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Original Article

Early life primary prevention against infant bronchial asthma: a 3-year follow-up

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Abstract: Objective: To investigate effects of early life prevention on the incidence of infant bronchial asthma and the related risk factors for infant bronchial asthma. Methods: The present study enrolled 502 infants who were born in our hospital during January 2014 to July 2015. All cases were randomly divided into the prevention group and the control group. Additionally, 132 infants (<1 year) who were diagnosed with bronchial asthma were included as a positive control. A combination of rational strategy included antenatal education, nutrition supplement, smoke avoidancd, control of delivery mode and feeding were performed for the prevention group. No prevention methods were used for the control. Basic characteristics for both groups of mothers and infants were collected and the risk factors for bronchial asthma were analyzed. Results: The vaginal delivery rate was remarkably higher in the prevention group. The prevention group had significantly higher rate of the folic acid and vitamin D intake for mothers and vitamin D intake for infants, higher rates of being breast-feeding ≥6 months, intake of Vitamin D and the rate for complementary feeding after 6 months, as well as significantly lower rates of the smoke exposure and the rate of having flowers or pets. Meanwhile, the prevention group had significantly lower rates of wheezing, eczema and respiratory tract infection during the follow-up period. The bronchial asthma rate in the prevention group was 3.98% (1/251), remarkably lower than the rate of 19.92% (5/251) in the control group. Allergy history, smoke condition, nutrition conditions and delivery mode for mothers, and allergic constitution, breast-feeding, vitamin D, and respiratory tract infection for the infants were independent risk factors for bronchial asthma. Conclusion: The prevention strategy significantly reduced the bronchial asthma incidence rate. Allergy history, smoke condition, nutrition conditions and delivery mode for mothers, as well as allergic constitution, breast-feeding, vitamin D, and respiratory tract infection for the infants were risk factors for bronchial asthma incidence.

Keywords: Early life primary prevention, infant bronchial asthma, risk factors

Introduction

Asthma is one of the most common chronic respiratory diseases in children who are less than 6 years old [1, 2]. For infants less than 3 years old, it is reported that 25%-30% infants have at least one wheezing attack, of whom 40% may have recurrent wheezing when they are 3 years old, and the rates may enhance to 50% when they are 6 years old [3, 4]. Among the infants with wheezing attacks, almost 40% of cases may develop to asthma [5]. The incidence rate for infant asthma is considered to be rising from 1980s [6, 7].

Many risk factors are reported to be associated with infant bronchial asthma, such as smoking, air pollution and hereditary factors [8-10]. Prevention factors are also reported, including breast-feeding, complementary foods, etc [11, 12]. Although there are already several research studies for epidemic and treatment studies on infant bronchial asthma, research on prevention methods are still inadequate. In this study, we aimed to investigate effects of early life primary prevention on incidence of infant bronchial asthma and the related risk factors for infant bronchial asthma. This study may give a new direction for asthma prevention.

Methods and materials

Patients

The present study enrolled 502 infants who were born in our hospital during January 2014 to July 2015. For all included infants, their parents were informed and they agreed to partici-

pate, and all the mothers were enrolled during gestational age 12-16 weeks. All pregnant mothers were within 22-35 years, with no severe diseases such as severe diabetes, pre-eclampsia, hypothyroidism or severe renal, liver or cardiovascular diseases. Mothers who refused to participate, failed to deliver, didn't meet the inclusion criteria or were lost to follow-up were excluded. All cases were randomly divided into two groups by a computer-generated list with 251 cases in each group, 1) the prevention group, 2) the control group.

Additionally, 132 infants (<1 year) who were diagnosed with bronchial asthma during January 2014 to July 2015 in our hospital were included as a positive control group. All the patients were consecutively enrolled during the study period. The diagnosis for infant bronchial asthma was according to the guidelines for diagnosis and treatment of bronchial asthma in children by the Respiratory Group, Society of Pediatrics, Chinese Medical Association [13]. The diagnosis of infant bronchial asthma was as follows: 1) infants (1-3 years) with wheezing attack >3 times; 2) during wheezing the attack, both lungs could be heard with scattered or diffuse wheezing, wheezing occurred mainly in the expiratory phase, and the expiratory phase was prolonged; 3) infants with allergic constitution, such as allergic eczema, allergic rhinitis; 4) parents with history of asthma or other allergies; 5) other diseases inducing wheezing were excluded, such as bronchiolitis, asthmatic bronchitis, asthmatic bronchopneumonia. Infants with characteristics listed above 1), 2) and 5) could be diagnosed with bronchial asthma. If wheezing occurred two times, and the infants had the characteristics of 3) and 4), the infants could be given diagnostic treatment. Written informed consent was obtained from all the parents. The present study was approved by ethic committee of Wuxi Children's Hospital.

Prevention methods

The prevention group (n=251) was given early life primary prevention. The prevention strategy included intervention on the parents' part and infants' part. For the parents, health education was given for several months during the pregnancy, mainly educating the parents to 1) avoid environmental exposure factors including active and passive smoking, exposure to allergens if the mother had allergic constitution; 2) have a reasonable diet and avoid high sugar, high protein, high fat, high calcium diet. All mothers in the prevention group were treated with folic acid 600 IU/D every day for 3 months after admission and were treated with vitamin D 600 IU/D every day after admission. All mothers in the prevention group were suggested to choose vaginal delivery if possible. For the infants, all infants received breast-feeding for at least 6 months if possible and the infants all received vitamin D 400 IU/D every day from 2 weeks after birth for 6 months and all infants were asked for complementary feeding after 6 months. For the control group (n=251), none of the above methods were used.

For both groups, all parents were followed-up every month and the infants were followed-up every two months after being born. The follow-up lasted for 3 years by the outpatient department, follow-up visit or by telephone.

Data collection

Basic characteristics for both mothers and infants were collected, including age, BMI, history of allergy, smoke condition (active or passive), nutrition condition (folic acid and vitamin D), allergen condition (having flowers and pets or not), as well as delivery mode, birth weight, premature birth and asphyxia at birth, mechanical ventilation, pathological jaundice, infection condition, allergic constitution, feeding mode, smoke condition after birth, supplementation of nutrients (vitamin D, calcium).

Statistical analysis

Data was expressed as mean ± SD. For continuous data, the Student's *t*-test was used for Comparison between two groups. Chi square test was used to compare the rates. For logistic analysis, univariate analysis was performed using χ^2 test and Student's *t*-test and logistic regression was performed by stepwise method. $P<0.05$ was considered as significantly different. All calculations were made using SPSS 20.0.

Results

Basic characteristics for all mothers at admission and infants at birth

The present study included a total of 502 mothers and their infants. As shown in **Table 1**, among the prevention group, the mean age was 28.56±4.09, with 87 cases who had aller-

Table 1. Basic characteristics for all mothers upon admission

Variables	Prevention group, n=251	Control group, n=251	*P* value
Age, year	28.56±4.09	28.80±3.87	0.502
BMI, kg/m^2	23.28±3.22	23.70±3.10	0.138
Gestational age when admission, week	14.05±1.36	14.05±1.36	0.974
Allergy history, n (%)	57 (22.70)	52 (20.72)	0.737
Smoke condition, n (%)			0.898
Smoker	2 (0.80)	3 (1.20)	
Passive (family or at work)	121 (48.21)	127 (50.60)	
None	128 (50.99)	121 (48.21)	
Nutrition, n (%)			0.651
Folic acid	132 (51.59)	141 (56.18)	
Vitamin D	122 (48.61)	117 (46.61)	
Havinf flowers or pets, n (%)	57 (22.71)	62 (24.70)	0.869

Table 2. Basic characteristics for all infants at birth

Variables	Prevention group, n=251	Control group, n=251	*P* value
Gestational age, week	38.88±2.11	38.63±2.06	0.172
Gender, female (%)			
Birth weight, g	3152.70±450.78	3186.34±488.02	0.423
Delivery mode, n (%)			0.028
Vaginal delivery	151 (60.16)	112 (44.62)	
Caesarean birth	100 (39.84)	139 (55.38)	
Premature birth, n (%)	10 (3.98)	20 (7.97)	0.642
Asphyxia, n (%)	7 (2.79)	9 (3.59)	0.748
Mechanical ventilation, n (%)	3 (1.20)	2 (0.80)	0.776

gy history and 130 cases who were exposed to a smoking environment, while in the control group, the mean age was 28.80±3.87, with 82 cases who had allergy history and 122 cases who were exposed to a smoking environment. No significant difference was found between the two groups for all characteristics upon admission.

For infant characteristics, no significant difference was found in gender, gestational age, birth weight, asphyxia and mechanical ventilation rate (**Table 2**). The vaginal delivery rate was remarkably higher in the prevention group (P<0.05). Meanwhile, the prevention group showed lower rates of premature birth, however the difference was not statistically significant.

Effects of early life primary prevention on incidence of wheezing and bronchial asthma

Characteristics for mothers and infants during the whole 3-years study period were analyzed. As shown in **Table 3**, the smoke exposure rate for the mothers in the prevention group was significantly lower than the control group (P<0.05), while no significant difference was found for the infection rate. Meanwhile, the folic acid and vitamin D intake was remarkably higher, while the rate of having flowers or pets was significantly lower in the prevention group (P<0.05). For the infants, the prevention group had a significantly higher rate of breast-feeding ≥6 months and remarkably higher intake of Vitamin D (P<0.05). Additionally, the rate for complementary feeding after 6 months was also remarkably higher in the prevention group (P<0.05). All the above results suggested that the early life primary prevention affected the infants' nutrition and life condition.

For the incidence of wheezing, bronchial asthma and related diseases, the prevention group had significantly lower rates of wheezing, eczema and respiratory tract infection during the follow-up period (P<0.05, **Table 4**). The bronchial asthma rate in the prevention group was 3.985 (1/251), remarkably lower than the rate of 19.92% (5/251) in the control group (P<0.05), indicating that the early life primary prevention reduced the bronchial asthma incidence.

Risk factors for bronchial asthma

At last, we included 132 infants (<1 year) who were diagnosed with bronchial asthma during the study period and we did the same data col-

Table 3. Characteristics for mothers and infants during the study period (after admission)

Variables	Prevention group, n=251	Control group, n=251	*P* value
Mothers			
Infection during pregnancy, n (%)	69 (27.49)	73 (29.08)	0.803
Delivery mode, n (%)			
Vaginal delivery	151 (60.16)	112 (44.62)	0.028
Caesarean birth	100 (39.84)	139 (55.38)	
Smoke condition, n (%)			0.004
Smoker	1 (0.40)	2 (0.80)	
Passive (family or at work)	54 (21.51)	109 (43.43)	
None	196 (78.09)	140 (55.78)	
Folic acid, n (%)			<0.001
600 IU/D for 3 months or more	103 (41.04)	61 (24.30)	
<600 IU/D	128 (51.00)	89 (35.46)	
None	20 (7.87)	101 (40.24)	
Vitamin D, n (%)			<0.001
600 IU/D for 3 months or more	101 (40.24)	56 (22.31)	
<600 IU/D	122 (48.61)	81 (32.27)	
None	28 (11.16)	114 (45.42)	
Having flowers or pets, n (%)	29 (11.55)	58 (23.11)	0.031
Infants			
Premature birth, n (%)	10 (3.98)	20 (7.97)	0.373
Allergic constitution, n (%)	40 (15.94)	49 (19.52)	0.507
Breast-feeding, n (%)			0.002
≥6 months	176 (70.12)	122 (48.61)	
Vitamin D, n (%)			<0.001
400 IU/D for 6 months	117 (46.61)	81 (32.27)	
<400 IU/D	104 (41.43)	66 (26.29)	
None	30 (11.95)	104 (41.43)	
Complementary feeding after 6 months, n (%)	239 (95.22)	202 (80.48)	0.001

Table 4. Incidence of wheezing, bronchial asthma and related diseases

Variables	Prevention group, n=251	Control group, n=251	*P* value
Wheezing, n (%)			0.024
≥3 times	4 (1.59)	11 (4.38)	
<3 times	13 (5.18)	39 (15.54)	
None	234 (93.23)	201 (80.08)	
Eczema, n (%)	11 (4.38)	32 (12.75)	0.034
Respiratory tract infection, n (%)			0.014
≥3 times	9 (3.59)	26 (10.36)	
<3 times	31 (12.35)	58 (23.02)	
None	211 (84.06)	167 (66.53)	
Bronchial asthma, n (%)	1 (3.98)	5 (19.92)	0.001

lection and following with them. The data of the 132 bronchial asthma infants along with the above 502 cases were all arranged together to analyze the risk factors for bronchial asthma. As shown in **Table 5**, a significant difference was found in allergy history, smoke condition, nutrition conditions and delivery mode for mothers, and in allergic constitution, breast-feeding, vitamin D, and respiratory tract infection for the infants. Further logical regression showed all the above factors were independent risk factors for bronchial asthma (**Table 6**).

Discussion

Despite the development for treatment and molecular mechanisms of infant bronchial asthma, the risk factors of infant bronchial

Table 5. Risk factors for bronchial asthma

Variables	Health, n=496	Bronchial asthma, n=138	*P* value
Mothers			
Age, year	28.67±3.98	28.57±3.85	0.794
BMI, kg/m^2	23.48±3.16	23.66±3.14	0.562
Allergy history, n (%)	107 (21.57)	69 (50.00)	<0.001
Infection during pregnancy, n (%)	141 (28.43)	43 (31.16)	0.673
Delivery mode, n (%)			0.141
Vaginal delivery	260 (52.41)	58 (42.03)	
Caesarean birth	236 (47.58)	80 (57.97)	
Smoke condition, n (%)			0.005
Smoker	0 (0.00)	1 (0.72)	
Passive (family or at work)	159 (32.06)	74 (53.62)	
None	337 (67.94)	63 (45.65)	
No folic acid, n (%)	121 (24.40)	59 (42.75)	0.025
No vitamin D, n (%)	138 (27.82)	65 (47.10)	0.005
Having flowers or pets, n (%)	85 (17.14)	36 (26.09)	0.124
Infants			
Gestational age, week	38.80±2.05	38.75±1.77	0.808
Birth weight, g	3175.29±465.45	3191.38±516.96	0.726
Gender, female (%)	245 (49.40)	68 (49.28)	0.874
Premature birth, n (%)	26 (5.24)	7 (5.07)	0.957
Allergic constitution, n (%)	84 (16.94)	62 (44.93)	<0.001
Breast-feeding, n (%)			0.005
≥6 months	296 (59.68)	55 (39.86)	
No Vitamin D, n (%)	131 (26.41)	58 (42.03)	0.020
Complementary feeding after 6 months, n (%)	440 (88.71)	119 (86.23)	0.596
Respiratory tract infection, n (%)	120 (24.19)	53 (38.41)	0.030

Table 6. Logical regression for risk factors of bronchial asthma

	Wald	Odds ratio	95% CI	*P* value
Mothers				
Allergy history	40.732	1.291	3.636 (2.446~5.404)	<0.001
Delivery mode	4.629	0.418	1.520 (1.038~2.225)	0.031
Smoke condition	22.271	0.926	2.532 (1.718~3.706)	<0.001
No folic acid	17.374	0.839	2.315 (1.560~3.434)	<0.001
No vitamin D	17.916	0.837	2.310 (1.568~3.404)	<0.001
Infants				
Allergic constitution	44.079	1.387	4.001 (2.657~6.025)	<0.001
Breast-feeding	16.724	0.804	2.233 (1.520~3.283)	<0.001
No vitamin D	12.324	0.703	2.020 (1.364~2.991)	<0.001
Respiratory tract infection	10.776	0.670	1.954 (1.310~2.914)	0.001

asthma are still controversial and prevention methods for infant bronchial asthma is still lacking [14, 15]. In the present research, we have performed a 3-year follow-up study to see whether early life primary prevention could prevent infants from having bronchial asthma. We found that by rational prevention strategy, the bronchial asthma incidence rate could be significantly reduced. We also demonstrated that allergy history, smoke condition, nutrition conditions and delivery mode for mothers, and allergic constitution, breast-feeding, vitamin D, and respiratory tract infection for the infants were risk factors for bronchial asthma incidence.

There are several studies focusing on risk factors for infant bronchial asthma. In a popula-

tion-based birth cohort study between 1995 and 2003, Wu et al found that maternal urinary tract infections, c-section delivery, maternal antibiotic use and infant antibiotic use might increase the incidence of asthma [16]. In another case-controlled study, the authors demonstrated that antigen sensitivity, positive Asthma Predictive Index and exposure to environmental smoke were independent risk factors for infant recurrent wheezing [8]. In recent research by Nascimento et al, it was found cesarean section, exposure to tobacco for the infants, as well as high pregestational BMI and high soft drink consumption for the mothers were associated with the incidence of asthma [17]. In the present research, we also found that allergy history, allergic constitution and smoke condition were risk factors for bronchial asthma. We also observed that the nutrition intake and delivery mode, as well as breast-feeding might be associated with bronchial asthma, which might need more studies and data to confirm.

Prevention and treatment for infant bronchial asthma were also reported in much research. Nwaru et al demonstrated that low breast-feeding time was associated with an increased risk of nonatopic asthma, while the introduction of complementary feeding was associated with lower asthma rate [11]. Cabana et al used early probiotic supplementation as the method for prevention of asthma however found early probiotic supplementation in the first 6 months of life did not show preventive effects on asthma [18]. In an early study, it was found that inhaled fluticasone propionate 100 mug did not influence the incidence of current wheezing and physician-diagnosed asthma [19]. In a recent study, it was observed that the intake of vitamin D might reduce the asthma incidence rate [20]. In our study, we used a combination and rational strategy including antenatal education, nutrition supplement, smoke avoidance, control of delivery mode etc. to prevent the infant bronchial asthma and successfully reduced the incidence rate.

However, the present research still has some limitations. First, the study population is still small, since the incidence of infant asthma is around 1.5% in most cities in China. Secondly, this is a single center research, with all Chinese cases. All these need further research to provide a better understanding.

Conclusion

In conclusion, we used rational early life prevention to successfully reduce the incidence of infant bronchial asthma. We also found that allergy history, smoke condition, nutrition conditions and delivery mode for mothers, and allergic constitution, breast-feeding, vitamin D, and respiratory tract infection for the infants were risk factors for infant bronchial asthma. This study might give more clinical evidence for the risk factors of infant bronchial asthma and might provide a new direction for asthma prevention.

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Disclosure of conflict of interest

None.

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