
Childhood asthma hospitalization risk after cesarean delivery in former term and premature infants

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Background: Cesarean delivery modifies infant gut bacterial flora composition, which may result in hindered tolerance to allergenic substances, thereby increasing the risk of asthma in accordance with the hygiene hypothesis. Results of previous studies regarding an association between birth route and asthma are conflicting, and these studies have not evaluated some potential confounding effects, including prematurity and maternal asthma.

Objective: To determine whether cesarean delivery in full-term and premature infants increases the risk of subsequent childhood asthma hospitalization.

Methods: We conducted a case-control study using the Washington State Birth Events Record Database linked to statewide hospitalization data. The study included 2,028 children hospitalized for asthma (cases) and 8,292 age-matched controls.

Results: Cesarean delivery was modestly associated with an increased risk of asthma hospitalization (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.04–1.39). However, when analyzed separately, there was an association between cesarean delivery and asthma hospitalization in premature infants (OR, 1.90; 95% CI, 1.09–3.02) but not in full-term infants (OR, 1.15; 95% CI, 0.97–1.34).

Conclusions: Cesarean delivery was associated with subsequent asthma hospitalization only in premature infants. Because mothers with asthma are reported to have increased rates of cesarean delivery and premature delivery, other factors in addition to the hygiene hypothesis, including genetic and in utero influences associated with maternal asthma, may contribute to the increased risk of asthma in premature infants.

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INTRODUCTION

Asthma is the most common chronic disease in children, with at least 5 million individuals younger than 18 years affected in the United States.¹ Epidemiologic data indicate an unexplained rise in asthma prevalence in affluent countries in the past several decades.^{2–6} One possible explanation, termed the *hygiene hypothesis*,⁷ postulates that factors related to improved hygiene and smaller family units lead to lack of, or delayed exposure to, some microbial stimuli during infancy. Delayed exposure to bacteria and infections in early childhood has been proposed to account for recent increases in the prevalence of atopic diseases, including eczema and asthma.⁸

The composition of intestinal microbial flora in the neonatal period may be a key factor that affects immune system maturation and the development of tolerance to allergenic

substances.⁹ Gaboriau et al¹⁰ showed that when germ-free mice are colonized with human fecal microbial flora from birth onward, they are protected against *Escherichia coli* heat-labile enterotoxin-mediated abrogation of oral tolerance to ovalbumin compared with germ-free mice not exposed to human fecal flora. In addition, differences in the intestinal microbial flora between allergic and nonallergic infants have recently been reported. Specifically, Björkstén et al¹¹ showed in a prospective study of 44 infants that the prevalence of bifidobacteria in feces was lower between 1 week and 12 months of age in atopic children than in controls. Kalliomäki et al¹² prospectively followed up 76 infants at risk of atopy and reported that the ratio of fecal counts of bifidobacteria to clostridia was reduced at 3 weeks of age in children who subsequently developed atopy by the age of 12 months.

An important mechanism by which bacterial gut flora are acquired during infancy is via exposure to maternal vaginal and fecal flora during vaginal delivery.^{13,14} Some investigators hypothesize that cesarean delivery may alter gut bacterial flora, changing microbial stimuli that may influence immune system maturation and the development of antigenic tolerance, thereby increasing the risk of asthma and other allergic diseases. Although differences in intestinal microbial flora between infants born vaginally and by cesarean delivery are small,¹⁵ Grönlund et al¹⁶ followed up 64 newborn infants prospectively (34 born via cesarean delivery and 30 born via

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vaginal delivery) and showed that in the cesarean delivery group the prevalence of fecal bifidobacteria was lower in the first month of life and that the prevalence of fecal *Bacteroides* species was lower through 6 months of life. However, recent epidemiologic studies provide conflicting results regarding a possible association between mode of delivery at birth and asthma or allergy, with 1 study¹⁷ reporting a 3-fold increased risk of adult asthma with cesarean birth, others reporting either a modest^{18,19} or a weak²⁰ association, and others reporting no association.^{21–23}

Maternal rupture of membranes (ROM) is common before cesarean delivery, occurring in 16% to 30% of women who ultimately require a cesarean delivery.^{24–26} The prevalence of intra-amniotic microbial colonization in mothers with ROM before cesarean delivery is high, with nearly 70% of direct amniotic fluid cultures collected during cesarean delivery being positive for bacterial growth.²⁷ Furthermore, amniotic fluid is commonly invaded by anaerobic bacteria, including *Bacteroides* species, after ROM.^{28,29} To our knowledge, previous studies that investigated an association between delivery route and asthma have not attempted to evaluate the effect of cesarean delivery separately in children born with and without previous maternal ROM. If maternal ROM status results in different microbial exposures to infants born via cesarean delivery, neonatal intestinal flora may differ between infants born by cesarean delivery with and without previous ROM, perhaps leading to different stimuli affecting the developing immune system.

Women with asthma are at higher risk of premature delivery³⁰ and cesarean delivery^{31–34} than women without asthma. Thus, premature delivery and maternal asthma history are factors that may confound an apparent association between cesarean delivery and asthma. Most studies^{17–19} that report an association between cesarean delivery and asthma did not adequately adjust for premature birth or maternal asthma history.

The risk of childhood asthma hospitalization is affected by multiple factors, including asthma prevalence and severity, access to appropriate medical care, socioeconomic status, and compliance with therapy.^{2,35} If cesarean delivery is associated with a relative increase in asthma prevalence, it should also be associated with a concomitant increase in the number of asthma hospitalizations. We hypothesized that birth via cesarean delivery is associated with an increased risk of childhood asthma hospitalization. We conducted a case-control study to estimate the association between cesarean delivery and hospitalization for asthma in children aged 6 to 12 years born at full term or prematurely. Furthermore, we evaluated the effect of previous ROM on the association between cesarean delivery and asthma hospitalization.

METHODS

We conducted a retrospective, population-based, case-control study using the Washington State Birth Events Record Database (BERD) linked to the Washington State Comprehensive Hospital Abstract Reporting System (CHARS); both files

were created by the Washington State Department of Health, Office of Hospital and Patient Data Systems. The BERD links birth certificate records to hospital discharge records (CHARS) for the mother and the infant for deliveries occurring in all nonfederal hospitals in Washington State. The BERD contains birth certificate data concerning maternal demographic characteristics and pregnancy complications, adverse maternal and infant outcomes, infant status, and hospital discharge data concerning the length of hospital stay, medical insurances billed, and up to 9 associated *International Classification of Diseases, Ninth Revision (ICD-9)*, diagnostic codes for the mother and infant. Information about subsequent hospitalizations of the infant that occurred after the birth hospitalization was obtained from the CHARS database. Children in the BERD and CHARS are given a unique identifier used to link the 2 files. The procedures used in the conduct of this study were approved by the human subjects protection review boards at the University of Washington and the Washington State Department of Health before the study.

Cases ($n = 2,028$) were selected by linking birth records to CHARS to identify children born between January 1, 1987, and December 31, 1994, who were hospitalized at least once with a diagnosis of asthma (*ICD-9* code 493.0, 493.1, 493.2, or 493.9) between 6 and 12 years of age. Controls ($n = 8,292$) were randomly selected from among infants born during the same birth years as the cases who were not hospitalized for asthma or reactive airway disease between 6 and 12 years of age.

The odds ratios (ORs) and test-based 95% confidence intervals (CIs), calculated using Mantel-Haenszel methods, were estimated for associations between maternal and infant characteristics and the risk of hospital admission for asthma between the ages of 6 and 12 years. Characteristics evaluated as possible risk factors included prematurity (gestation ≤ 36 vs >36 weeks), birth weight ($<2,500$ vs $\geq 2,500$ g), sex, maternal smoking history (yes vs no), maternal asthma (maternal delivery hospitalization discharge *ICD-9* code 493.1, 493.1, 493.2, or 493.9), maternal race/ethnicity, maternal insurance status at the time of delivery (Medicaid, health maintenance organization, commercial, or other), and lack of older siblings (maternal history of previous live births listed on the birth certificate). We also evaluated neonatal respiratory distress syndrome (RDS) as a possible risk factor owing to previously reported associations among RDS, bronchopulmonary dysplasia, and childhood asthma.^{36,37} Initially, the risk of asthma hospitalization after birth by cesarean delivery was separately estimated for cesarean delivery without preceding ROM and cesarean delivery with a history of ROM for 12 hours or longer. Multivariable logistic regression analyses were used to identify perinatal factors independently associated with asthma hospitalization. For those analyses, all children born via cesarean delivery were included to evaluate the strength of the evidence in support of the hygiene hypothesis as an explanation for an association between cesarean delivery and asthma hospitalization. Data analyses were conducted

using a statistical software package (SAS version 6.12; SAS Institute Inc, Cary, NC).

RESULTS

Mothers of children hospitalized for asthma between 6 and 12 years of age (cases) were similar in age to mothers of children who were not hospitalized (controls). However, case mothers were more likely to be of African American, Asian/Pacific Islander, or American Indian race/ethnicity, to be covered by Medicaid, and to have smoked cigarettes during pregnancy (Table 1). Case children were more likely to be male, to have been born prematurely or be of low birth weight, and to have had RDS as an infant. There was no association between case status and the presence or absence of older siblings. Compared with controls, a significantly larger percentage of children hospitalized with asthma had a cesarean birth (without previous maternal ROM: 16.5% vs 13.2%; OR, 1.3; 95% CI, 1.2–1.5; and with maternal ROM for ≥ 12 hours: 2.5% vs

1.7%; OR, 1.5; 95% CI, 1.1–2.1). There was no evidence that the association between cesarean delivery and subsequent childhood asthma hospitalization differed by the presence or absence of previous maternal ROM.

We had limited ability to evaluate the role of maternal asthma because we were restricted in identifying women with such a history to those whose hospital delivery records included a discharge diagnosis of asthma as specified by *ICD-9* coding. Although only 0.45% of delivery records of case mothers compared with 0.16% of control mothers included an *ICD-9* code for asthma (22 women total), maternal asthma as indicated by *ICD-9* code at delivery was strongly associated with risk of subsequent asthma hospitalization among their children (OR, 2.8; 95% CI, 1.2–6.6).

We performed multivariable logistic regression analysis to determine factors that were independently associated with an increased risk of childhood asthma hospitalization (Table 2). Variables evaluated in the model included cesarean delivery,

Table 1. Selected Characteristics of Children Hospitalized for Asthma Between the Ages of 6 and 12 Years (Cases) and Their Controls and of the Mothers of Cases and Controls*

Characteristic	Cases, No. (%) (n = 2,028)	Controls, No. (%) (n = 8,292)	Odds Ratio (95% CI)
Maternal characteristics			
Age, y			
<20	233 (11.5)	899 (10.8)	1.04 (0.88–1.23)
20–25	682 (33.6)	2,736 (33.0)	1.00 (Referent)
26–29	483 (23.8)	1,994 (24.0)	0.97 (0.85–1.11)
30–35	478 (23.6)	2,052 (24.7)	0.93 (0.82–1.07)
>35	151 (7.4)	597 (7.2)	1.01 (0.83–1.24)
Race			
White	1,544 (76.1)	6,743 (81.3)	1.00 (Referent)
African American	137 (6.8)	336 (4.1)	1.78 (1.44–2.20)
Hispanic	104 (5.1)	467 (5.6)	0.97 (0.78–1.22)
Asian/Pacific Islander	147 (7.2)	404 (4.9)	1.59 (1.30–1.94)
American Indian	49 (2.4)	149 (1.8)	1.44 (1.02–2.02)
Insurance (at delivery)			
Medicaid	676 (33.3)	2,173 (26.2)	1.33 (1.16–1.52)
HMO	251 (12.4)	928 (11.2)	1.16 (0.97–1.38)
Commercial	475 (23.4)	2,029 (24.5)	1.00 (Referent)
Other	626 (30.9)	3,162 (38.1)	0.85 (0.74–0.97)
Smoking	500 (24.7)	1,690 (20.4)	1.31 (1.17–1.47)
Pregnancy characteristics			
Prematurity (≤ 36 wks gestation)	140 (6.9)	347 (4.2)	1.70 (1.39–2.08)
Birth weight, g			
<2,500	155 (7.6)	361 (4.4)	1.82 (1.50–2.20)
$\geq 2,500$	1,870 (92.2)	7,906 (95.3)	1.00 (Referent)
Birth route			
Cesarean, without ROM	335 (16.5)	1,094 (13.2)	1.32 (1.16–1.51)
Cesarean, with ROM (≥ 12 h)	50 (2.5)	145 (1.7)	1.49 (1.08–2.06)
Vaginal	1,643 (81.0)	7,053 (85.1)	1.00 (Referent)
Infant characteristics			
≥ 1 older siblings	1,144 (56.4)	4,741 (57.2)	0.96 (0.87–1.06)
Male	1,312 (64.7)	4,239 (51.1)	1.75 (1.59–1.94)
History of RDS as a neonate	49 (2.4)	81 (1.0)	2.51 (1.78–3.55)

Abbreviations: CI, confidence interval; HMO, health maintenance organization; RDS, respiratory distress syndrome; ROM, rupture of membranes.

* Totals for some variables do not sum to the total sample size owing to missing data.

Table 2. Multivariable Logistic Regression Analysis Assessing Risk Factors for Asthma Hospitalization Between the Ages of 6 and 12 Years in All Infants, Premature Infants, and Term Infants

Risk factor	OR (95% CI)*		
	All (N = 1,589)†	Premature infants (n = 115)	Term infants (n = 1,474)
Cesarean section	1.20 (1.04–1.39)	1.90 (1.09–3.02)	1.15 (0.97–1.34)
Gestational age ≤36 weeks	1.19 (0.91–1.55)	NA	NA
Maternal smoking during pregnancy	1.22 (1.07–1.38)	0.78 (0.47–1.27)	1.26 (1.1–1.44)
Male	1.73 (1.54–1.94)	1.79 (1.13–2.89)	1.72 (1.53–1.94)
Birth weight <2,500	1.40 (1.03–1.85)	1.41 (0.86–2.32)	1.44 (1.01–2.02)
History of RDS (infant)	1.85 (1.14–2.95)	1.48 (0.76–2.85)	NA
Nonwhite/non-Hispanic (mother)	1.54 (1.31–1.81)	1.06 (0.57–1.93)	1.58 (1.34–1.87)
Medicaid insurance (at delivery)	1.33 (1.17–1.50)	1.59 (0.99–2.57)	1.32 (1.16–1.50)

Abbreviations: CI, confidence; NA, not available; OR, odds ratio; RDS, respiratory distress syndrome.

* Relative to controls who were not hospitalized for asthma between the ages of 6 and 12 years (all: N = 6,612; premature: n = 289; and term: n = 6,323).

† The sample size for multivariable logistic regression analysis is smaller than the total sample size owing to missing data.

maternal race (white/Hispanic vs other), type of medical insurance billed for the birth hospitalization (Medicaid vs other), maternal smoking during pregnancy, infant sex, gestational age at delivery, birth weight, and history of infant RDS. We found that birth by cesarean delivery was associated with an increased risk of childhood asthma hospitalization (OR, 1.20; 95% CI, 1.04–1.39), even after adjusting for maternal race, Medicaid insurance status, prenatal maternal smoking, male sex, low birth weight, prematurity, and history of RDS. Next we performed similar multivariable logistic regression analyses separately in full-term (n = 7,797) and premature (n = 404) infants, with the exception that history of RDS was included only in the model for premature infants, and premature delivery was not applicable. The association between birth via cesarean delivery and childhood asthma hospitalization was not significant in full-term infants (OR, 1.15; 95% CI, 0.97–1.34) but was significant and of greater magnitude in premature infants (OR, 1.90; 95% CI, 1.09–3.02) despite a smaller sample size in the premature group. Among full-term infants, 17% of children hospitalized for asthma and 15% of controls had a cesarean birth. Among premature infants, 29% of children hospitalized for asthma and 18% of controls had a cesarean birth.

DISCUSSION

Although affected by multiple factors, including socioeconomic status, compliance with therapy, and access to health care, asthma hospitalization rates should reflect the prevalence of severe asthma in the population. If cesarean delivery truly results in increased asthma prevalence rates (of mild and severe forms of the disease), then cesarean delivery should also be associated with an increased risk of asthma hospitalization. If cesarean delivery is only associated with an increased risk of mild asthma, then subsequent asthma hospitalization rates may not differ by birth route. We found that cesarean birth was independently associated with a 20% increased risk of asthma hospitalization in children aged 6 to

12 years. However, in full-term infants we found that cesarean delivery was not associated with subsequent childhood asthma hospitalization. In addition, among all births there was not a significant difference in the association between cesarean delivery and subsequent asthma hospitalization between children with a cesarean birth with maternal ROM for 12 hours or longer vs those with a cesarean birth without maternal ROM.

Genetic predisposition (as evaluated by maternal asthma history) may in part explain the observed association between delivery mode and childhood asthma. In this and previous studies, maternal asthma history may confound the association between mode of delivery and risk of childhood asthma. Thirty percent to 45% of women with asthma require a cesarean delivery compared with 15% to 20% of women without asthma.^{31–34} The estimate of asthma prevalence (<1%) in our study mothers grossly underestimates the true asthma prevalence in this population; the prevalence of asthma among women of childbearing age is estimated to be 5% to 10%.³⁸ The inability to adequately address potential confounding by maternal asthma history in our study and in previous studies^{17–23} may partially explain the association between birth route and asthma observed in this and previous studies. A prospective study design is needed to more rigorously evaluate the effect of maternal asthma on the association between cesarean delivery and asthma by more accurately identifying maternal asthma prevalence.

Cesarean delivery is associated with an increased risk of asthma hospitalization, but only in prematurely born infants. The risk of asthma hospitalization in premature infants was increased by 90%. However, in the much larger sample of full-term infants, the association between cesarean delivery and asthma hospitalization later in childhood was not statistically significant. Higher rates of premature³⁰ and cesarean^{31–34} delivery are reported in women with asthma. Therefore, premature infants are more likely than full-term infants to have a maternal genetic predisposition for asthma. In

addition, of women who deliver prematurely, those with asthma may be more likely to undergo cesarean delivery if a similar mechanism underlies bronchial and uterine smooth muscle dysfunction.^{39,40} Long-term follow-up studies^{41,42} have also shown that premature infants, especially those with bronchopulmonary dysplasia, have decreased lung function compared with full-term infants into the school-aged years. The strong association in premature infants and the lack of an association in full-term infants suggests that genetic and in utero influences associated with maternal asthma or diminished lung function in children born prematurely may at least partially explain the previously reported association between mode of delivery and risk of childhood asthma. An alternative explanation for the association between cesarean delivery and subsequent asthma hospitalization in preterm infants would be that the same environmental stimulus—altered gut flora after cesarean delivery—may have a greater effect on the immune system of premature infants owing to exposure at an earlier developmental stage than in full-term infants.

We found that the risk of asthma hospitalization was increased by 30% in children whose mothers reported smoking during pregnancy. This finding is consistent with findings of smaller-caliber airways in children whose mothers smoked during pregnancy.^{43,44} The presence of older siblings did not seem to be associated with a decreased risk of asthma hospitalization. However, we were limited to using a variable on the Washington State birth certificate that reported “prior maternal live births” as a proxy for older siblings in the home. As such, we could not determine the number of siblings or half-siblings in each child’s home between birth and the age of 6 years.

We chose to examine asthma hospitalization between the ages of 6 and 12 years for 3 reasons. First, information from the CHARS database was available for 1987 and forward only. Second, maternal smoking status was added to the Washington State birth certificate in 1987. Last, and perhaps most important, the diagnosis of asthma in children younger compared with those 6 years and older is subject to greater misclassification owing to the inherent difficulties in diagnosing asthma in young children with acute respiratory illnesses who present with wheezing.

In conclusion, we found that birth via cesarean delivery was modestly associated with an increased risk of asthma hospitalization in children aged 6 to 12 years. When premature and full-term infants were analyzed separately, the association was not significant in full-term infants, but it was significant in the much smaller sample of premature infants. During the past decade, data that support the hygiene hypothesis as an explanation for the rising prevalence of asthma and other allergic diseases have come from multiple sources.^{45–49} The hygiene hypothesis has also been suggested by several investigators to explain the previously reported association between cesarean delivery and asthma.^{17–19} Although the lack of an association between birth route and asthma hospitalization in full-term children in our study clearly does not invalidate the hygiene hypothesis, it does raise the question as to

whether genetic predisposition or other factors related to perinatal environment in premature infants may explain the association between delivery mode and childhood asthma.

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