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Cesarean Section and Development of Childhood Bronchial Asthma: Is There A Risk?

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Abstract

BACKGROUND: Asthma is a chronic inflammatory disease of the airways that results from complex interactions between multiple environmental and genetic influences. In recent years, studies have observed an increase in caesarean section rates, and have suggested a strong association with the rapid increase in the incidence of childhood asthma that cannot be explained by genetic factors alone. In this case-control study, we investigate the association between the developments of childhood asthma with the mode of delivery. We also explored the relationship between mode of delivery and control of asthma.

METHODS: Two groups (509 pediatric patients in total) were assessed between January 1, 2017, and January 1, 2018. Part of these patients, 257 (50.4%) were asthmatic children visiting specialised clinics, and 252 (49.6%) controlled cases selected from a primary health care clinic from the same institution (control group).

RESULTS: The Chi-square test revealed a significant association between cesarean sections and bronchial asthma (OR, 1.483 [95% CI, 1.013–21.71]; P = 0.042). However, the adjusted OR from our binary logistic regression model revealed this association to be insignificant (adjusted OR, 1.417 [95% CI, 0.885–2.269]; P = 0.804). The value of the chi-square of the model shows that the overall model is statistically significant at 1%. The Nagelkerke R square indicates that 34.9% of the variation in having asthma is explained by the risk factors included in the model.

CONCLUSION: We do not believe that the rise in cesarean sections explains the increase in childhood bronchial asthma – at least not in our population. We also found no association between the mode of delivery and asthma control. We encourage further research into this topic, namely to recruit a larger number of patients, and to adjust for the significant risk factors found in our study.

Introduction

Asthma is a common chronic inflammatory disease of the airways resulting from complex interactions between multiple environmental and genetic influences. In children, several risk factors for asthma have been identified, such as male sex, atopy, allergens, infections, secondhand smoke, and perinatal factors including reduced lung function in early infancy, maternal age, prematurity, and in utero exposure to antibiotics. It is well documented that asthma is more common in children with other atopic diseases, such as atopic dermatitis or allergic rhinitis [1]. In recent years, numerous studies have observed a significant increase in cesarean section rates, and have suggested a strong association with the rapid increase in the incidence of childhood asthma that cannot be explained by genetic factors alone [2], [4]. One explanation for this association is the 'hygiene hypothesis', which states that reduced exposure to bacteria causes dysregulation of the immune system by altering the neonatal gut microflora [5]. Compared to normal vaginal deliveries, during which neonates are exposed to the mother's microflora through the birth canal. This exposure is absent in cesarean section deliveries. In turn, this alters the neonatal cytokine response patterns that can consequently result in changes in the stability of Th1/Th2 (T helper) cells, thereby increasing the risk of developing chronic inflammatory conditions [6]. The association between mode of delivery and chronic inflammatory diseases such as inflammatory bowel disease and celiac disease has been extensively investigated [7], [8], [9]. Other studies have also studied the association between the mode of delivery and bronchial asthma

[2], [3], [4], [10], [11], [12], [13], [14], [15], [16], [17]. Although several studies have discussed the association between the mode of delivery and atopic diseases, their findings have been inconsistent. This might be attributed to a failure to adjust for confounding risk factors of atopy; for example, in a cohort that did adjust for family history of atopy, children born by cesarean section were two times more likely to have atopy than those born by normal vaginal delivery [10]. Other confounders are affecting the association, such as sex, have also not been accounted for. Identifying risk factors for bronchial asthma is particularly useful in recognising the influence of the mode of delivery and its effect on children's immune systems.

Finding new independent risk factors is essential in understanding the pathophysiology of asthma, which in turn, may improve its treatment and prevention. For instance, this study has the potential to affect a mother's choice in undertaking an elective cesarean section. Additionally, it might prompt paediatricians to screen for asthma among children by cesarean section. In this study, we investigated the association between the developments of childhood asthma with the mode of delivery. To our knowledge, this is the first study of its kind in our local population. We also explore the relationship between mode of delivery and asthma severity (control of asthma).

Methods

Patient selection

This is a case-control study involving children aged 2–14 years, selected from the pediatric asthma clinic, allergy immunology clinic, and the pulmonology clinic at King Abdulaziz Medical City, King Khalid National Guard Hospital (a tertiary hospital), Jeddah, Saudi Arabia. Ethical approval was obtained from our local institutional ethics committee, and informed consent was obtained from the parents before recruiting children into the study. Two hundred and fifty-seven children with a definite diagnosis of asthma (according to the criteria set by the Global Initiative for Asthma, GINA) were invited to join the study. Asthma was diagnosed if the child had a history of recurrent intermittent episodes of a cough; chest tightness; shortness of breath; bilateral wheezing occurring at night, with activity, or when exposed to cold, smoke, fumes or dust; and/or if pulmonary function tests indicated that the child had an airflow obstruction (i.e. if the forced expiratory volume [FEV] in 1 second [FEV1)] was reduced to less than 80% of that predicted; if the FEV_1/forced vital capacity [FVC] ratio was less than 0.85 [85%]; or if a low dose of inhaled steroids, and bronchodilators as needed, demonstrated clinical improvement during a trial period of 2–3 months with symptoms worsening on cessation of treatment) [18], [19]. Children with chronic lung diseases, e.g. cystic fibrosis, congenital cystic adenoid malformation, bronchopulmonary dysplasia, and ciliary dyskinesia, were excluded, as well as children with congenital and chromosomal anomalies. Cases in which the child's family was unable to provide the birth or perinatal history were also excluded. Two hundred and fifty-seven age-matched, non-asthmatic pediatric patients who presented to the primary health care clinic or general pediatric clinic were concurrently enrolled as control subjects. These children were seen in the hospital for other, unrelated problems. Control patients with a history of allergic rhinitis or eczema were not excluded from this study.

Data collection and investigations

The parents of children enrolled in the study provided the following data about their children: demographic data; risk factors of bronchial asthma, including parental history of atopy, defined as current allergy to house dust mites or pets, current hay fever or ever having asthma; diagnosis of other atopic diseases, e.g. atopic dermatitis, allergic rhinitis, and conjunctivitis (based on history alone) [19]; parents' smoking habits; and presence of furry pets in the home. Prenatal and perinatal risk factors were also provided, including smoking during pregnancy; maternal exposure to indoor or outdoor allergens (dust or grass); birth order; maternal history of taking any of the following during pregnancy: antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), or beta-blockers; maternal age; maternal history of gastroesophageal reflux disease (GERD) or obstructive sleep apnea; and gestational age. Parents also disclosed the mode of delivery of their child (normal vaginal delivery, emergency cesarean section, or elective cesarean section), and the mode of infant feeding categorized as no breastfeeding, partial breastfeeding (introduction of formula or weaning before 6 months), and exclusive breastfeeding (breastfeeding only for at least 6 months). Control of asthma was assessed using GINA guidelines and was categorised as controlled asthma, partly controlled asthma, and uncontrolled asthma [190].

Statistical analysis

Data were analysed using IBM SPSS software (version 23). Descriptive analysis of the characteristics of the control and asthma groups was performed. Univariate analysis, which compared differences between the control and asthma groups, was done using Student's t-test, the Chi-squared test, and Fisher's exact test (where appropriate). A P-value of < 0.05 was considered to be statistically significant. Binary logistic regression was used to assess the independent relationship between asthma and cesarean section. Confounding factors included in the

final model are listed in Table 3. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI).

Results

Demographic characteristics of the study population

The two groups of patients, amounting to 509 pediatric patients in total, were assessed between January 1, 2017, and January 1, 2018. Of these, 257 (50.4%) patients visiting the pediatric asthma clinic, allergy immunology clinic or pulmonology clinic at King Abdulaziz Medical city was diagnosed with bronchial asthma. Two hundred fifty-two control cases (49.6%) were selected from a primary health care clinic or the general pediatric clinic in the same institution. In univariate analysis, cases and controls were similar with regards to weight, height, and body mass index. However, there was a significant difference in age between asthma and control groups (mean, 7.55 years in the asthma group versus 6.8 years in the control group; P = 0.014). Most (62.3%) of the asthma cases were males.

On the other hand, in the control group, there was no significant difference in sex distribution. Patients' main demographic and clinical characteristics are provided in Table 1. Factors associated with a higher risk of developing bronchial asthma were: a history of atopy in case patients, a family history of atopy (such as atopic dermatitis, allergic rhinitis, conjunctivitis), maternal age (calculated by mean), order of child (calculated by mean), maternal use of NSAIDs during pregnancy, maternal diagnosis of GERD, and premature birth (see Table 1).

Table 1: Demographic characteristics of the study population

Characteristics (N = 509)	Children without asthma (N =252, 49.6%)	Children with asthma (N = 257, 50.4%)	Odds ratio	95% confidence interval	*P*-value
Demographics					
Age mean (SD)	6.80 (3.3%)	7.55 (3.56%)			0.014
Height mean (SD)	116.45 (19.5%)	119.70 (20.40%)			0.052
Weight mean (SD)	23.24 (12.7%)	25.64 (13.71%)			0.080
Body mass index mean (SD)	16.12 (3.8%)	16.65 (3.90%)			0.138
Sex					
Male	127 (50.4%)	160 (62.3%)	1.624	1.142–2.309	0.007
Female	125 (49.6%)	97 (37.7%)			
Asthma risk factors					
FHx of atopy	80 (31.5%)	122 (47.5%)	1.966	1.370–2.819	0.000
Hx of atopy	43 (16.9%)	125 (48.6%)	4.647	3.087–6.996	0.000
Parent smoking	91 (35.8%)	76 (29.6%)	0.752	0.519–1.090	0.132
Pets	25 (9.8%)	40 (15.6%)	1.688	0.991–2.877	0.052
Prenatal risk factors for asthma					
Maternal age mean (SD)	27.83 (5.9)	30.05 (6.44)			0.000
Maternal smoking	4 (1.6%)	0 (0.00%)	0.984†	0.969–1.000	0.060*
Exposure to smoke	88 (34.6%)	72 (28.00%)	0.734	0.504–1.069	0.106
Order of child mean (SD)	2.73 (2.7%)	3.46 (2.36%)			0.001
Medication use					
Antibiotics	20 (7.9%)	17 (6.6%)	0.829	0.424–1.621	0.302
NSAIDs	45 (17.7%)	21 (8.2%)	0.413	0.238–0.717	0.001
Beta-blockers	2 (0.8%)	0 (0%)	0.992†	0.981–1.003	0.247*
Maternal history					
GERD	93 (36.6%)	48 (18.7%)	0.398	0.26–0.596	0.000
OSA	26 (10.2%)	25 (9.7%)	0.945	0.530–1.685	0.848
Natal risk factors					
Preterm	21 (8.3%)	45 (17.5%)	2.355	1.358–4.084	0.002
Mode of delivery					
Emergency cesarean section	38 (15.0%)	44 (17.1%)	1.174	0.731–1.885	0.506

*These have at least 1 cell with an expected count of less than 5. Therefore, for these odds ratios, we relied on the *P*-value of Fisher's Exact Test instead of Pearson's Chi-square: †Risk estimate for the cohort.

Cesarean sections and the risk of developing asthma

The Chi-square test revealed a significant association between cesarean sections and bronchial asthma (OR, 1.483 [95% CI, 1.013–21.71]; P = 0.042); Table 2. However, the adjusted OR from our binary logistic regression model revealed this association to be insignificant (Adjusted OR, 1.417 [95% CI, 0.885–2.269]; P = 0.804); Table 3. The value of the chi-square of the model shows that the overall model is statistically significant at 1%. The Nagelkerke R square indicates that 34.9% of the variation in having asthma is explained by the risk factors included in the model.

Table 2: Univariate analysis of cesarean section delivery and bronchial asthma

	Children without asthma (N = 252, 49.6%)	Children with asthma (N = 257, 50.4%)	Odds ratio (95% confidence interval)	*P*-value
Children born by cesarean section	66 (26.2%)	88 (34.2%)	1.483 (1.013-21.71)	0.042
Children born by natural delivery	186 (73.8%)	169 (65.8%)		

The overall percentage of classification ability of the model is 74.8%. According to our regression model, other risk factors include a family history of atopy, history of atopy, use of NSAIDs during pregnancy, a diagnosis of GERD during pregnancy, gestational age, duration of breastfeeding and maternal age were found to be significant (Table 3).

Table 3: Binary logistic regression model for asthma risk factors

Variables in the equation

	B	S.E.	Wald	df	Sig.	Exp (B)	95 % CI for Exp (B) Lower	95 % CI for Exp (B) Higher	Exp (B)$^{-1}$
FHxA*	0.675	0.231	8.549	1	0.003	1.964	1.249	3.088	
HxA*	1.750	0.248	49.634	1	0.000	5.753	3.536	9.360	
PS	–0.288	0.225	1.628	1	0.202	0.750	0.482	1.167	
Pets	0.643	0.330	3.783	1	0.052	1.902	0.995	3.634	
		18087.36							
MS	–20.8785		0.000	1	0.999	0.000	0.000	0.001	
MES	–0.369	0.243	2.303	1	0.129	0.692	0.430	1.113	
OC	0.113	0.061	3.446	1	0.063	1.120	0.994	1.263	
AB	0.124	0.437	0.080	1	0.777	1.132	0.481	2.664	
NSAIDS*	–1.027	.354	8.411	1	0.004	0.358	0.179	0.717	0.9737
		26285.76							
BB	–21.3222		0.000	1	0.999	0.000	0.000	0.001	
GERD*	–1.228	0.260	22.311	1	0.000	0.293	0.176	0.487	0.8143
OSA	–0.265	0.376	0.496	1	0.481	0.767	0.367	1.604	
GA*	1.212	0.332	13.328	1	0.000	3.362	1.753	6.445	
C-sec	0.348	0.240	2.104	1	0.147	1.417	0.885	2.269	
DBF*	0.041	0.012	11.240	1	0.001	1.042	1.017	1.067	
MA*	–0.036	0.011	11.979	1	0.001	0.964	0.945	0.984	27.7

*Significant risk factor; FHxA: family history of atopy; HxA: history of atopy; PS: parent smoking; Pets: owning pets; MS: maternal smoking during pregnancy; MES: maternal exposure to smoke; OC: order of child; AB: antibiotics taken during pregnancy; NSAIDs: non-steroidal anti-inflammatory drugs taken during pregnancy; BB: beta-blockers taken during pregnancy; GERD: gastroesophageal reflux disease diagnosis during pregnancy; OSA: obstructive sleep apnea; GA: gestational age; C-sec: cesarean section; DBF: duration of breastfeeding; MA: maternal age. The overall percentage of classification is 74.8%. The Nagelkerke R square is 0.349. The chi-square of the model is 153.998.

Cesarean sections and the control of bronchial asthma

Among the 88 asthmatic children born by cesarean section, 34.1% had their asthma under control, 31% had it partially controlled, and 42.1% did not have it under control. On the other hand, among

the children born by natural delivery, 65.9% had their asthma under control, 69% had it partially controlled, and 57.9% had uncontrolled asthma. The results of the Chi-square test shows that there is insufficient evidence to suggest an association between the control of asthma and mode of delivery (χ^2 = 1.449, P = 0.485) (Table 4).

Table 4: Univariate analysis of cesarean section delivery and control of asthma

	Controlled asthma (N = 135, 52.5%)	Partly controlled asthma (N = 84, 32.7%)	Uncontrolled asthma (N = 38, 14.8%)	*P*-value
Children born by cesarean section	46 (52.3%)	26 (29.5%)	16 (18.2%)	0.485
Children born by natural delivery	89 (52.7%)	58 (32.7%)	22 (14.8%)	

Discussion

Many previous studies have investigated the association between cesarean section delivery and bronchial asthma in children, but the topic remains controversial. In our study, as illustrated in our regression model, delivery by cesarean section was not independently associated with childhood bronchial asthma. And consistent with other reports, our data suggest that any relationship between cesarean section and bronchial asthma may be explained by the influence of other confounding variables and not the mode of delivery itself [10], [11], [12], [13], [14]. However, some other studies have found a significant association, including two meta-analyses [2], [3], [4], [15], [16], [17]. with pooled ORs of 1.18 and 1.20 [15], [16]. Discrepant findings may be attributed to some factors. Firstly, the studies included in the meta-analysis were from high-income countries, and this might have affected their results; a large cohort study in Brazil found no evidence of an association between mode of delivery and risk of wheezing [11]. Perhaps the children in our population have alternative sources of microbiological exposure, other than normal vaginal delivery. Secondly, several of the studies that did find a positive association did not account for the many confounding risk factors, such as duration of breastfeeding, use of NSAIDs, or a diagnosis of GERD during pregnancy [2], [3], [17]. To our knowledge, our study is the first to investigate the effect of mode of delivery on the control of asthma (asthma severity). This association was explored to determine whether children born by cesarean section have a deregulated immune system that causes their asthma to be more sensitive to triggers, thus more difficult to control. However, our results show no association between control of asthma and cesarean section.

Our study has a few limitations. Firstly, we did not investigate the relationship between cesarean section and atopy because only a few of our patients had undergone relevant objective investigations, such as IgE levels or allergy skin testing. Secondly, we were not able to determine whether the children in our study born by cesarean section were subject to premature rupture of membranes, which would have exposed them to maternal microflora. Thirdly, since our study is retrospective, data regarding cofounding risk factors may have been affected by recall bias. Nevertheless, the parents of the patients included in this study were confident of the mode of delivery of their children. Finally, limited statistical power means we could not separately investigate emergency cesarean section rates versus scheduled cesarean sections.

In conclusion, we do not believe that the rise in cesarean sections explains the increase in childhood bronchial asthma – at least not in our population. We also found no association between the mode of delivery and asthma control. We encourage further research into this topic, namely to recruit a larger number of patients, follow a cohort study design, and to adjust for the significant risk factors found in our study.

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