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Association between prenatal and neonatal risk factors and development of bronchiolitis in early life

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ABSTRACT

Background: Bronchiolitis is the most common seasonal viral respiratory disorder in infants. However, risk factors for the development of bronchiolitis, particularly during pregnancy, remain unclear.

Methods: A questionnaire was administered to the parents of the hospitalized infants with acute bronchiolitis to obtain information regarding patients' medical, family, and prenatal exposure history. Logistic regression with adjustment was performed to evaluate risk factors associated with bronchiolitis in the infants.

Results: Among the enrolled patients, 55 (36.7%) were diagnosed as having bronchiolitis, and the majority (89%) of the patients had moderate-to-severe bronchiolitis. The bronchiolitis group had lower C-reactive protein levels than did the control group. Fewer patients in the bronchiolitis group developed fever. However, hospital stays were longer in the bronchiolitis group than in the control group. Respiratory syncytial virus was the most detected virus (23/26, 88.6%) in the bronchiolitis group. Male sex (odds ratio [OR], 5.71; 95% confidence interval [CI], 2.02–16.12; $P < 0.001$), antibiotic usage during pregnancy (OR, 27.2; 95% CI, 1.12–660.84; $P = 0.04$), and viral infection (OR, 49.3; 95% CI, 9.01–270.26; $P < 0.001$) during the postnatal period were significantly associated with hospitalization for acute bronchiolitis in the infants. By contrast, pet exposure during the perinatal period was significantly and negatively associated with acute bronchiolitis (OR = 0.21, 95% CI = 0.07–0.69, $P < 0.01$).

Conclusion: Environmental exposures during pregnancy may affect respiratory health in offspring, and effective strategies should be developed to prevent bronchiolitis in early life.

Keywords: Bronchiolitis; environment; pregnancy; respiratory syncytial virus; risk factors

1. Introduction

In infants, bronchiolitis is the leading cause of virus-induced respiratory diseases that involve the inflammation of small bronchioles and their surrounding tissues. Clinically, bronchiolitis is characterized by respiratory difficulty and lower respiratory tract symptoms such as productive cough, tachypnea, chest hyperinflation, and intercostal wall retraction [1, 2]. Moreover, expiratory wheezing and inspiratory crackles are often noted. Because of the broad spectrum of disease severity and difficulties in predicting the disease course, hospital admissions without severe symptoms are common [3]. In the United States and the United Kingdom, 2% to 3% of children aged <12 months are hospitalized annually with a diagnosis of bronchiolitis [4–6]. Studies have investigated risk and protective factors for severe bronchiolitis in infants [6–11]. Premature infants and those with bronchopulmonary dysplasia or congenital heart disease have a high risk of severe bronchiolitis requiring hospital admission [12–14]. Infants with chronic conditions such as Down syndrome, congenital malformations, especially pulmonary and airway anomalies, cystic fibrosis, and neuromuscular diseases may be more vulnerable to severe bronchiolitis [15]. Studies have reported the protective effect of maternal breastfeeding [16, 17]. By contrast, studies have reported inconsistent findings regarding the effect of prenatal cigarette exposure [17, 18].

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis, followed by other viruses such as rhinovirus, influenza, and human metapneumovirus (HMPV) [1, 3, 4]. Chen and colleagues reported that RSV was the most common pathogen implicated in the viral etiology of bronchiolitis in children, followed by human bocavirus, HMPV, and rhinovirus [19]. RSV bronchiolitis damages the airway epithelium and contributes to airway obstruction. RSV infection promotes type 2 inflammation in the critical stage of infant lung development, thus possibly leading to allergic asthma [20–22]. In an animal study, prenatal exposure to RSV altered immune responses in offspring mice and suppressed interferon (IFN-γ) and interleukin (IL-2) production

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when infected with the same virus [23]. However, studies examining infections during pregnancy and bronchiolitis in infants are scant. Infants belonging to different age groups may vary in response to the virus owing to the rapid development of the immune system immediately after birth [24]. A recent systematic review highlighted the need for large studies to more effectively identify risk factors associated with the development of virus-associated bronchiolitis including environmental factors and prenatal exposure during pregnancy [12–15]. Because of the lack of studies on exposure to perinatal factors and respiratory health in early life, we hypothesized that environmental exposures in early life and maternal factors during prenatal periods are associated with the development of virus-associated bronchiolitis in infants.

2. Methods

2.1. Study population

Ethical approval for this study and questionnaire (approval no: A-ER-106-017) were approved by the Human Research Ethics Committee of National Cheng Kung University Hospital, Tainan, Taiwan (Superintendent, Dr. Meng-Ru Shen) on November 1, 2018. In this case–control study, we enrolled infants who were hospitalized for acute bronchiolitis at National Cheng Kung University Hospital, Tainan, and Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan, from January 1, 2017 to December 31, 2018. Patients who developed acute episodes of coughs, tachypnea, frequent crackles, wheezing, labored breathing, and lung hyperinflation resulting in respiratory distress were diagnosed as having acute bronchiolitis, the main outcome of this study. The inclusion criteria for the study group were a diagnosis of acute bronchiolitis, age ≤12 months, and admission to a hospital ward. We recruited infants at the same age who were hospitalized during the same period without a diagnosis of bronchiolitis to the control group. No previous admission history due to bronchiolitis was recorded in the control group. Admission history due to bronchiolitis in the control group after the survey of questionnaire was not followed. Preterm infants and those with congenital heart disease, metabolic disease, and neuromuscular diseases were excluded. In this study, we recruited a total of 150 children. Of the 50 children recruited from National Cheng Kung University Hospital, 18 had bronchiolitis. Of the 100 children recruited from Kaohsiung Chang Gung Memorial Hospital, 37 had bronchiolitis. Ninety-five hospitalized infants without other lower respiratory tract infections, although few had acute tonsillitis (n = 2), croups (n = 1), and acute pharyngitis (n = 1), were assigned as control group

2.2. Study methods

The severity of bronchiolitis in the hospitalized infants was examined using the modified Wood's Clinical Asthma Score (M-WCAS), as described by Duarte-Dorado et al. [25]. The 5-item M-WCAS is a clinical scoring system that considers oxygen saturation, inspiratory breath sounds, expiratory wheezing, accessory muscle usage, and mental status, with scores for each sign ranging from 0 to 2. A score of 0 to 3, 4 to 6, and >6 represents mild, moderate, and severe illness, respectively. Informed consent was obtained from the parents or guardians of the infants. The parents of the infants with and without bronchiolitis were asked to complete questionnaires to obtain information regarding sex, race, age at admission, the infant's feeding habits, smoking at home, exposure to pets, respiratory or other infections during pregnancy, medications received during pregnancy, use of probiotics by the mother during pregnancy, and presence of allergic disorders among family members. Laboratory data were collected from medical records. White blood cell and eosinophil count and C-reactive protein (CRP) levels were measured through blood samples. A throat swab was used for virus culture and identification. Enterovirus, influenza A virus, influenza B virus, parainfluenza virus, adenovirus, RSV, HMPV, herpes simplex virus type 1, Epstein Barr virus, and cytomegalovirus were detected through serology assays and validated by PCR or virus culture.

Table 1.

Baseline characteristics of hospitalized infants with and without bronchiolitis

	Cases (n = 55)	Controls (n = 95)	P value*
Age (SD), mo	6.96 ± 2.93	6.63 ± 3.10	0.58
Sex, male n (%)	38 (69.09)	44 (46.32)	7×10^{-3}
Body weight, kg	7.96 ± 1.49	7.76 ± 1.72	0.67
Length of hospital stay, d	5.48 ± 2.57	4.31 ± 2.92	$<10^{-4}$
Duration of fever, d	0.74 ± 1.43	1.03 ± 1.73	0.08
White blood cells (SD), 1,000/μL	12.38 ± 5.53	13.46 ± 6.02	0.23
C-reactive protein (SD), mg/L	10.96 ± 16.10	42.56 ± 64.43	2×10^{-4}
Eosinophil (SD), %	2.41 ± 4.08	1.66 ± 2.68	0.20
Severity of bronchiolitis†			
Moderate, n (%)	49 (89.09)	0	
Mild, n (%)	6 (10.91)	0	
Nonrespiratory disease, n (%)	0	95 (100)	
Viral measurement			
Not detected	26 (47.27)	23 (24.21)	
Not performed	3 (5.45)	69 (72.63)	
Detected	26 (47.27)	3 (3.16)	
Adenovirus	1 (1.82)	1 (1.05)	
Cytomegalovirus	1 (1.82)	1 (1.05)	
Epstein-Barr virus	0	1 (1.05)	
Respiratory syncytial virus	23 (41.82)	0	
Influenza B	1 (1.82)	0	

M-WCAS, Wood's Clinical Asthma Score; SD, standard deviation.

*$P < 0.05$ is bold.

†The modified M-WCAS [25] is a clinical scoring system that considers oxygen saturation, inspiratory breath sounds, expiratory wheezing, accessory muscle usage, and mental status, with scores for each sign ranging from 0 to 2. A score of 0–3, 4–6, and >6 represents mild, moderate, and severe illness, respectively. All measurements were obtained when the child was awake and not crying.

2.3. Statistical analysis

Baseline characteristics, namely, demographic, clinical, laboratory, and questionnaire data, were analyzed using the chi-square test for categorical variables and Student *t* test for continuous variables. Univariate and multivariate logistic regression were performed to determine risk factors for bronchiolitis. Because acute bronchiolitis has been known to dominantly occur in male infants, we treated sex as a covariate and adjusted in the analytical models. A *P* value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

3. Results

Of the 150 hospitalized infants recruited to this study, 55 (36.6%) were diagnosed as having acute bronchiolitis. **Table 1** lists the baseline characteristics of the infants with and without acute bronchiolitis. The age and body weight of the infants did not significantly differ between the bronchiolitis and control groups. A higher proportion (69.1%) of the infants hospitalized for bronchiolitis were boys. The majority of the infants hospitalized for bronchiolitis (89.0%) were moderately ill according to the M-WCAS. The bronchiolitis group had lower CRP levels than did the control group. Moreover, fewer patients in the bronchiolitis group than in the control group developed fever; however, the hospital stay was longer in the bronchiolitis than in the control group. Approximately half (47.3%) of the bronchiolitis group had confirmed virus infection compared with the control group (3.2%). RSV was the most common virus isolated from the throat swabs of the patients with acute bronchiolitis (23/26, 88.5%).

Table 2 lists perinatal and postnatal risk factors for acute bronchiolitis. A higher proportion of the mothers of the infants developed respiratory infections during pregnancy (67.3% vs 53.7%) and had lower breastfeeding rate (10.9% vs. 16.8%) in the bronchiolitis group than in the control group; however, the differences between the 2 groups were not significant. Furthermore, the use of probiotics by the mothers during pregnancy and cigarette exposure did not differ between the bronchiolitis and control groups. By contrast, a significantly higher proportion of the infants in the bronchiolitis group had a family history of allergic disorders. However, significantly fewer infants in the bronchiolitis group had pet exposure.

Table 3 presents risk factors associated with acute bronchiolitis. Variables included in the adjusted model were breastfeeding, sex, pet exposure, respiratory tract infection during pregnancy, drug use during pregnancy, virus detection, and family history of allergic disorders. It was observed that male sex (OR = 5.71, 95% CI = 2.02–16.12), antibiotic use during pregnancy (odds ratio [OR], 27.2; 95% confidence interval [CI], 1.12–660.84), and virus infection during the postnatal period (OR, 49.3; 95% CI, 9.01–270.26) were significantly associated with acute bronchiolitis. By contrast, pet exposure in the perinatal period was a protective factor that was significantly negatively associated with acute bronchiolitis (OR, 0.21; 95% CI, 0.07–0.69).

Table 2.

Clinical features of maternal participants during pregnancy

	Cases (*n* = 55)	Controls (*n* = 95)	*P* value*
	n (%)	*n* (%)	
Respiratory tract infection during pregnancy	37 (67.27)	51 (53.68)	0.15
Drug use during pregnancy, *n* (%)	7 (12.73)	13 (13.83)	0.99
Antipyretics use during pregnancy	3 (5.45)	9 (9.57)	0.54
Antibiotics use during pregnancy	6 (11.11)	6 (6.52)	0.49
Probiotics use during pregnancy	20 (36.36)	24 (25.26)	0.21
Breastfeeding, *n* (%)	6 (10.91)	16 (16.84)	0.32
Probiotics, *n* (%)	18 (33.33)	36 (37.89)	0.58
Cigarette exposure, *n* (%)	22 (40.00)	41 (43.16)	0.71
Pet exposure, *n* (%)	5 (9.09)	33 (35.11)	4×10^{-4}
Family allergic history, *n* (%)	32 (58.18)	35 (36.84)	0.01
Mother has allergic disease	20 (36.36)	46 (49.46)	0.12
Father has allergic disease	24 (43.64)	25 (27.47)	0.05

*$P < 0.05$ is given in bold.

Table 3.

Crude and adjusted models of risk factors associated with acute bronchiolitis in the study

	Crude model		Adjusted model*	
	OR (95% CI)	*P* value†	OR (95% CI)	*P* value
Breastfeeding	0.61 (0.22–1.65)	0.33	0.59 (0.18–1.94)	0.38
Sex	2.59 (1.29–5.22)	8 × 10-3	5.71 (2.02–16.12)	10^{-3}
Pet exposure	0.19 (0.07–0.51)	10^{-3}	0.21 (0.07–0.69)	0.01
Respiratory tract infection during pregnancy	1.77 (0.89–3.55)	0.11	1.74 (0.68–4.45)	0.25
Antipyretics use during pregnancy	0.55 (0.14–2.11)	0.38	1.01 (0.05–20.61)	0.99
Antibiotics use during pregnancy	1.79 (0.55–5.86)	0.34	27.2 (1.12–660.84)	0.04
Probiotics use during pregnancy	1.69 (0.82–3.47)	0.15	1.45 (0.52–4.10)	0.481
Viral detection	27.49 (7.75–97.50)	$<10^{-4}$	49.34 (9.01–270.26)	$<10^{-4}$
Family allergic history	0.96 (0.48 – 1.93)	0.91	0.73 (0.29–1.89)	0.52

CI, confidence interval; OR, odds ratio.

*Variables included in the adjusted model: breastfeeding, sex, pet exposure, respiratory tract infection during pregnancy, drug use during pregnancy, virus detection, and family allergic history.

†$P < 0.05$ is shown in bold.

4. Discussion

Acute bronchiolitis is the leading cause of respiratory diseases in infants, and most of the children were hospitalized for bronchiolitis within the first year of life [24]. The results of this study revealed that male sex, absence of pet exposure, and antibiotic usage during pregnancy were risk factors for acute bronchiolitis. Other environmental exposure factors during prenatal and neonatal periods examined in this study, including breastfeeding, cigarette exposure, and respiratory tract infection during pregnancy, were not significant.

Among 310 healthy term infants, those who developed the first episode of bronchiolitis had lower birth weights, younger gestational ages, lower postnatal weights, younger postnatal ages, and higher likelihoods of being born through cesarean delivery [26]. Elevated CRP values (>0.8 mg/dL) and pulmonary consolidation on chest radiographs were more common among infants with severe bronchiolitis; however, no significant differences in epidemiological variables were noted [26]. The findings of this study accord with previous studies indicating that severe bronchiolitis was uncommon in healthy term infants and the severity of bronchiolitis could be predicted based on clinical characteristics, such as young age and virus infection (eg, that with RSV). In our study, infectious diseases accounted for 94% of the diagnoses in both the bronchiolitis and control groups (**Supplementary Table S1 http://links.lww.com/PA9/A0**). Urinary tract infection was the leading diagnosis for hospitalization in the control group. Hence, the control group had higher CRP levels. Acute gastroenteritis was the second most common diagnosis in the control group that resulted in hospitalization for severe dehydration. Antibiotic therapy for urinary tract infection and rehydration therapy for acute gastroenteritis resulted in a shorter hospital stay in the control group.

In our study, approximately half (47.3%) of the hospitalized infants with bronchiolitis had confirmed viral infection, and RSV was the most common virus isolated from throat swabs. This finding is in agreement with a previous study conducted in North America during seasonal epidemics; this study reported that 41.82% of infants with bronchiolitis had RSV infection [2]. In this study, the use of virus culture for detecting viral infection may have contributed to the low rate of virus positivity. RSV bronchiolitis causes histological changes including epithelial cell sloughing, inflammatory cell infiltration, and increased mucus secretion along with other symptoms. Furthermore, RSV bronchiolitis is associated with weaker antiviral innate IFN responses and ineffective inflammatory and adaptive immune responses, which are the crucial factors contributing to severe RSV disease [27]. An animal study reported suppressed IFN-γ and IL-2 production in offspring during RSV infection when their mothers had RSV infection during pregnancy, suggesting that viral infection during pregnancy may be a risk factor for severe bronchiolitis in offspring [23]. In particular, B-cell function is not developed in young infants (aged <6 months), and more time is required to achieve sufficient and sustained antibody production. Hence, a vaccine for RSV that targets pregnant mothers instead of young children should be developed. Vaccinating mothers during pregnancy can lead to the increased transfer of protective maternal antibodies against RSV to children [28, 29].

An Italian case–control study conducted in 2 pediatric centers reported an association between exposure to various indoor and outdoor pollutants and acute bronchiolitis in hospitalized infants [30]. Our study results reported that pet exposure in the prenatal and neonatal periods protected against acute bronchiolitis. A previous study reported that perinatal exposure to indoor pets among urban infants protected them from wheezy bronchitis and resulted in compositional differences in gut microbiota [31]. Our results indicated that antibiotic use in the prenatal period was significantly associated with acute bronchiolitis, suggesting that not only the infection itself but also the effects of antibiotics during the prenatal period can affect respiratory health in later life. This finding is in agreement with that of our nationwide study conducted using the health database provided by the National Health Research Institutes of Taiwan; our previous study indicated a temporal relationship between exposure to acetaminophen and antibiotics in early life and the development of allergic diseases in later childhood [32].

Breastfeeding is considered a protective factor against severe bronchiolitis. An Italian multicenter cohort study conducted in 2013 reported that breastfeeding reduced hospitalization for bronchiolitis [33]. Breast milk exerts a protective effect and protects infants against RSV through direct binding to the RSV surface protein and inducing a reduction in proinflammatory cytokine secretion [34]. Exclusive breastfeeding reduced the necessity for oxygenation and the severity of RSV infection in infants with bronchiolitis [34]. The protective effect of breastfeeding was observed only when infants were breastfed for 4 to 6 months [35]. In this study, the breast milk feeding rate was not significantly lower (10.9%) in the bronchiolitis group than in the control group (16.8%). We could not evaluate the bottle and breast milk feeding rates in these 2 groups; hence, we could not draw a conclusion regarding the protective effect of breastfeeding.

This study findings revealed that acute bronchiolitis was associated with RSV infection in the study infants as well as with the prenatal usage of antibiotics. Household pet exposure during the prenatal and neonatal periods was associated with less severe bronchiolitis in the study infants. This study has several limitations that should be noted. First, a history of bronchiolitis was not investigated in our questionnaire in both the study and control groups. Moreover, throat swabs were collected for fewer infants without bronchiolitis than that for those with bronchiolitis. Second, we were only able to evaluate whether breast feeding was associated bronchiolitis because the duration of breast feeding was not available. It would be interesting to explore the duration effect of breast feeding on bronchiolitis in future studies. Third, in this case-control study, some demographic or clinical characteristics of the control subjects might have biased the observed results. Hence, the results should be interpreted with caution. Fourth, this study included a relatively small number of children. Future cohort studies with large sample sizes are warranted.

In conclusion, the study results demonstrated several risk and protective factors during the prenatal and neonatal periods. The findings can help public health authorities and medical care professionals to develop effective measures to prevent severe bronchiolitis in the first year of life.

Conflicts of interest

The authors have no financial conflicts of interest.
Preliminary data was presented once on European Academy of Allergy and Clinical Immunology annual congress in 2019.

Supplementary material

Supplementary Table S1 can be found via 10.5415/apallergy.2022.12.e38.
Supplementary Table S1
Click here to view

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