Caesarean section and asthma in Malaysian children: a case-control study

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Summary

Background: **Birth cohort studies in some countries have shown a link between caesarean section and asthma.**

Aim: **To determine if there is an association between asthma and delivery via caesarean section in Malaysian children.**

Method: **This is a case-control study involving 156 children aged 3-15 years old, in a tertiary hospital in Kuala Lumpur, Malaysia. Seventy-eight children with a confirmed diagnosis of asthma and seventy-eight age-matched controls (no history of asthma or wheezing) were enrolled. Demographic data including mode of delivery and family history of allergic disorders was obtained. Total serum immunoglobulin E (IgE) was measured and skin prick tests (SPT) to 6 common aeroallergens were performed.**

Results**: The median age of the patients was 8 years old. One hundred and three (66%) children were delivered via normal vaginal delivery, 8 (5.1%) via assisted vaginal delivery and 45 children (28.9%) via caesarean section. Delivery via caesarean section was not significantly associated with asthma (OR = 1.21 [95% CI 0.60 - 2.41], *p* = 0.596). Children delivered via caesarean section did not have higher IgE levels nor were they more sensitized to aeroallergens. Multiple logistic regression showed that asthma was significantly associated with a positive family history of atopy (OR = 13.8 [95%CI 5.96, 32.1], *p* < 0.001). Introduction of semi-solid food after 6 months old had a protective effect against asthma (OR = 0.97 [95%CI 0.94, 0.99], *p* = 0.034).**

Conclusion: **Childhood asthma in Malaysian children was not associated with delivery by caesarean section.** ***(Asian Pac J Allergy Immunol 2012;30:204-8)***

Key words: *asthma, caesarean section, child, hypersensitivity, Malaysia*

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Introduction

The rise in asthma worldwide has resulted in immense research in the hope of determining the cause for this rising trend.[1] Genetic factors alone cannot explain this rapid increase.[2] The "Hygiene hypothesis", as suggested by Strachan in 1989, whereby reduced microbial exposure due to smaller families and cleaner environment may result in lack of stimulation of the Th1 lymphocyte and hence a preference for the Th2 allergic response, is controversial.[3] The immunological explanation for this is that exposure to micro-organisms results in lipopolysaccharide stimulation of Toll-like receptors to produce IL-12 and IFNs which in turn promotes the development of the naive Th cell into Th1 effector cells.[4] Similarly reduced activity of T regulatory cells has also been implicated as a cause for increase in allergic conditions.[5]

Concurrently, worldwide and also in Asia, there are emerging reports of increasing rates of caesarean section(CS).[6] Local data suggest that the rate of CS has increased from 10% in 2000 to 15-25% in 2006.[7] CS have been linked with disturbances in many physiological processes, most importantly delay in establishing normal intestinal flora.[8] The gut and its flora are an important early source of immune stimulation and immune tolerance in neonates.[9] Delivery via CS instead of vaginal delivery is thought to result in reduced microbial exposure of the fetal intestine to maternal vaginal flora.[10]

Hence it has been postulated that the increase in asthma and other atopic diseases may be linked to the concurrent increase in the rates of CS. This increase in the risk of asthma may be more

prominent in children with parental atopy and in females.[11-13]

Our hypothesis is that children with asthma have an increased risk of being delivered via CS.

The primary aim of this study was to determine if Malaysian children with asthma have an increased risk of having been delivered via CS. Furthermore, we wanted to determine other factors associated with childhood asthma in our population.

Methods

Patient Selection

This is a case-control study involving children aged 3-15 years old in a tertiary hospital, University Malaya Medical Centre, Kuala Lumpur, Malaysia. Ethics approval was obtained from our local institutional ethics committee and informed consent obtained before recruitment into this study. Eighty children with a definite diagnosis of asthma were invited to join the study. Asthma was diagnosed if the child had recurrent episodes of doctor-diagnosed wheezing which necessitated the use of either acute reliever (e.g. salbutamol) and/or preventer inhaler medication. The classification of asthma was divided into intermittent or persistent asthma using the GINA guidelines.[14] Children with other significant diseases that may increase the risk of asthma e.g. congenital cyanotic or acyanotic heart disease (not corrected) or extreme prematurity (≤ 28 weeks gestation) were excluded. Children of parents who could not confirm the birth or perinatal history were also excluded. Premature infants who had significant perinatal events e.g. respiratory distress syndrome or required admission during the neonatal period for respiratory illness were excluded. Children/parents who refused to have blood samples taken or skin prick tests were not excluded. Eighty age-matched controls with no history of doctor diagnosed asthma or wheezing were concurrently enrolled. 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

Demographic data regarding mode of delivery, birth weight, presence of other diseases, exposure to environmental tobacco smoke (antenatal and postnatal exposure by any smoker in the home), duration of breast feeding, the age that semi-solid food was introduced, the age that cow's milk was introduced and a family history of atopic diseases were obtained from parents. Patients who had not consumed anti-histamines within 5 days had skin prick tests done to aeroallergens commonly isolated in Malaysia i.e. *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* mix [ALK Abello, Denmark], cat, dog, cockroach (*Blattela germanica), Blomia tropicalis* [Aloystal, France] on the volar aspect of the forearm or back, with histamine as the positive control and saline as the negative control.[15] A skin prick test was considered positive if the induration after 20 minutes was ≥ 3 mm than the saline control. The patient was considered atopic if a positive result was obtained for ≥ 1 aeroallergen.[16] Blood for total Immunoglobulin E was also taken.

Statistical Analysis

Data were analysed using the STATA Version 11 Statistical software (StataCorp LP, USA). Descriptive analyses of the characteristics of the control and asthma group were performed. Univariate analysis comparing differences between the control and asthma groups were 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. Multiple logistic regression was used to assess the independent relationship between asthma and CS. The confounding factors included in the final model were gender, prematurity, post-natal exposure to cigarette smoke, the age that semi-solid food was introduced, breastfeeding duration, mode of delivery and a family history of atopy on the grounds that univariate analysis showed them to be significant factors or that they were thought to be biologically important. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI).

Result

One hundred and sixty-nine children were recruited in this study but results for only 156 children were analysed. The reasons for excluding 13 children were: incomplete demographic data (9 children) and to ensure age matched case and control patients (4 children).The median age of the children was 8 years old (range 3-15 yrs). The female to male ratio was 1:1.2.One-hundred and three children (66%) were delivered via normal vaginal delivery, forty-five children (28.9%) via CS and 8 (5.1%) via assisted vaginal delivery. Their demographic characteristics are shown in Table 1. Children with asthma were more likely to be born prematurely, have had post-natal cigarette smoke exposure and had semi-solid food introduced into

Table 1. Characteristics of the study population

	Asthma n =78	Control n = 78	*p* value
Female	34	37	0.630
Ethnicity			
Malay	54	47	
Chinese	7	14	0.244
Indian	17	17	
Birth weight			
< 2500 gms	15	13	0.676
≥ 2500 gms	61	63	
Prematurity	16	5	0.011Ⱨ
IUGR (< 10th centile)	5	3	0.495*
Maternal smoking during pregnancy	1	1	1.00
Antenatal exposure to cigarette smoke	32	22	0.104
Postnatal exposure to cigarette smoke	34	21	0.039 Ⱨ
Significant neonatal illness	6	3	0.495*
Exclusive breast-feeding > 6 months	17	27	0.095 Ⱨ
Introduced semi-solid food after 6 months old	26	51	<0.001 Ⱨ
Personal history of atopy∞	60	3	0.001 *
Family history of atopy∞	60	16	<0.001 Ⱨ
Family members with asthma			
None	13	62	
Mother	16	4	
Father	12	1	
Siblings	6	4	<0.001 Ⱨ
Parent/s + Siblings	27	4	
Exposure to pets	33	21	0.703

*Fishers exact test; **Ⱨ** Confounding factors used in multiple logistic regression

∞ Atopy is defined as presence of eczema, allergic rhinitis or allergic conjunctivitis

their diet ≤ 6 months old compared to controls. Other expected findings were the significant personal and family history of atopy as well as a family member with asthma in children with asthma compared to controls.

The risk of delivery via CS was not increased in children with asthma after adjusting for possible confounders (Table 2). The median serum IgE levels in children delivered via CS (n = 43) was 359 IU/L (IQR 90,820) and 335 IU/L (IQR 106,790) if delivered via vaginal delivery (n = 109). The IgE levels were not significantly different between the children delivered by CS and normal vaginal delivery

Table 2. Crude and adjusted odds-ratios showing the association between caesarean birth and asthma

	Crude odds ratio	Adjusted odds-ratio*	*P* value
Caesarean section	1.21 (0.60 – 2.41)	1.17 (0.47 -2.91)	NS

*adjusted for gender, post-natal smoke exposure, prematurity, exclusive breast feeding > 6 months , introduction of semi-solid food after 6 months old, family history of atopy

(Z= -0.56, p = 0.58). Delivery via CS was also not associated with a positive SPT (OR = 1.40 [95%CI 0.58-3.34], p = 0.46). In children with asthma, delivery via CS was not associated with increased severity of asthma (persistent versus intermittent asthma) with OR = 1.06 (95%CI 0.53-2.13), p = 0.87. There were significant differences between sensitization to aeroallergens and serum IgE between the asthma and control groups (Table 3).

Multiple logistic regression modelling that included significant and biologically important confounders revealed that the only significant risk factor associated with asthma was a positive family history of atopy. (Table 4) Introduction of semi-solid food after 6 months old had a small protective effect against asthma.

Discussion

We did not demonstrate a significant association between childhood asthma and delivery via CS. The association between the two remains contentious. There are large birth cohort studies that support this association[13,17-19] and those that do not.[11,20-22] Two meta-analyses done in 2008 by Thavagnam et al. and Bager et al. concluded that there is an increased risk of asthma after caesarean section with an OR 1.20 and 1.18 respectively.[23,24] However, in both of these meta-analyses, inclusion of studies mainly from affluent countries may have influenced the outcome. A large cohort study done in Brazil did not demonstrate a significant association between CS and risk of wheezing.[22] Similarly a hospital based study in Korea failed to show a positive association between asthma and CS too.[25]

The lack of association in our patients, we think, is due to the fact that children in our population have other significant microbiological exposures that can be contracted from sources other than from the maternal vaginal tract. The type of food consumed by breast-feeding mothers and the environmental exposures of both the pregnant mother and newborn

Table 3. Results of sensitization to aeroallergens and serum immunoglobulin E levels in the asthma and control group

Aeroallergen	Asthma	Controls	*p* value
Positive to ≥ 1 aeroallergen (Skin Prick tests)	n = 73 (%) 65 (89)	n = 78 (%) 51 (65.4)	*P* = 0.001
Median Immunoglobulin E IU/L (IQR)	n =75 627 (227,1380)	n= 77 142 (52,390)	Z = -5.49, *P* < 0.001

* Only Chinese and Indian patients had skin prick test to dog dander due to religious reasons.

Table 4. Multiple logistic regression analysis of variables of interests that may be associated with an increased risk of asthma in children

Variables	Odds ratio	95% Confidence intervals	*P* value
Prematurity	2.14	0.55 – 8.26	NS
Post-natal smoke exposure	0.99	0.91 – 1.07	NS
Exclusive breast feeding > 6 months	0.52	0.15 – 1.82	NS
Introduction of semi-solid food after 6 months old	0.97	0.94 – 0.99	0.034
Family history of atopy	13.8	5.9 – 32.1	< 0.001

infant may have been different from children born in Western countries.

Limitations of our study are recognised. Our rate of CS is not as high i.e. 25% in this study versus 45% in Brazil.[22] However the other positive studies have lower or similar rates of CS to us.[13,17] Another limitation of our study could be the small numbers in each group. However, this is a case-control study which usually does not require large numbers. The patients selected, especially the controls may not have been from a stable population or may not have been representative of the general population of normal children. We also did not confirm if there was premature rupture of membranes in children finally born via CS, as this may have exposed these infants to maternal microflora. However this factor has not been shown to be an important factor in determining gut microflora in infants.[26] Finally, the retrospective nature of this study and different recall of life events may have affected the results. However the parents enrolled in this study were certain of the mode of delivery.

While there are many studies in Western countries looking at risk of asthma in children delivered via CS, there are none in our population. However, the role of gene-environment interactions cannot be underplayed. Asthma, being a polygenic disease with many other important modulators for risk of disease e.g. environmental tobacco smoke and environmental pollution and perhaps mode of delivery by itself may not impact greatly on the risk of asthma, at least in our population.

In conclusion, in this case control study, there was no association between delivery via caesarean section and asthma in Malaysian children. Delivery via CS was not associated with an increased risk of SPT positivity or higher IgE levels. A family history of atopy and the age that semi-solid food was introduced (≤ 6 months old) was associated with risk of asthma. Large longitudinal birth cohort studies are necessary to determine if there is truly an increased risk of asthma in children born via CS in Malaysia.

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