

Cord blood IgE: its determinants and prediction of development of asthma and other allergic disorders at 12 months

A Kaan*, H Dimich-Ward*, J Manfreda†, A Becker†, W Watson†, A Ferguson*, H Chan*, and M Chan-Yeung*

Background: The value of cord blood IgE in predicting the development of asthma and other IgE-mediated allergic diseases is unclear.

Objective: The purpose of this study is twofold: (1) to determine factors affecting cord blood IgE level and (2) to determine whether cord blood IgE predicts the development of asthma and other IgE-mediated allergic diseases in high risk (defined as those with at least one first degree relative with asthma or 2 first degree relatives with other IgE-mediated allergic diseases) infants at 12 months.

Methods: The study utilized cord blood obtained from a group of high risk infants who took part in a randomized controlled trial to assess the effectiveness of an intervention program in the primary prevention of asthma and other IgE-mediated allergic diseases. Total IgE and cotinine in the cord blood were measured. Assessment of the infants was done at 12 months for these diseases.

Results: Sixty-four (17.8%) infants had detectable total IgE in cord blood >0.5 kU/L. The proportion of infants with elevated cord blood IgE was significantly higher among nonwhites, birth during winter months, and those with a maternal history of asthma. There was no correlation between cord blood IgE and cord blood cotinine level. Cord blood IgE was found to be a significant predictor for the development of urticaria due to food allergy but not for other outcomes.

Conclusion: Both genetic and environmental risk factors play a role in determining the level of IgE in cord blood. Cord blood IgE was a significant risk factor for the development of urticaria due to food allergy at 12 months of life. As urticaria due to food allergy is a prodrome for anaphylaxis, measurement of IgE in cord blood may be indicated in infants at high risk for developing allergic diseases so that preventive measures can be applied.

Ann Allergy Asthma Immunol 2000;84:37–42.

INTRODUCTION

The prevalence of asthma and other allergic diseases have increased in many developed countries.^{1,2} Because of the high direct and indirect costs of management of these diseases^{3,4} there is considerable interest in preventing

these diseases by environmental control measures such as house dust mite and pet avoidance. As these measures are expensive and have to be implemented for a prolonged period of time, it is a cost effective approach to apply them only to a high risk group. The value of measuring cord blood IgE (CB-IgE) as a predictor of asthma and other IgE-mediated allergic diseases has been studied but the results are controversial. While some studies showed that it is a good predictor,^{5,6} others failed to do so.^{7–10}

The purpose of this study is to determine factors affecting cord blood IgE and whether cord blood IgE predicts the development of asthma and

other IgE-mediated allergic diseases in a group of high risk infants who took part in a randomized controlled trial to assess the effectiveness of an intervention program in the primary prevention of these diseases.

MATERIALS AND METHODS

Subjects

High risk infants, defined as those with at least one first degree relative with asthma or two first degree relatives with other IgE-mediated allergic diseases (allergic rhinitis, atopic dermatitis, and urticaria due to food allergy), were identified before birth from prenatal clinics based in a maternity hospital in Vancouver and offices of obstetricians in Winnipeg. Using a short questionnaire, 641 women were identified as eligible in Vancouver from 2278 who were registered to give birth at a maternity hospital and 271 (42.3%) were enrolled in the study. In Winnipeg, 428 were identified as eligible from 1,473 women attending antenatal clinics; 274 (62.4%) were enrolled. A research nurse explained the purpose of the study to eligible women during their prenatal visits. Informed consent was obtained from those willing to participate. Five hundred forty-five families were then randomized into either an intervention or a control group. Seven families dropped out after the birth of the infants because of the poor health of the infants. The intervention group received the following measures: house dust mite avoidance, removal of pets, a smoke free environment for the infants, breast feeding for at least 4 months, delayed introduction of solids, and avoidance of major food allergens until 12

* From the University of British Columbia and † University of Manitoba.

Supported by Inspiraplex, Respiratory Health, Network of Centres of Excellence; British Columbia Association; National Health and Research Development Program, Health Canada; The British Columbia Children's Hospital Foundation.

Received for publication October 26, 1998.

Accepted for publication in revised form August 19, 1999.

months. The details of this study have been reported elsewhere.¹¹ Cord blood was obtained from 397 infants at birth. At 12 months, an additional 49 families had dropped out from the study for various reasons, equally distributed between the control and the intervention group. Three hundred ninety-four (72.3%) infants were available for assessment. The study has the approval of the ethics committees of both institutions in Vancouver and Winnipeg.

Methods

Data on parental history were gathered by trained nurses using a modified European Community Survey asthma questionnaire.¹² Home visits were carried out by research nurses to survey the home environment, to confirm the number of smokers and pets in the home, and to apply intervention measures.

Measurement of Total IgE

Total CB-IgE levels were measured using paper radioimmunoabsorbent test (PRIST) commercially available kits (Pharmacia Diagnostics Inc). Briefly, 0.1 mL of either the standard IgE (0.5 to 100 IgE kU/L) or the serum sample was added to individual test tubes containing a paper disc to which anti-IgE was covalently coupled. The tubes were incubated for 3 hours at room temperature. The tubes were then washed 3 times with 2 mL of washing solution which was aspirated completely each time. ¹²⁵I-labelled anti-IgE (0.1 mL) was added to each tube and the tubes were incubated at room temperature overnight. The next day, the discs were washed 3 times again. The radioactivity in each tube was measured in a gamma counter. The activity of the standard or the sample was expressed as a % of the total activity.¹³ A sample was assayed in duplicate. There was good agreement with 93.8% of replicate measures being within 0.05 kU/L. A standard curve was plotted with the % values obtained for the standards against the concentration on a linear-log paper. The concentration of the samples was read from the standard curve.

Measurement of Cotinine in Cord Blood

Cotinine levels in cord blood were determined by a radio-immunoassay.¹⁴ Briefly, 0.1 mL of the cotinine standard (20 to 2000 picograms) or 0.1 mL of sample (diluted 1:10) was added to a test tube, followed by 0.1 mL of tritiated-cotinine. Anti-cotinine antiserum, 0.1 mL, was added to each tube and mixed. The tubes were incubated at 37°C for 60 minutes. After incubation, 0.1 mL of diluted normal rabbit serum was added to each tube followed by the addition of 0.1 mL of goat anti-rabbit gamma-globulin. The tubes were vortexed and incubated at 4°C overnight. They were then centrifuged at 1000 g for 45 minutes. The supernatant was removed and the pellet was dissolved in 0.1 mL of 0.1M NaOH. 2.5 mL of Ecolume was added and the radioactivity was counted in a beta-counter. A standard curve was constructed. The concentration of cotinine in the samples was read from the standard curve and then multiplied by the dilution factor. A sample was assayed in duplicate. There was good agreement between measurements; 86.5% were within 0.7 ng/mL.

Assessment of Outcome

At 12 months, each child was seen by a pediatric allergist, blinded to the randomization process in each center. In addition to a standardized questionnaire and physical examination, allergy skin prick tests were done by nurses using lancetters with 11 allergens, as well as positive (histamine mg/mL) and negative (saline) controls. The allergens used were *Dermatophagoides pteronyssinus*; *Dermatophagoides farinae*, cat, dog, cockroach, *Alternaria*, *Cladosporium*, cow milk, egg white, soy, and peanut. The pediatric allergists did not have knowledge of the skin test results during their assessment.

"Asthma" was defined as at least two distinct episodes of cough each lasting for 2 or more weeks; or at least two distinct episodes of wheeze each lasting for 1 or more weeks; or in the absence of a cold, at least one of the

following: nocturnal cough (at least once a week), hyperpnea-induced cough, exercise-induced cough. Rhinitis without colds was defined as two or more episodes of runny nose and sneezing in the absence of an apparent cold; atopic dermatitis as characteristic skin lesion (scaly, erythematous, and itchy) in at least two typical areas, eg, face, postauricular area, scalp, extensor surface of arms and legs, and flexures of neck, elbows etc according to the definition of Hanifin and Lobitz.¹⁵ Urticaria due to food allergens was defined as the appearance of wheals on the skin within 30 minutes of ingestion of a certain food. Gastrointestinal symptoms due to food allergy was defined as vomiting and/or colic within 2 hours of ingesting the same food on two or more occasions.

Analysis

Ten infants were excluded from the analysis: the second of each of the three pairs of twins and seven infants with cord blood IgE greater than 10 kU/L because of possible contamination with maternal blood.⁵ The results of 384 infants were available for analysis. As cord blood IgE levels were not normally distributed even after logarithmic transformation, analysis was also carried out with cord blood IgE level dichotomized at the detection limit of 0.5 kU/L. The proportion of infants with detectable or high (≥ 0.5 kU/L) and nondetectable (< 0.5 kU/L) IgE in cord blood for each of the risk factors was compared using chi-square test. Cotinine levels in cord blood were also not normally distributed and the values were transformed into logarithms.

Bivariate relationships between cord blood IgE level and the following familial and environmental factors (a maternal or paternal history of asthma and other allergic disorders, gender, season of birth, birth order, ethnicity, socioeconomic status, maternal and paternal smoking, and maternal age) were examined by ANOVA or chi-square test. Multiple logistic regression analysis was then carried out to examine which factors were important

Table 1. Characteristics of Study Subjects

	<0.5 kU/L	≥0.5 kU/L
Mother's age (yr)	320 31.6 ± 4.9	64 30.5 ± 5.8
Father's age (yr)	34.2 ± 5.7	33.7 ± 7.1
Birth weight (kg)	3.6 ± 0.5	3.5 ± 0.5
Gender n (%)		
Male	161 (80.5)	39 (19.5)
Female	159 (86.4)	25 (13.6)
Ethnic origin n (%) [*]		
White	262 (85.3)	45 (14.7)
Non-white	24 (75.0)	8 (25.0)
Mixed	26 (81.3)	6 (18.7)
Birth order n (%)		
1st born	138 (81.5)	31 (18.5)
2nd born	117 (84.8)	21 (15.2)
3rd born and greater	65 (84.4)	12 (15.6)
Season n (%) [†]		
Winter	67 (72.8)	25 (27.2)
Spring	107 (89.2)	13 (10.8)
Summer	69 (87.3)	10 (12.7)
Fall	77 (82.8)	16 (17.2)
SES n (%)		
Low	79 (84.0)	15 (16.0)
High	237 (83.5)	47 (16.5)
Mother n (%) [†]		
Asthma	130 (40.6)	40 (62.5)
Other allergic diseases	130 (40.6)	16 (25.0)
No allergic disease	60 (18.8)	8 (12.5)
Father n (%)		
Asthma	119 (38.1)	14 (23.9)
Other allergic disease	113 (36.0)	26 (44.1)
No allergic disease	82 (26.1)	19 (32.2)

SES = socioeconomic status; and CG-IgE = cord blood IgE.

^{*} 13 infants had single parents.

[†] $P < .05$, differences between <0.5, ≥0.5 kU/L group by chi-square test.

in determining the level of cord blood IgE. Socioeconomic status was calculated according to the Blishen score based on the occupation of the parents.¹⁶ Infants were divided into quintiles: the lower three quintiles (low) were compared with the higher two quintiles (high). Exposure to environmental tobacco smoke (ETS) was classified into three groups according to the smoking history at the time of recruitment: no exposure to ETS (no one smoked at home); father and/or other member of the household smoked; mother smoked. Infants were also divided into groups by season of birth according to their birth date as follows: spring (March 20 to June 21), summer (June 22 to September 21), fall (Sep-

tember 22 to December 21), and winter (December 22 to June 21). Ethnic groups were divided into whites, nonwhites (consisting of Asians and blacks), and mixed (parents of different ethnic origin).

To assess whether cord blood IgE is an important determinant of outcomes at 12 months, multiple logistic regression was used taking into consideration known risk factors of allergic diseases and the presence or absence of the intervention program.

RESULTS

All infants were fullterm. The mean birth weight was 3.58 ± 0.56 kg. Cord blood IgE was detectable in 64 (16.7%) infants. There were no differ-

ences in the distribution of gender, ethnic origin, birth order, season of birth, socioeconomic status, and family history of asthma and other IgE-mediated allergic diseases between the study subjects and those whose cord blood was not available for measurement of IgE (data not shown).

Determinants of cord blood IgE

Table 1 shows that 39 (19.5%) of the boys and 25 (13.6%) of the girls had detectable IgE levels. Boys had a higher proportion with detectable cord blood IgE than girls; nonwhites had a higher proportion with detectable IgE compared with whites and those of mixed ethnic origin, but the differences between groups were not significant. Most of the infants in the study were first-borns (44.9%).

There was a significant variation in the proportion of infants with detectable cord blood IgE by season of birth ($P < .01$). The highest proportion of infants with detectable cord blood IgE was born in winter months (27.2%), the lowest in the summer (12.7%). No association was found between cord blood IgE levels and the socioeconomic status of the families, gestational age, the weight of the infant at birth, and maternal and paternal ages. Infants with a maternal history of asthma had a significantly higher proportion with detectable IgE in cord blood than those without such a history while a paternal history of asthma was associated with a lower proportion with detectable IgE.

Cord blood cotinine levels according to ETS exposure are shown in Table 2. Infants whose mother smoked had a significantly higher level of cotinine compared with those whose father or other members of the family smoked and those without any ETS exposure. On the other hand, cord blood IgE levels were not affected by ETS exposure. No correlation was found between IgE and cotinine levels in cord blood.

Multiple logistic regression analysis was carried out to examine the predictors of cord blood IgE. Birth in winter (versus spring) months (OR 3.3, 95%

Table 2. Exposure to ETS and Cord Blood Cotinine mg/mL (geometric mean, median, and range)

	N	Geometric Mean†	Median	Range
No ETS* exposure	271	0.23	0.0	0.0–235
Father/others smoke	64	0.60	0.34	0.0–58
Mother smokes	33	51.4	79.0	0.69–580

* ETS = environmental tobacco smoke.

† $P < .001$, differences between ETS exposure group by analysis of variance.

CI 1.5 to 7.3) and a maternal history of asthma (OR 2.2, 95% CI 1.2 to 3.9) remained significantly associated with high cord blood IgE level after adjusting for gender, birth order, socioeconomic status, and exposure to ETS.

Prediction of subsequent allergic diseases

Table 3 shows the incidence of “asthma” and allergic diseases at 12 months according to cord blood IgE level and the crude and adjusted odds ratios from multiple logistic regression analysis. The covariates included in the analysis were ethnic origin, gender, a maternal and paternal history of asthma or other allergic disorders, ETS exposure, birth order, socioeconomic status, and treatment groups. Measurable cord blood IgE was a significant risk factor for urticaria due to food (OR 4.0, 95% CI 1.46 to 10.99) but not for any other outcomes.

DISCUSSION

In this study, we found detectable or high cord blood IgE levels in 17.8% of infants at high risk for developing asthma and other IgE-mediated aller-

gic diseases. It is difficult to compare the results of the present study with some of the reports in the literature because of different methods for determination of IgE and different cut-off points used in the analysis as well as differences in population group examined. Using the same analytical method and the same cut point as our study, Hansen et al¹⁷ found 14.8% with cord blood IgE ≥ 0.5 kU/L in a population sample of infants.

We found that a maternal history of asthma was the most important determinant for high cord blood IgE. It is of interest that a paternal history of asthma or other allergic diseases was not associated with increase in IgE in cord blood. This observation of a significant relationship with maternal history of asthma and lack of relationship with paternal history of asthma has been reported by several investigators^{5,6,18} and suggests that in addition to genetic influences, there may be other environmental factors that might affect both the mother and the fetus. Recent data indicate that food and even inhalant allergens may pass through the pla-

cental barrier. Cord blood T lymphocytes have been shown to proliferate when stimulated with ovalbumin, lactoglobulin as well as house dust mite, and Lolp 1 suggesting that priming has taken place.^{19–22} Whether T lymphocyte proliferation of cord blood will eventually lead to the production of specific IgE antibodies and allergic disorders is unknown.

It has been suggested that high levels of cord blood IgE could be due to contamination by maternal blood.^{5,17} Measurement of IgA level in cord blood has been carried out by some investigators to detect maternal blood contamination. We did not measure the IgA level in cord blood in this study but we used the approach of excluding IgE higher than 10 kU/L in cord blood from analysis.⁵ Such an approach may not be sufficient to exclude all samples with maternal blood contamination and may partly explain the association between a maternal history of asthma and high cord blood IgE level. Michel and colleagues,⁶ however, obtained cord blood by using direct needle aspiration of the cord vein to avoid contamination at sampling. They found high cord blood IgE in a proportion of infants and that high IgE in cord blood in their series was associated with a higher incidence of allergic diseases.

An interesting observation is the significantly higher risk of infants born in winter months having high IgE in cord blood. Variation in cord blood IgE by season of birth has been reported, but

Table 3. Incidence of Outcome at 12 months by Cord Blood IgE, Unadjusted and Adjusted Odds Ratios and 95% Confidence Intervals

	<0.5 kU/L n (%)	≥ 0.5 kU/L n (%)	Unadjusted		Adjusted*	
			OR	(95% CI)	OR	(95% CI)
Asthma 51 (16.8)	11 (17.7)	1.07		(0.52–2.19)	0.84	(0.39–1.85)
Rhinitis without colds	73 (24.0)	15 (24.2)	1.01	(0.53–1.91)	0.91	(0.49–1.66)
Atopic dermatitis	26 (8.0)	4 (6.5)	0.74	(0.25–2.19)	0.70	(0.23–2.13)
Urticaria due to food allergy	13 (4.3)	8 (13.1)	3.38	(1.34–8.55)	4.00	(1.46–10.99)
GI† symptoms due to food allergy	51 (16.8)	7 (11.3)	0.63	(0.27–1.47)	0.66	(0.28–1.56)
Positive skin test to any allergen	62 (20.5)	15 (24.6)	1.26	(0.66–2.41)	1.26	(0.63–2.51)

* Adjusted OR (95% CI) derived from multiple logistic regression analysis with the following covariates: gender (male versus female), socioeconomic status (low versus high), ethnicity (nonwhite versus white), EST exposure (mother smoked, father/other household member smokes versus none), maternal history of asthma or allergies (yes versus no), treatment (intervention versus control), birth order (1st born versus others), and city (Winnipeg versus Vancouver).

† GI = gastrointestinal.

different peaks in different studies: winter,¹⁷ late autumn,¹⁸ end of April,²³ and May.²⁴ The relationship between the month or season of birth and cord blood IgE suggests possible in utero exposure to inhalant allergens.

The role of maternal smoking is controversial. Maternal smoking was found to be associated with high cord blood IgE and subsequent risk of allergic diseases.^{25,26} This finding was not substantiated by several investigators^{7,27,28} as well as by our study; however, the prevalence of maternal smoking in our study population was low. Other environmental factors associated significantly with high IgE in cord blood were consumption of alcohol and caffeine during pregnancy.¹⁸

The value of cord blood IgE in predicting subsequent atopy is also controversial. Magnusson determined cord IgE in 190 infants using a high cut-off point of >1.2 IU/mL for prediction of atopy at 18 months.⁵ He found that the predictive value was high. Croner and colleagues⁸ demonstrated that children with high cord blood IgE had a 5-fold risk for developing bronchial asthma in a follow-up study at 11 years of age. Other studies failed to find such an association.⁸⁻¹⁰ Hansen and colleagues⁹ failed to find an excess of atopic infants at 18 months irrespective of the cut-off values; family history of atopy was found to be a better predictor of atopy than IgE in cord blood. The discrepancy in findings between different studies could be related to several factors: the level of cut-off point, the short duration of follow-up, and the definition of asthma or other allergic diseases. We studied a group of high risk infants rather than infants from a general population; as a result, the effect of various risk factors is more difficult to elicit.

In this study, we have shown that detectable or high IgE in cord blood is a good predictor of urticaria due to food allergy during the first 12 months of life, adjusted for other factors. There is clinical evidence that urticaria may be a prodrome of anaphylaxis from food allergy.²⁹ While atopic dermatitis and food allergies manifest during the

first 2 years of life, asthma usually develops after that period. It is important to follow up this cohort of infants to assess outcome for various IgE-mediated allergic diseases before one can draw any firm conclusion on the predictive value of cord blood IgE.

In conclusion, we found that a maternal history of asthma and season of birth but not maternal smoking influenced IgE levels in cord blood in a group of high risk infants. Detectable or high cord blood IgE was associated with four times the risk of urticaria due to food allergy at 12 months. There may be a role for screening cord blood IgE in infants at high risk for developing IgE-mediated allergic diseases in order that measures can be applied early to prevent the development of food allergy.

REFERENCES

1. Burney PGJ. Epidemiology trends. In: Barnes PJ, Grunstein MM, Leff AR, Woolcock A. eds. *Asthma*. Philadelphia: Lippincott-Raven Publishers, 1997:35-47.
2. Sears M. Epidemiology of childhood asthma. *Lancet* 1997;350:1015-1020.
3. Krahn MD, Berka C, Langlois P, Detsky AS. Direct and indirect costs of asthma in Canada, 1990. *Can Med Assoc J* 1996;154:821-831.
4. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. *N Engl J Med* 1992;326:862-866.
5. Magnusson CGM. Cord serum IgE in relation to family history and as predictor of atopic disease in early infancy. *Allergy* 1988;32:241-251.
6. Michel FB, Bousquet J, Greillier P, et al. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. *J Allergy Clin Immunol* 1980;65:422-430.
7. Halonen M, Stern D, Lyle S, et al. Relationship of total serum IgE levels in cord and 9 month sera of infants. *Clin Exp Allergy* 1991;21:235-241.
8. Croner S, Kjellman NI M. Development of atopic disease in relation to family history and cord blood IgE levels. Eleven year follow up in 1654 children. *Pediatr Allergy Immunol* 1990;1:14-20.
9. Hansen L, Host A, Halken S, et al. Cord blood IgE II. Prediction of atopic disease. *Allergy* 1992;47:398-403.
10. Ruiz RGG, Richards D, Kemery DM, Price JF. Neonatal IgE: a poor screen for atopic disease. *Clin Exp Allergy* 1991;21:467-472.
11. Chan-Yeung M, Ferguson A, Dimich-Ward H, et al. Primary prevention of asthma and other allergic disorders: a multifaceted intervention program in high risk infants. *Am J Respir Crit Care Med* 1998;157:A12.
12. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medications in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687-695.
13. Ceska M, Erickson R, Varga JM. Radioimmunosorbent assay of allergens. *J Allergy Clin Immunol* 1972;49:1-9.
14. Van Vunakis H, Gjika HB, Langone JJ. Method 19: radio-immunoassay for nicotine and cotinine. *Environmental carcinogens methods of analysis and exposure measurement*. V. 9: Passive smoking. Lyons, France: International Agency for Research on Cancer, 1987.
15. Hanifin JM, Lobitz WC. Newer concepts of atopic dermatitis. *Arch Dermatol* 1977;113:663-670.
16. Blishen BR, Carroll WK, Moore C. The 1981 socioeconomic index for occupations in Canada. *Can Rev Soc Anthropol* 1987;24:465-488.
17. Hansen LG, Halkem S, Holmskoc A, et al. Cord blood IgE 1. IgE screening in 2814 newborn children. *Allergy* 1992;47:391-396.
18. Bjerke T, Hedegaard M, Henriksen TB, et al. Several genetic and environmental factors influence cord blood IgE concentration. *Pediatr Allergy Immunol* 1994;5:88-94.
19. Szepefalusi Z, Nentwich I, Gerstmayr M, et al. Prenatal allergen contact with milk proteins. *Clin Exp Allergy* 1997;27:28-35.
20. Piastra M, Stabile A, Fioravanti G, et al. Cord blood mononuclear cell responsiveness to beta-lactoglobulin: T cell activity in 'atopy-prone' and 'non-atopy-prone' newborns. 1994;104:358-365.
21. Piccinni MP, Mecacci F, Shampognaro S, et al. Aeroallergen sensitization can occur during fetal life. *Int Arch Allergy Immunol* 1993;102:301-303.

-
-
22. Chan-Yeung M, Manfreda J, Ferguson A, et al. Does sensitization to inhalant allergens occur in utero? *Am J Respir Crit Care Med* 1977;155:A73.
23. Kimpen J, Callaert H, Embrechts P, Bosmans E. Cord blood IgE and month of birth. *Arch Dis Child* 1987;62:478-482.
24. Croner S, Kjellman NM. Predictors of atopic disease: cord blood IgE and month of birth. *Allergy* 1986;41:68-70.
25. Magnusson CG M. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J Allergy Clin Immunol* 1986;78:898-904.
26. Bergmann RL, Schulz J, Gunther S, et al. Determinants of cord blood IgE concentrations in 6401 German neonates. *Allergy* 1995;50:65-71.
27. Oryszczyn M-P, Godin J, Annesi I, et al. In utero exposure to parental smoking, cotinine measurements, and cord blood IgE. *J Allergy Clin Immunol* 1991;87:1169-1174.
28. Ownby DR, Cole Johnson C, Peterson E. Maternal smoking does not influence cord serum IgE or IgD concentrations. *J Allergy Clin Immunol* 1991;88:555-560.
29. Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E. Jr, Reed CE, Ellis EF, et al, eds. *Allergy: principles and practices*. Mosby Year St. Louis; Mosby Year Book Inc. 1999:1079-1092.

*Requests for reprints should be addressed to:
Dr Moira Chan-Yeung
Respiratory Division
Department of Medicine
University of British Columbia
2775 Heather St
Vancouver, BC, Canada V5Z 3J5*