin, n (%)	1441 (3.5)	135 (5.1)	
Triplet, n (%)	79 (0.2)	8 (0.3)	<.001
Boy, n (%)	20 939 (50.4)	1612 (60.6)	
Gestational age, wk, mean (± 2 SD)	39.2 (2.2)	38.4 (3.3)	<.001
Birth weight, g, mean (± 2 SD)	3481 (616)	3341 (812)	<.001
Birth height, cm, mean (± 2 SD)	49.9 (4.5)	49.3 (3.7)	<.001
Head circumference, cm, mean (± 2 SD)	34.9 (1.8)	34.6 (2.4)	<.001
Abdominal circumference, cm, mean (± 2 SD)	33.8 (2.1)	33.7 (2.1)	.001
Apgar score 1 min <7. n (%)	2063 (5.0)	225 (8.6)	<.001
Apgar score 5 min <7, n (%)	806 (1.9)	73 (2.7)	.004
Age at disease onset, y, mean (± 2 SD)		4.2 (3.6)	
Asthma prevalence by age group, n (%)			
0-6 y	16 237 (39.1)	482 (18.1)	
7-12 y	10 822 (26.1)	997 (37.5)	
≥13 y	14 455 (34.8)	1182 (44.4)	

P values obtained in the univariate model.
*Including chronic bowel disease, hypothyroidism, and autoimmune diseases.
†Data available for 1989-2007.
‡ART includes in vitro fertilization, intracytoplasmic sperm injection, insemination, and ovulation induction by clomiphene and other medicines.
§Data missing in 1984 cases (4.5%).

Information on maternal prepregnancy characteristics was based on data from a self-administered questionnaire at 20 weeks of pregnancy. Public health nurses and midwives completed missing data by way of interview during visits to prenatal maternal clinics or labor wards at Kuopio University Hospital. The questionnaire consisted of 75 background items. Nurses and midwives present during delivery and the neonatal period added information on pregnancy complications, pregnancy outcome, and the neonatal period to the database. All childbearing women gave informed consent for the register study at the time of data collection. The participation rate for delivery and neonatal items was 100%.

Information on the need for antiasthma drugs during childhood was obtained from the Drug Prescription Register maintained by the Social Insurance Institution. In Finland, to be eligible to receive reimbursement payments under the Special Refund Categories, a patient must obtain a certificate from a doctor, and the disorder must be based on clinical diagnosis and standardized criteria (*International Statistical Classification of Diseases and Related Health Problems, 10th Revision*). For children, an asthma certificate is usually provided by a pediatrician to confirm the nature of the disease and the need for medication. Antiasthma drugs are 72% reimbursed.[12]

Statistical analyses were performed using SPSS 17.0 for Windows (SPSS, Chicago, Illinois). The χ^2 and Mann-Whitney *U* tests were used to assess differences between the study and control groups. Logistic regression analysis was used to investigate multivariate-adjusted associations between gestational age at birth and diagnosis of asthma. The analyses were adjusted for maternal asthma, diabetes mellitus, gestational diabetes mellitus, hypertension, chronic diseases (eg, chronic bowel disease, hypothyroidism) at the time of pregnancy (no vs yes), maternal age (≤25, 26-35, ≥36 years), maternal parity (0, 1 vs ≥2), prepregnancy body mass index (<21, 22-24, ≥25 kg/m^2), smoking during pregnancy (no vs yes, smoking >5 cigarettes per day), marital status (unmarried vs married), and assisted reproduction technology (ART; no vs yes). Further confounding factors included the child's sex, child's age (0-6, 7-12, ≥13 years), umbilical cord length (≤55 vs >55 cm), Apgar score at 5 minutes (<7 vs 7-10), mode of delivery (vaginal vs cesarean), and number of fetuses (single, twin, or triplet pregnancies). Gestational age at the time of delivery was further categorized as ≤32, 33-36, 37-38, 39-40, or ≥41 weeks. The reference gestational age at birth for each disease was 40 weeks (**Table II**; available at www.jpeds.com) or 39-40 weeks (**Table III**). In **Table IV**, the reference gestational age was selected from **Table III**, where the incidence of asthma was lowest after 41 weeks of gestation. A *P* value of .05 was deemed statistically significant.

To examine whether background information (ie, mode of delivery, maternal smoking, ART, fetal sex, and maternal asthma, epilepsy, or diabetes mellitus) contributed to the differences in childhood asthma incidence related to gestational age at birth, we estimated the contribution of each of these factors by using logistic regression and comparing the percentage reductions in OR. Each confounder was added separately to model 2, and the contribution of each factor (models A/B/C/D/E) was measured by the percentage reduction in OR of childhood asthma.[13] The following formula was used: (OR model 2 − OR model *X* [A/B/C/D/E])/(OR model 2 − 1) (**Table IV**). We estimated the extra cases of asthma among offspring because of prematurity using the following formula: (n [asthma/1000 deliveries] − n [reference asthma group] × n [total number of deliveries])/1000 (**Table V**).