Risk of Asthma from Cesarean Delivery Depends on Membrane Rupture

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Objective To assess our prospective mother-child cohort and the national registry data to analyze the risk of asthma by delivery mode and whether cesarean delivery before or after membrane rupture affects this risk differently.

Study design The Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ is a high-risk birth cohort of 411 Danish children. Asthma was diagnosed prospectively by physicians at the research site, and associations with cesarean delivery were investigated using Cox proportional hazard models. From the Danish national prospective registry we included data from 1997-2010. Childhood asthma was defined from recurrent use of inhaled corticosteroids filled at pharmacies. Cesarean delivery was classified as either before or after rupture of membranes, and the risk of asthma was compared with vaginal delivery. Results were adjusted stepwise for age and calendar year, sex, birth weight, gestational age, multiple births, parity, and maternal factors (age, smoking/antibiotics during pregnancy, employment status, and asthma).

Results In the Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ cohort, the adjusted hazard ratio for asthma was increased by cesarean delivery relative to vaginal birth 2.18 (1.27-3.73). Registry data replicated these findings. Cesarean delivery performed before rupture of membranes carried significantly higher risk of asthma, (incidence rate ratio to vaginal delivery 1.20 [1.16-1.23]) than cesarean delivery after rupture of membranes (incidence rate ratio to vaginal delivery 1.12 [1.09-1.16]).

Conclusions We confirmed cesarean delivery to be a risk factor for childhood asthma. This effect was more pronounced for cesarean delivery performed before rupture of membranes. *(J Pediatr 2016;171:38-42)*.

Birth by cesarean delivery seems to be a risk factor for childhood asthma.[1,2] However, the mechanisms leading to this increased risk remain unknown. Population-based studies have previously investigated the risk for asthma after delivery by emergency or planned cesarean delivery reporting conflicting results.[3-5] Emergency cesarean delivery may be performed for different reasons most commonly during labor because of delivery complications. However, emergency cesarean delivery may also be performed before onset of labor because of pregnancy complications.

We speculate that cesarean delivery could mediate the asthma risk through alterations of the newborn's microbiome.[6] Hence, the rupture of membranes and thereby possible microbial transmission may cause different effects of cesarean delivery. We analyzed the association between cesarean delivery and asthma in our prospective clinical birth cohort Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$ (COPSAC$_{2000}$) with stringent asthma criteria. To further investigate the potential mechanisms leading to an increased asthma risk after cesarean delivery, we used registry data on the entire Danish pediatric population between 1997-2010.

Methods

The COPSAC$_{2000}$ cohort study was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (KF 01-289/96) and the Danish Data Protection Agency (2008-41-1754). Both parents gave written informed consent before enrollment. The registry study was based on existing data in national registries and was approved by the Danish Data Protection Agency (J.no. 2012-41-0388). Because subjects were not contacted in the registry study, written informed consent was not required.

COPSAC$_{2000}$ Birth Cohort

The COPSAC$_{2000}$ birth cohort consists of 411 children born 1998-2001 to mothers with a history of asthma, excluding children born before 36 weeks of gestation and anyone suspected of chronic diseases or lung symptoms prior to inclusion, as previously described in detail.[7]

COPSAC$_{2000}$	Copenhagen Prospective Studies on Asthma in Childhood$_{2000}$
HR	Hazard ratio
IRR	Incidence rate ratio

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COPSAC is funded by the Lundbeck Foundation (R16-A1694), The Danish Ministry of Health (903516), Danish Council for Strategic Research (0603-00280B), and The Capital Region Research Foundation. H.B. has acted as consultant for Chiesi and Boehringer-Ingelheim. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.12.066

Registry Study Population

In the prospective registry based cohort study, we identified a cohort of live born children in Denmark in the period 1997-2010 and used their unique identification number to link information on maternal age, sex, parity, maternal smoking during pregnancy, mode of delivery, and maternal identification number from the Danish Medical Birth Registry; information on prescribed antibiotics and anti-asthmatic steroids from the National Prescription Registry; information on hospital admissions (inpatient and outpatient attendance) with asthma as primary diagnosis from the Danish National Patient Registry; information on maternal employment status from Statistics Denmark; and information on date of migration from the Danish Person Registry. The diagnoses are based on the International Statistical Classification of Diseases and Related Health Problems version 10.[8]

Cesarean Delivery Classification

In the $COPSAC_{2000}$ cohort, we defined delivery by cesarean delivery as a dichotomous variable. The National Registry classified cesarean delivery as: (1) elective cesarean performed before delivery; (2) emergency cesarean because of delivery complications performed during delivery; (3) emergency cesarean because of pregnancy complications performed during delivery; and (4) emergency cesarean performed before onset of labor. Children with no registration of cesarean delivery were coded as vaginal delivery. We combined the different classifications to comprise either cesarean delivery performed before rupture of membranes (1 and 4) or cesarean delivery performed after rupture of membranes (2 and 3).

Asthma Definitions

In the $COPSAC_{2000}$ cohort, asthma was diagnosed by trained physicians at the research unit in accordance with strict, standardized criteria based on daily diary cards since birth. The burden of recurrent symptoms was quantified from an algorithm of 5 episodes of at least 3 consecutive days of troublesome lower lung symptoms within 6 months and need of short-acting ß2-agonists as previously described in detail.[9] Furthermore, the diagnosis required symptom improvement during a 3-month trial of inhaled corticosteroids and relapse when this medication was stopped. Asthma exacerbations were defined by need for oral prednisolone, high-dose inhaled corticosteroids, or acute hospitalization with asthmatic symptoms.

In the registry, we defined asthma as long-term recurrent use of inhaled corticosteroids: at least 200 defined daily doses (World Health Organization index) filled at a pharmacy (R03BA01; R03BA02; R03BA05; R03BA07). The child becomes a case at first collection of medication. In the sensitivity analyses, we investigated 2 alternative definitions of childhood asthma based on asthma hospitalizations as described earlier[10]: (1) recurrent hospital admissions for asthma: at least 2 inpatient admissions (primary diagnosis of asthma ICD10: J45.x; J46.x) separated by at least 1 month (child is considered case at first admission); or (2) long-term outpatient attendance related to asthma: child followed in outpatient care (primary diagnosis of asthma ICD10: J45.x; J46.x) for minimum 1 year (child becomes case at date of outpatient treatment initiation). For each definition, cases were compared with noncases where noncases were all children not fulfilling case definitions.

Confounders

Confounders were chosen a priori as sex, parity, birth weight, gestational age, maternal age, mother smoking during pregnancy, maternal disease, multiple births, mother's use of antibiotics during pregnancy, and maternal employment/education. All confounders were included in the regression models as categorical variables in registry analyses: parity (first child, second child, third child or more), birth weight (2.5-3.0 kg, 3.0-3.5 kg, 3.5-4.0 kg, >4.0 kg), gestational age (<37 weeks, 37-39 weeks, 40-41 weeks, 42 or more weeks), maternal age (4 categories), maternal disease (mothers ever hospital admission for asthma or mothers prescription of inhaled steroid ever), multiple births (singleton, twins, triplets or more), mothers use of antibiotics during pregnancy (ever prescription of antibiotics 14 days before last menstruation until offspring's birthdate), mothers smoking during pregnancy (yes/no), and maternal employment status in the year of child birth or the previous year if child is born during the first 8 months (7 categories).

Statistical Analyses

Time to first asthma diagnosis before the age of 7 years was illustrated with Kaplan Meier plots. For clinical cohort data, confounder adjusted hazard ratios (HRs) were calculated with Cox regression. All confounders were investigated for proportionality, and nonproportional variables (sex and parity) were added as stratifying variables to get adjusted estimates of cesarean delivery.

In the registry analyses, children contributed to person time of observation from date of birth to becoming asthmatic, death, migration, or December 31, 2010. The number of asthma cases by cesarean delivery was investigated with log-linear Poisson regression models offset by the log-transformed person years of observation adjusted for attained age (1-year group) and attained calendar year (1-year group) (Model 1). In 2 additional models, we included stepwise the a priori chosen confounders. Model 2: adding sex, parity, multiple birth, maternal factors (age, smoking during pregnancy, usage of antibiotics during pregnancy, employment status, asthma [ever prescription of steroid or ever admission for asthma]); and model 3: adding birth weight and gestational age. The offset of log-transformed person-years models the rate of diseases, and with the categorical adjustment for timing variable (attained age and calendar year), the resulting incidence rate ratios (IRRs) with 95% CIs can be interpreted as HRs from Cox regression.

Term children (birth weight >2.5 kg) were investigated in a separate sensitivity analysis. In another sensitivity analysis for children above 6 years of age, only children born from 1997-2005 were included and contribute only from the date of the 6-year birthday to case definition, death, migration, or December 31, 2010.