

Relationship between mode of delivery in childbirth and prevalence of allergic diseases in Korean children

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Purpose: We tested the hypothesis that cesarean section might increase the risk for allergic diseases compared to vaginal delivery, by depriving the newborn of exposure to maternal microflora. **Methods:** We evaluated the prevalence of allergic diseases, allergic inflammation, and allergic sensitization according to mode of delivery for 279 Korean children aged ≤ 16 years. Data were extracted from medical records and a questionnaire filled out by parents. Logistic regression was used to determine the association between cesarean section and the outcomes of interest. **Results:** Of the 279 children, 179 (62.6%) were delivered vaginally and 100 (37.4%) by cesarean section. There were no differences in the prevalence of allergic diseases, allergic inflammation, or allergic sensitization according to mode of delivery. Children born by cesarean section had no higher risk of allergic disease than those delivered vaginally, regardless of a parental history for allergic disease. Adjusted odds ratios (95% confidence intervals) for cesarean section compared to vaginal delivery were not statistically significant for any outcome considered: asthma, 0.76 (0.37-1.57), allergic rhinitis, 1.14 (0.61-2.10), atopic dermatitis, 1.01 (0.59-1.71). **Conclusions:** Delivery by cesarean section may not be associated with the subsequent development of asthma, allergic rhinitis, or atopic dermatitis in Korean children.

Key Words: Hypersensitivity; cesarean section; obstetric delivery, child

INTRODUCTION

The prevalence of allergic diseases is increasing due to rapid industrialization, changes in lifestyle, air pollution, and the occurrence of new allergens. The 2002-2003 phase 3 study performed by the International Study of Asthma and Allergies in Childhood (ISAAC) reported that the prevalence of bronchial asthma, allergic rhinitis, and atopic dermatitis tended to increase in most institutions compared to data from 5 years earlier (provided in a report by the ISAAC phase 1 study).¹ The relationship between the prevalence of allergic diseases and mode of delivery in childbirth has been actively investigated as the proportion of cesarean sections has increased.² In the United States, the frequency of cesarean sections increased from 23.0% in 1990 to 28.0% in 2003 and to 31.1% in 2006.^{3,4} According to the Korean Health Insurance Review and Assessment Service, the rate of cesarean sections continuously increased from 13.3% in 1990 to 40.5% in 2001, but decreased to 36.0% in 2006, although this rate was considerably higher than that proposed by the World Health Organization (WHO, 5-15%). Cesarean section babies have a different gut flora, which has been suggested to prolong immunological immaturity and thereby increase the

risk for the development of allergic disease.⁵⁻⁷ The hygiene hypothesis states that decreased exposure to microorganisms early in life leads to insufficient stimulation of Th1 lymphocytes and, therefore, a predominance of the Th2 allergic response.⁸ However, the association between mode of delivery and the prevalence of allergic diseases has not been completely elucidated. Some investigators have reported increased risk for developing asthma among children born by cesarean section compared to those born by vaginal delivery,⁹⁻¹² whereas others have found no such relationship.¹³⁻¹⁵ Although the relationship between mode of delivery and the prevalence of allergic diseases has been investigated continuously in many countries, there has been no report on this relationship in Korea. Therefore, we investigated the effects of mode of delivery on the prevalence of allergic diseases in Korean children.

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MATERIALS AND METHODS

Study subjects

A total of 279 children aged ≤ 16 years who visited Severance Children's Hospital, Yonsei University College of Medicine between January and December 2008.

Methods

The following data were identified through a questionnaire: gender, age, mode of delivery, gestational age, birth weight, history of admission to neonatal intensive care unit (NICU), duration of breast feeding, maternal age at delivery, exposure to household pets or smoking, and physician-diagnosed allergic diseases in children and their parents. Data on the diagnosis of allergic diseases, allergic inflammation, and allergic sensitization were collected from medical records and analyzed retrospectively. We evaluated the relationship between mode of delivery and prevalence of three common childhood allergic diseases: asthma, allergic rhinitis, and atopic dermatitis.

Definition of allergic disease

Bronchial asthma was defined as recurrent wheezing or coughing episodes in the absence of the common cold in the preceding 12 months. In addition, a physician's diagnosis of bronchial hyperresponsiveness upon methacholine challenge ($PC_{20} \leq 16$ mg/mL) and at least a 12% reversibility of forced expiratory volume in 1 second (FEV1) after inhaling a β_2 agonist, as per the American Thoracic Society (ATS) criteria,¹⁶ were required. A diagnosis of allergic rhinitis was made according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,¹⁷ and a diagnosis of atopic dermatitis was made based on the diagnostic criteria proposed by Hanifin and Rajka in 1980.¹⁸

Measurement of blood eosinophils, serum total IgE, and serum specific IgE levels

Serum specific IgE against *Dermatophagoides farinae* (Df) and *Dermatophagoides pteronyssinus* (Dp) and serum total IgE were measured using the CAP radioallergosorbent technique (UniCAP; Phadia, Uppsala, Sweden). The NE-8000 system (Sysmex, Kobe, Japan) was used to count eosinophils automatically in peripheral blood. Allergic sensitization was identified in 177 (63.4%) of the 279 subjects.

Skin-prick tests

Skin-prick tests, using 65 inhalant and food allergens, were performed on 41 subjects who had not taken antihistamines before the test. Normal saline was used as a negative control, and a 0.1% histamine solution was used as a positive control. Test results were considered positive if the following criteria were met: (1) there was no erythema or wheal in response to the negative control and (2) the allergen/histamine wheal size ratio was ≥ 1 or (3) the wheal measured ≥ 3 mm. Atopy was de-

defined as a positive reaction to one or more allergens, a specific IgE level of ≥ 0.35 kU/L, or a serum total IgE level of ≥ 100 kU/L.

Statistical analysis

The clinical characteristics between the cesarean and vaginal delivery groups were compared using the Student's *t*-test, the Chi-square test, and the Fisher's exact test. The effects of confounding variables were removed by logistic regression analysis. Statistical analyses were performed using SPSS version 13.0 (SPSS Inc, Chicago, IL, USA). A *P* value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of the study subjects

Of the 279 subjects, 179 (62.6%) were born by vaginal delivery, and 100 (37.4%) were born by cesarean section. The mean (\pm SD) age of the subjects was 4.6 (± 3.8) years. Atopy was assessed in 197 subjects (70.6%). There were no significant differences between the two groups for gender, gestational age, birth weight, season of birth, maternal age at birth, the number of family members, birth order, duration of breast feeding, admission to NICU, exposure to household pets or smoking, and a parental history of allergic diseases. Furthermore, there were no significant differences in blood eosinophil counts or serum total IgE levels between the two groups (Table 1).

Prevalence of allergic diseases

The prevalence of bronchial asthma, allergic rhinitis, and atopic dermatitis did not differ significantly between the two groups, nor did sensitization to Dp or Df (Table 2). There were also no significant differences in the odds ratios for the prevalence of allergic diseases, sensitization to Dp or Df, or after adjusting for confounding variables including age, gender, gestational age, birth weight, duration of breast feeding, and a parental history of allergic diseases (Table 3).

Prevalence of allergic diseases according to parental history of allergic disease

The subjects were divided into three subgroups: those with both parents, one parent, and no parent with a history of allergic disease. The prevalence of allergic diseases according to mode of delivery was not significantly different among the three subgroups. In addition, there were no significant differences among the odds ratios of each group after adjusting for confounding variables including age, gender, gestational age, birth weight, and breast feeding (Table 4).

DISCUSSION

Mode of delivery in childbirth has been implicated in the development of allergic disorders during childhood.¹⁹ According

Table 1. Characteristics of study subjects (n=279) by the mode of delivery

Variables	Total number No. (%)	Vaginal delivery No. (%)	Cesarean section No. (%)	P value
All	279 (100.0)	179 (62.6)	100 (37.4)	
Sex of child				
Male	180 (64.5)	112 (62.6)	68 (68.0)	0.3633
Female	99 (35.5)	67 (37.4)	32 (32.0)	
Gestational age (weeks)				
<37	17 (6.1)	7 (3.9)	10 (10.0)	0.0986*
37-42	256 (91.8)	167 (93.3)	89 (89.0)	
>42	6 (2.2)	5 (2.8)	1 (1.0)	
Birth weight (g)				
<2,500	9 (3.2)	4 (2.2)	5 (5.0)	0.2037*
2,500-4,000	259 (92.8)	170 (95.0)	89 (89.0)	
>4,000	11 (3.9)	5 (2.8)	6 (6.0)	
Maternal age at birth				
<25	5 (1.8)	4 (2.2)	1 (1.0)	0.1624*
25-30	88 (31.5)	62 (34.6)	26 (26.0)	
30-35	138 (49.5)	88 (49.2)	50 (50.0)	
>35	48 (17.0)	25 (14.0)	23 (23.0)	
Number of family members				
2	3 (1.1)	2 (1.1)	1 (1.0)	0.5530*
3	111 (39.8)	68 (38.0)	43 (43.0)	
4	111 (39.8)	73 (40.8)	38 (38.0)	
5	45 (16.1)	28 (15.6)	17 (17.0)	
>5	9 (3.2)	8 (4.5)	1 (1.0)	
Birth order				
1	194 (69.5)	122 (68.2)	72 (72.0)	0.2799*
2	78 (28.0)	54 (30.2)	24 (24.0)	
3	7 (2.5)	3 (1.7)	4 (4.0)	
Duration of breast feeding (months)				
never	60 (21.5)	31 (17.3)	29 (29.0)	0.0710*
≤6	132 (47.3)	91 (50.8)	41 (41.0)	
>6	87 (31.2)	57 (31.8)	30 (30.0)	
NICU admission	44 (15.8)	28 (15.7)	16 (16.0)	0.9529
Environmental tobacco smoke exposure	128 (45.9)	82 (45.8)	46 (46.0)	0.7758
Household pet	13 (4.7)	9 (5.0)	4 (4.0)	0.7762*
Maternal history of allergy	62 (22.2)	35 (19.6)	27 (27.0)	0.1514
Paternal history of allergy	83 (29.8)	56 (31.3)	27 (27.0)	0.4528
Both parental history of allergy	26 (9.3)	17 (9.5)	9 (9.0)	0.8910
Season of birth				
Spring	73 (26.2)	51 (28.5)	22 (22.0)	0.4308
Summer	78 (28.0)	46 (25.7)	32 (32.0)	
Fall	60 (21.5)	36 (20.1)	24 (24.0)	
Winter	68 (24.4)	46 (25.7)	22 (22.0)	
Eosinophil count (/ μ L) [†]	370.00 (250.00-600.00)	370.00 (190.00-610.00)	380.00 (235.00-577.50)	0.5835
Serum total IgE (U/mL) [†]	183.00 (45.80-478.50)	216.00 (47.60-530.00)	154.00 (36.30-394.00)	0.1643

*Fisher's exact test.

[†]Median (interquartile range).

Table 2. Prevalence of allergic diseases and allergic sensitization according to the mode of delivery

Variables		Vaginal delivery (n=179)	Cesarean section (n=100)	P value*
Physician-diagnosed allergic diseases				
Asthma	Yes	30 (16.8)	14 (14.0)	0.5442
	No	149 (83.2)	86 (86.0)	
Allergic rhinitis	Yes	50 (27.9)	30 (30.0)	0.7143
	No	129 (72.1)	70 (70.0)	
Atopic dermatitis	Yes	64 (35.8)	35 (35.0)	0.8995
	No	115 (64.3)	65 (65.0)	
Allergic sensitization against				
Dp	Positive	63 (50.4)	29 (40.3)	0.1703
	Negative	62 (49.6)	43 (59.7)	
Df	Positive	70 (56.0)	30 (41.7)	0.0526
	Negative	55 (44.0)	42 (58.3)	

*Chi-square test.

Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.**Table 3.** Proportion of children with outcome variable according to the mode of delivery

	Vaginal delivery (n=179)	Cesarean section (n=100)	Crude OR [95% CI]	P value	Adjusted OR* [95% CI]	P value
Physician-diagnosed allergic diseases						
Asthma	30/179 (16.8)	14/100 (14.0)	0.81 [0.41,1.61]	0.5447	0.76 [0.37,1.57]	0.4596
Allergic rhinitis	50/179 (27.9)	30/100 (30.0)	1.11 [0.65,1.89]	0.7143	1.14 [0.61,2.10]	0.6873
Atopic dermatitis	64/179 (35.8)	35/100 (35.0)	0.97 [0.58,1.62]	0.8997	1.01 [0.59,1.71]	0.9818
Allergic sensitization against						
Dp	63/125 (50.4)	29/72 (40.3)	0.66 [0.37,1.19]	0.1712	0.62 [0.30,1.27]	0.1918
Df	70/125 (56.0)	30/72 (41.7)	0.56 [0.31,1.01]	0.0537	0.48 [0.23,1.01]	0.0501

*Adjusted for gender, age, gestational age, birth weight, breast feeding, and parental allergy.

Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.**Table 4.** Associations between the mode of delivery and allergic diseases according to parental allergic diseases

	Total population (n=279)		Non-allergic parents (n=160)		Only one allergic parent (n=93)		Two allergic parents (n=26)	
	N (%)	OR* [95% CI]	N (%)	OR* [95% CI]	N (%)	OR* [95% CI]	N (%)	OR* [95% CI]
Asthma								
Vaginal delivery	30/179 (16.8)	1.00	11/105 (10.5)	1.00	12/57 (21.1)	1.00	7/17 (41.1)	1.00
Cesarean section	14/100 (14.0)	0.76 [0.37, 3.07]	7/55 (12.7)	2.48 [0.82, 7.57]	6/36 (16.7)	0.91 [0.23, 3.57]	1/9 (11.1)	0.08 [0.00, 1.68]
Allergic rhinitis								
Vaginal delivery	50/179 (27.9)	1.00	17/105 (16.2)	1.00	22/57 (38.6)	1.00	11/17 (64.7)	1.00
Cesarean section	30/100 (30.0)	1.14 [0.61, 2.10]	13/55 (23.6)	1.45 [0.57, 3.68]	12/36 (33.3)	1.11 [0.39, 3.16]	5/9 (55.6)	<0.001 [<0.001, 305.77]
Atopic dermatitis								
Vaginal delivery	64/179 (35.8)	1.00	36/105 (34.3)	1.00	21/57 (36.8)	1.00	7/17 (41.1)	1.00
Cesarean section	35/100 (35.0)	1.01 [0.59, 1.71]	19/55 (34.5)	1.12 [0.54, 2.30]	11/36 (30.6)	0.78 [0.30, 2.04]	5/9 (55.6)	1.53 [0.20, 11.79]

*Adjusted for gender, age, gestational age, birth weight, and breast feeding.

to the Nationwide Study of Asthma and Allergies in Korean Children, the prevalence of the three allergic diseases studied herein increased from 1995 to 2000 as follows: for asthma, from 7.7% to 9.1% in elementary school students, and from 2.7% to 5.3% in middle school students; for allergic rhinitis, from 15.5% to 20.4%, and from 7.7% to 13.6%, respectively; and for atopic

dermatitis, from 16.6% to 24.9%, and from 7.3% to 12.8%, respectively.²⁰ Because the rate of cesarean sections in Korea is relatively high compared to other countries,²¹ investigating the association between mode of delivery and the prevalence of allergic diseases is warranted. However, no study has considered this association in Korea. We found no significant differences

between the cesarean section and vaginal delivery groups for the prevalence of allergic diseases, blood eosinophil counts, serum total IgE levels, or allergic sensitization to Dp and Df. The prevalence of allergic diseases according to mode of delivery was not significantly different between the three subgroups classified by a parental history of allergic diseases.

Although we analyzed confounding variables including age, gender, mode of delivery, gestational age, birth weight, admission to NICU, duration of breast feeding, maternal age at birth, exposure to household pets or smoking, physician-diagnosed allergic diseases, and a parental history of allergic diseases, we were unable to collect data on other variables, including parental educational level, residence, the time infants spent in a nursery, antibiotic administration at NICU admission, or peripartum complications.

This study has some limitations. It was a retrospective study with a small sample size, and it included subjects from a single institution and a wide range of age groups. Furthermore, it is possible that bias could have been introduced in the data that were collected through a questionnaire, and the insignificant differences in blood eosinophil counts, serum total IgE levels, and allergic sensitization to allergens may be explained by the fact that we did not perform these tests on all subjects.

Cesarean section is associated with delayed intestinal colonization,⁶ which could deprive newborns of immunostimulatory impulses at a very critical period in life when the immune system and the gut barrier mature.⁷ Cesarean section may also be associated with a lack of IL-10 or TGF- β production, which may redirect the constitutive Th2-phenotype of the newborn to normal.^{22,23} A recent meta-analysis reported that cesarean section increases the subsequent risk of asthma in children by 20%.²⁴ It has been demonstrated that cesarean section leads to an increased risk for allergic rhinitis and atopy among children with a parental history of asthma or allergies.²⁵ Koplin et al.²⁶ indicated that cesarean section increases the risk for sensitization to food allergens. In contrast, some investigators have proposed that mode of delivery is not related to allergic diseases such as asthma in children.^{19,27} Therefore, although cesarean section is considered a risk factor for allergic diseases, a definite association has not yet been determined. Moreover, such studies have shown different results according to the duration of follow-up, investigated variables, and the definition of allergic diseases.

In conclusion, this is the first study to investigate whether there is an association between mode of delivery in childbirth and the prevalence of allergic diseases in Korea, and we did not find a significant correlation. Further cohort studies with a larger sample size are needed to confirm our findings.

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