Elective Cesarean Delivery as a Predisposing Factor of Respiratory Syncytial Virus Bronchiolitis in Children

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Objective: To investigate the effect of cesarean delivery and other predisposing factors of respiratory syncytial virus (RSV)-positive acute bronchiolitis in children.

Material and Method: The case-control study was conducted in three main tertiary hospitals in Kunming, China between September 2012 and July 2013. Children with first episode of wheezing diagnosed as bronchiolitis and tested for RSV were included. RSV was detected by real-time reverse transcription polymerase chain reaction. Mode of delivery and characteristics of children, parents, and household were interviewed and analyzed with RSV-positive status by multiple logistic regression.

Results: Of 265 children, RSV-positive was found in 75.5%, and the majority of children (83.3%) were younger than 12 months. Compared to vaginal delivery, the odds of RSV-positive detection were double in children born by elective cesarean delivery (adjusted odds ratio 2.32; 95% confidence interval 1.19-4.52). Children aged less than 6 months, born in the rainy season, having maternal history of asthma and living in family that smoked more than 20 cigarettes per day were more likely to be RSV-positive.

Conclusion: Children born by elective cesarean delivery increased the risk of RSV-positive acute bronchiolitis after adjusting for age, birth season, maternal asthma, and family smoking status.

Keywords: Acute bronchiolitis, Elective cesarean delivery, Predisposing factor, Respiratory syncytial virus

Cesarean section rate has been increasing globally and its effect on children's respiratory illness has been reported[1,2]. In addition, the trend of cesarean section due to maternal request or elective indication is higher reported[3-5]. In China, the rate of cesarean section was reported to be the highest (46.2%) in the WHO Global Survey[1]. Two systematic reviews indicated that the risk of asthma was increased among children born by cesarean comparing to vaginal delivery[6,7]. Likewise, cesarean delivery was found to increase the risk of lower respiratory tract infection (LRTI) and severe acute bronchiolitis; however, these studies were not analyzed on RSV-positive acute bronchiolitis[8-11].

Acute bronchiolitis is the most common LRTI in children aged less than two years[12,13].

Respiratory syncytial virus (RSV) is the single most important etiology that has been shown to increase the risk of subsequent recurrent wheezing and asthma[14-16]. Children with prematurity, passive smoking, young age, and lack of breastfeeding were predisposed to severe RSV-positive acute bronchiolitis. On the contrary, the effects of maternal history of asthma, birth season, residency status, socioeconomic status, and mode of delivery are inconclusive[17].

Accordingly, it is assumed that cesarean delivery may be associated with RSV-positive acute bronchiolitis in children similar to other predisposing factors. However, there is no sufficient evidence to conclude whether cesarean delivery is one of the predisposing factors of acute bronchiolitis caused by RSV. The objective of the present study was to evaluate the effect of cesarean delivery on RSV-positive bronchiolitis in live born children adjusting for other predisposing factors.

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Material and Method

Study design and setting

The case-control study was conducted in three main tertiary hospitals in Kunming, Yunnan Province, China between September 2012 and July 2013, which was a part of a randomized controlled trial to evaluate the effect of Traditional Chinese Medicine. The study was approved by the Institute Ethics Committee of the Faculty of Medicine, Prince of Songkla University, and the Second Affiliated Hospital of Kunming Medical University. All children who were clinically diagnosed as acute bronchiolitis with first episode of wheezing by the pediatricians in these three hospitals were included. The case was the RSV-positive bronchiolitis child, and control was RSV-negative bronchiolitis child.

The sample size was calculated based on the proportion of elective cesarean section in case and control for 3-month pilot study, which showed that the elective cesarean section was 48% and 25% in RSV-positive and RSV-negative children, respectively. According to 95% confidence interval, type II error of 20% and ratio of case and control to be 3:1, at least 156 cases and 52 controls were needed. To compensate the variation of exposure, 20% of sample size were adjusted, thus 200 cases and 65 controls were required.

Data collection and measurement

Each child's guardian was approached and invited to participate in the study. They were given a full explanation of the study purpose and signed the consent forms before interview. The variables included characteristics of the child, parents and household. After the interview, nasopharyngeal aspirate (NPA) was performed in all children to test for RSV. Nasopharyngeal aspirates (NPA) were collected from children by inserting and swirling neonatal minitip plastic applicator (516C, bioMérieux, Shanghai, China) into the posterior nasopharyngeal space via the nostril with the children in the orthopnea or recumbent position. RSV-positive was detected from NPA specimens using the one-step Real-Time reverse transcription Polymerase Chain Reaction[18] by RealMasterMix kit (Tiangen Biotech Co., Ltd., Beijing, China). The RSV detection was considered positive if the cycling threshold value was ≤37. The interviewers were blinded from the RSV results.

Variable definition

Children's characteristics recorded were age, gender, ethnicity (Han vs. minorities), gestational age,

birth weight, birth region (urban vs. nonurban), presence of older sibling, sibling with similar disease, eczema, 0 to 3 months feeding, and birth season. Artificial feeding was defined as feeding only with cow or powder milk without breast milk and non-artificial feeding was breastfeeding with or without cow or powder milk. In Kunming, the rainy season occurs from May to October and the dry season occurs from November to April.

The parental characteristics comprised mode of delivery, maternal delivery age, maternal history of asthma, maternal education level, maternal employment status, paternal history of asthma, paternal education level, and paternal occupation.

Household characteristics included having a pet in the house, number of cigarettes smoked per day by all members in the same household, smoking indoors, number of household members sharing a child's bedroom, number of household members, and annual per capita disposable income (PCDI). Annual PCDI was classified into three categories: low (< $3,450 USD), medium ($3,450-7,885 USD), and high (> $7,885 USD)[19].

Statistical analysis

All data were entered in EpiData version 3.1 and analyzed using R version 2.15.0 (R Foundation for Statistical Computing 2012, Austria). The associations between RSV- positive bronchiolitis and predisposing factors were assessed by univariate analysis followed by multiple logistic regression. Wilcoxon rank-sum test was used for continuous variables and Chi-square or Fisher's exact test for categorical variables as appropriate. Variables having a *p*-value less than 0.2 from the univariate analysis were included in the initial multiple logistic regression model. The model provided crude and adjusted odds ratios (OR) and 95% confidence intervals (CI). A *p*-value less than 0.05 was considered statistically significant.

Results

Of all 265 children, ages ranged from 27 days to 34 months and about half were aged less than six months. The majority of them (87.2%) came to the hospital with their mother (73.2%). RSV-positive detection was found in 200 children (75.5%).

The association between RSV-positive bronchiolitis and children's characteristics was presented in Table 1. Children aged less than six months or those born in the rainy season were significantly more likely to be RSV-positive. Table 2

Table 1. Comparison of children's characteristics by RSV status

Children's characteristics	RSV-negative (n = 65)	RSV-positive (n = 200)	*p*-value
Age (months), n (%)			0.01
<6	25 (38.5)	113 (56.5)	
6-12	23 (35.4)	61 (30.5)	
>12	17 (26.1)	26 (13.0)	
Gender (male), n (%)	48 (73.8)	150 (75.0)	0.98
Ethnicity (Han), n (%)	52 (80.0)	160 (80.0)	1
Gestational age (weeks), median (IQR)	39 (38.3, 40)	39 (38, 40)	0.69
Birth weight (g), n (%)			0.06
<2,500	6 (9.2)	24 (12.0)	
2,500-3,499	47 (72.3)	117 (58.5)	
3,500-3,999	10 (15.4)	57 (28.5)	
≥4,000	2 (3.1)	2 (1.0)	
Birth region (urban), n (%)	44 (67.7)	141 (70.5)	0.78
Presence of older sibling (yes), n (%)	27 (41.5)	64 (32.0)	0.21
Sibling with similar disease (yes), n (%)	8 (29.6)	14 (21.9)	0.60
Eczema (yes), n (%)	40 (61.5)	144 (72.0)	0.15
0-3 months feeding, n (%)			0.06
Non-artificial feeding	50 (76.9)	127 (63.5)	
Artificial feeding	15 (23.1)	73 (36.5)	
Birth season, n (%)			0.01
Dry season	39 (60.0)	81 (40.5)	
Rainy season	26 (40.0)	119 (59.5)	

RSV = respiratory syncytial virus; IQR = interquantile range

Table 2. Comparison of parental characteristics by RSV status

Parental characteristics	RSV-negative (n = 65)	RSV-positive (n = 200)	*p*-value
Mode of delivery, n (%)			0.04
Vaginal delivery	32 (49.2)	69 (34.5)	
Elective cesarean delivery	22 (33.9)	104 (52.0)	
Emergency cesarean delivery	11 (16.9)	27 (13.5)	
Maternal delivery age (years), median (IQR)	28 (25, 30)	27 (24, 30)	0.42
Maternal history of asthma (yes), n (%)	2 (3.1)	34 (17.0)	0.01
Maternal education level (years), n (%)			0.90
0-6	9 (13.8)	27 (13.5)	
7-12	34 (52.3)	111 (55.5)	
≥13	22 (33.9)	62 (31.0)	
Maternal employment status, n (%)			0.78
Unemployed	39 (60.0)	114 (57.0)	
Employed	26 (40.0)	86 (43.0)	
Paternal history of asthma (yes), n (%)	9 (13.8)	14 (7.0)	0.15
Paternal education level (years), n (%)			0.80
0-6	10 (15.4)	25 (12.5)	
7-12	33 (50.8)	109 (54.5)	
≥ 13	22 (33.8)	66 (33.0)	
Paternal occupation			0.62
Farmer/worker	37 (56.9)	135 (67.5)	
Government officer/businessman	28 (43.1)	62 (31.0)	
Unemployment	0 (0)	3 (1.5)	

and 3 show the association with parental and household characteristics, respectively. Only mode of delivery and maternal history of asthma were significantly associated with RSV-positive bronchiolitis. Higher RSV-positive was detected in elective cesarean deliveries.

Table 4 shows the significant factors in multiple logistic regression. Mode of delivery, age, birth season, maternal history of asthma, and number of cigarettes smoked per day by household members were shown to be significant. Compared to vaginal delivery, the odds of RSV-positive bronchiolitis was significantly higher in elective cesarean delivery (adjusted OR 2.32, 95% CI 1.19-4.52) after adjusting for age, birth season, maternal history of asthma, and number of cigarettes smoked per day. Children younger than six months, born in rainy season, having a maternal history of asthma, and number of cigarettes

Table 3. Comparison of household characteristics by RSV status

Household characteristics	RSV-negative (n = 65)	RSV-positive (n = 200)	*p*-value
A pet in the house (yes), n (%)	16 (24.6)	57 (28.5)	0.65
Number of cigarettes smoked per day, n (%)			0.06
0	18 (27.7)	43 (21.5)	
1-20	43 (66.2)	121 (60.5)	
>20	4 (6.1)	36 (18.0)	
Smoking indoors (yes), n (%)	42 (64.6)	131 (65.5)	0.37
Number of household members sharing child's bedroom, n (%)			0.75
One	14 (21.5)	49 (24.5)	
2 or more	51 (78.5)	151 (75.5)	
Number of household members, n (%)			0.77
<4	18 (27.7)	47 (23.5)	
4	22 (33.8)	75 (37.5)	
>4	25 (38.5)	78 (39.0)	
Annual PCDI ($USD), n (%)			0.413
Low (<3,450)	14 (21.5)	60 (30.0)	
Medium (3,450-7,885)	37 (57.0)	101 (50.5)	
High (>7,885)	14 (21.5)	39 (19.5)	

PCDI = per capita disposable income

Table 4. Multiple logistic regression of predisposing factors with positive RSV in acute bronchiolitis children

Predisposing factors	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value	*p*-value (LR-test)
Mode of delivery					0.02
Vaginal delivery	Reference		Reference		
Elective cesarean delivery	2.19 (1.18, 4.08)	0.01	2.32 (1.19, 4.52)	0.01	
Emergency cesarean delivery	1.14 (0.50, 2.58)	0.76	0.93 (0.39, 2.24)	0.88	
Age (months)					0.06
>12	Reference		Reference		
6-12	1.73 (0.8, 3.77)	0.16	1.71 (0.74, 3.96)	0.20	
<6	2.96 (1.4, 6.25)	0.005	2.64 (1.17, 5.97)	0.02	
Birth season: rainy vs. dry	2.20 (1.25, 3.9)	0.007	2.01 (1.08, 3.72)	0.03	0.03
Maternal history of asthma: yes vs. no	6.45 (1.51, 27.65)	0.01	5.25 (1.19, 23.03)	0.03	0.007
Number of cigarettes smoked per day					0.04
0	Reference		Reference		
1-20	1.18 (0.61, 2.26)	0.62	1.13 (0.56, 2.27)	0.74	
>20	3.77 (1.17, 12.14)	0.03	3.85 (1.13, 13.13)	0.03	

LR = likelihood ratio

smoked more than 20 per day, increased the odds of RSV-positive bronchiolitis. There was no interaction effect among significant factors.

Discussion

Children were more susceptible to be RSV-positive bronchiolitis if they were born by elective cesarean delivery or in the rainy season, were aged younger than six months, had a mother with history of asthma, or lived in a household in which members smoked more than 20 cigarettes per day. More than two-fold risk of RSV-positive bronchiolitis in children born by elective cesarean delivery is alarming, since the trend of elective cesarean has been increasing worldwide and RSV infection is related to reactive airway diseases[1,14-16].

There were two previous studies[10,11] in which one of them was a population-based study with large sample size; however, the RSV status was not reported and concluded that elective cesarean section increased the hospitalization of children with bronchiolitis[10]. Another study shown that the incidence of severe bronchiolitis was higher in children with RSV-positive bronchiolitis or delivered by cesarean section[11]. The RSV-positive status was significantly associated with the children who born by elective cesarean delivery, not by emergency cesarean delivery, compared to vaginal delivery. An explicit explanation for this is still unknown. However, both vaginal and emergency cesarean deliveries involve the process of uterine contraction, which can squeeze fetal lung fluid and activate the maternal and neonatal immune systems by production of some cytokines[20-23]. Previous studies also showed that fetal lung fluid retention increased the risk of neonatal transient tachypnea, which may be associated with childhood wheezing[24,25]. In addition, the production of interleukin (IL)-6 and IL-10 helps to prevent the susceptibility of RSV infection, which is impaired in elective cesarean delivery[21,23].

Age, birth season, and maternal history of asthma were associated with RSV-positive bronchiolitis, which is consistent with previous studies[10,11,26,27]. Nevertheless, the definitions of these factors were slightly different. Birth season was variously classified in the studies of bronchiolitis[10,28]. Likewise, the relationship of maternal asthma was explained by a familial predisposition[26]. A systematic review found that passive smoking was a risk factor for bronchiolitis but it could not present the exposure-response relationship[29]. In the present study, number of cigarettes smoked by household members exceeding 20 per day, not passive smoking, was significant, which shows the effect of number of cigarettes over passive smoking and reassures the exposure-response relationship.

There have been previous studies on risk factors for RSV respiratory infection, not bronchiolitis in particular, and on risk factors for severity of RSV bronchiolitis, but not comparing RSV-positive and RSV-negative bronchiolitis[17,30]. As a result, this was the first study to assess the association between mode of delivery and RSV-positive bronchiolitis. There were a few limitations in the present study. First, only single RSV detection was used, thus the effect of multiple infections cannot be tested. However, RSV has been confirmed as the most common and aggressive viral cause of bronchiolitis[16]. Second, the sample size was calculated based on the proportion of elective cesarean sections as the hypothetically main predisposing factor, not for other factors, thus non-significance of some factors might be due to insufficient sample size to test other hypotheses. Third, recall bias of predisposing factors could have influenced the results in our case-control study but the factors in this present study were the informative events so this bias should be minimal.

In conclusion, mode of delivery, age of children, birth season, maternal asthma, and family smoking were associated with RSV-positive bronchiolitis. Children born by elective cesarean delivery and living in heavy household smoking attributed to RSV-positive bronchiolitis can be prevented. The awareness of the rising rate of elective cesarean delivery, especially the indication of maternal request and smoking in house with infants is crucial. A prospective cohort study with a larger sample size and the study to identify strategies to reduce elective cesarean delivery and heavy smoking in house are needed.

What is already known on this topic?

The trend of cesarean section, especially due to maternal request, has been increasing globally. Comparing to vaginal delivery, cesarean delivery increased the risk of children's asthma and severe acute bronchiolitis. Likewise, respiratory syncytial virus (RSV) is the most important etiology of bronchiolitis, which increases the risk of subsequent recurrent wheezing and asthma. The effect of mode of delivery on RSV status in bronchiolitis children is inconclusive.

What this study adds?

This study demonstrated that children aged less than six months, born in rainy season, having a maternal history of asthma, living in heavy smoking, and delivered by elective cesarean section are predisposing factors of RSV-positive bronchiolitis.

Potential conflicts of interest

None.

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การผ่าตัดคลอดทางหน้าท้องแบบเลือกผ่าตัดเป็นปัจจัยเสี่ยงของการพบเชื้อไวรัสอาร์เอสวีในเด็กที่เป็นโรคหลอดลมอักเสบเฉียบพลัน

เสี่ยวลี่ ช้าง, ทิพวรรณ เลียบสื่อตระกูล, ภาสุรี แสงศุภวนิช, เสี่ยวหลิง เซีย, ผิง เหอ, ฮง ฉาว

วัตถุประสงค์: เพื่อประเมินผลของการผ่าตัดคลอดทางหน้าท้องและปัจจัยที่เกี่ยวข้องอื่น ๆ กับการตรวจพบเชื้อไวรัสอาร์เอสวีใน เด็กที่เป็นโรคหลอดลมอักเสบเฉียบพลัน

วัสดุและวิธีการ: การศึกษาแบบควบคุมเปรียบเทียบระหว่างเด็กที่ตรวจพบเชื้อไวรัสอาร์เอสวีเป็นบวกกับเด็กที่มีผลตรวจเป็นลบ ในโรงพยาบาลระดับตติยภูมิ 3 โรงพยาบาล ในเมืองคุนหมิง ประเทศจีน ในช่วงเดือนกันยายน พ.ศ. 2555 ถึง เดือนกรกฎาคม พ.ศ. 2556 โดยศึกษาในเด็กที่มีอาการหายใจหอบครั้งแรกและวินิจฉัยว่าเป็นโรคหลอดลมอักเสบเฉียบพลัน และมีการตรวจหาเชื้อ ไวรัสอาร์เอสวี การตรวจเชื้อไวรัสอาร์เอสวีใช้วิธีปฏิกิริยาลูกโซ่พอลิเมอเรสแบบย้อนกลับ วิธีการคลอดและปัจจัยอื่น ๆ ของเด็ก บิดา และมารดา และครอบครัวได้จากการสัมภาษณ์ผู้ปกครองของเด็ก นำมาวิเคราะห์โดยใช้การถดถอยโลจิสติกหลายตัวแปร

ผลการศึกษา: จากเด็กจำนวน 265 ราย ที่เป็นโรคหลอดลมอักเสบเฉียบพลัน พบเชื้อไวรัสอาร์เอสวีจำนวน 200 ราย คิดเป็น ร้อยละ 75.5 โดยส่วนใหญ่ร้อยละ 83.3 มีอายุต่ำกว่า 12 เดือน เมื่อเปรียบเทียบกับเด็กที่คลอดเองทางช่องคลอด เด็กที่คลอดโดย การผ่าตัดคลอดทางหน้าคลอดแบบเลือกผ่าตัดมีโอกาสพบเชื้อไวรัสเพิ่มขึ้นสองเท่า (adjusted odds ratio เท่ากับ 2.32 และช่วง ความเชื่อมั่นร้อยละ 95 เท่ากับ 1.19-4.52) เด็กที่อายุต่ำกว่า 6 เดือน เกิดในฤดูฝน มารดามีประวัติโรคหอบหืด และมีคนในครอบครัว สูบบุหรี่มากกว่า 20 มวนต่อวัน มีโอกาสการตรวจพบไวรัสมาก

สรุป: เด็กที่เป็นโรคหลอดลมอักเสบเฉียบพลันที่เกิดโดยการผ่าตัดคลอดทางหน้าท้องแบบเลือกผ่าตัดมีความเสี่ยงพบไวรัสอาร์เอสวี มากขึ้นหลังจากปรับปัจจัยที่เกี่ยวข้องอื่น ๆ ได้แก่ อายุ ฤดูกาลที่เด็กเกิด มารดาเป็นโรคหอบหืด และคนในครอบครัวสูบบุหรี่