Prediction of Elevated Cord Blood IgE Levels by Maternal IgE Levels, and the Neonate's Gender and Gestational Age

Chieh-An Liu, MD; Chih-Lu Wang, MD; Hau Chuang, BS; Chia-Yu Ou¹, MD; Te-Yao Hsu¹, MD; Kuender D. Yang, MD, PhD

Background: Elevation of cord blood immunoglobulin E (IgE) is used to predict childhood atopy. In an effort to catch such problems at an earlier time, we sought to identify the impact of parental atopy as well as gestational age, the baby's gender, and the season of delivery on cord blood IgE levels.

Methods: The allergic history of parents was collected during pregnancy. Blood samples from parents were collected in the third trimester. Cord blood was collected immediately after birth. Total and specific IgE levels were determined using the Pharmacia CAP system.

Results: In total, 437 core family blood samples were collected. Male babies had a significantly higher IgE level (0.535±0.898 vs. 0.369±0.565 KU/L, \( p = 0.021 \)) and a higher frequency of IgE ≥ 1.0 KU/L (14.6% vs. 7.5%, \( p = 0.018 \)) compared to female babies. A cyclic trend in higher cord blood IgE levels was found in babies born in early summer and early winter. Multiple logistic regression analyses revealed that elevation of cord blood IgE levels could be predicted by higher maternal IgE levels (odds ratio [OR] = 6.35; \( p = 0.000 \)), male baby gender (OR = 2.31; \( p = 0.021 \)), and increases in gestational age by 1 week (OR = 1.34; \( p = 0.039 \)). In contrast, neither the allergic history of parents nor elevation of paternal IgE levels could be correlated with elevated cord blood IgE levels of neonates.

Conclusion: The baby's gender and gestational age, and maternal IgE levels influence cord blood IgE levels. Avoiding allergens and decreasing allergic activities during pregnancy may be the most important means of preventing the fetus from having allergic sensitization.

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Key words: cord blood, immunoglobulin E, family atopic history, gender, gestational age.

The prevalence of atopic disorders in children has dramatically increased worldwide over the past 2 decades.\(^1\)\(^,\)\(^2\) Possible reasons for this increase are multifactorial, with genetic inheritance, fetal sensitization, house dust mites, air pollutants, etc. having been implicated.\(^1\)\(^,\)\(^2\) Results from epidemiological studies have shown that childhood asthma is probably a hereditary disorder since monozygotic twins are more frequently affected than are heterozygotic twins,\(^3\) and the offspring of affected parents also

From the Department of Pediatrics; Department of Obstetrics and Gynecology, Chang Gung Children's Hospital, Kaoshiung. Received: Jan. 24, 2002; Accepted: Apr. 15, 2003
Address for reprints: Dr. Kuender D. Yang, Office of the Vice Superintendent, Chang Gung Children's Hospital. 123, Dabi Road, Niaosung Shiang, Kaohsiung, Taiwan 833, R.O.C. Tel.: 886-7-7317123 ext. 2031; Fax: 886-7-7312867; E-mail: yangkd@cgmh.org.tw
have a higher risk for developing asthma. Cookson and colleagues first proposed a linkage of chromosome 11q13 with asthma in certain families in Oxford, UK. They further identified that the transmission of atopy at chromosome 11q13 was detectable only through the maternal line. Piccinni et al. showed that sensitization to aeroallergens can occur in utero. Some studies have shown that exposure of infants and fetuses to direct or indirect contact with dust mites early in life may result in an increased asthma prevalence. Based on these studies, the management of atopic disorders is now focused on primary prevention. In order to avoid early allergen exposure, early detection or early prediction of high-risk groups in the perinatal stage may provide a better strategy for preventing childhood atopic disorders.

Since the 1970s, the role of cord blood immunoglobulin E (IgE) levels in predicting the development of atopy has been widely discussed. Some studies have demonstrated that elevation of cord blood IgE levels is a good predictor for atopic diseases at the age of 12 months, 18 months, and even at the age of 11 years. Although a number of different cutoff points of cord blood IgE levels have been used as reference values to predict atopic disease in different areas, there are also conflicting studies regarding the usefulness of cord blood IgE values in predicting childhood atopy as cord blood IgE levels may be influenced by both family inheritance and environmental factors. Furthermore, it is not well understood how cord blood IgE levels are influenced by the fetal environment, such as maternal, paternal, placenta, and fetal characters.

In order to identify a better early predictor of prenatal atopic sensitization, we sought to explore the impact on cord blood IgE levels of gestational age, fetal gender, season of birth, and parental atopy including allergic history, and total and specific IgE levels.

METHODS

Subjects and materials

In total, 437 families were enrolled. These were all ethnic Chinese families except for 3 aboriginal families. A research nurse was trained to explain the purpose of the study to eligible pregnant women during their prenatal visits starting in September 1998 at Chang Gung Memorial Hospital, Kaohsiung, Taiwan. Informed consent was obtained from parents willing to participate in the study. Blood sampling from parents was performed in the third trimester. Cord blood samples were collected immediately after birth. Serum from each parent and cord blood were separated by centrifuging them at 3000 rpm for 15 min and storing them at -70°C until analysis. By means of a standard questionnaire, the family history of atopic diseases was obtained from the parents at the time of enrollment.

Detection of total and specific IgE levels

Serum total IgE levels and specific IgE antibodies in the parents' blood and cord blood samples were determined using the Pharmacia CAP system (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). The low range (0.35–100 KU/L) of the total IgE detection system was used to detect cord blood IgE levels; whereas the full range was applied to measure IgE levels in parental blood. In a pilot study, we identified 2 possibly detectable specific IgE antibodies directed against egg white and cow milk in cord blood. In parental blood, we assayed the Dermatophagoides pteronyssinus (Der p)-specific IgE since the Der p allergen is responsible for 92% of allergen sensitization in Taiwan.

Data analysis

Parental history of atopy was considered positive if either parent had a medical history of asthma, atopic dermatitis, or allergic rhinitis. Cord blood IgE values were divided into 3 groups according to previous referential cut-off points of ≥ 0.5, ≥ 0.7, and ≥ 1.0 KU/L. Elevation of maternal and paternal IgE levels was set at a cut-off point of 100 KU/L, based on the level ≥ 70th percentile of the population studied. Mean values with standard deviation (mean ± SD) are presented. In the present study, the following variables with a possible association with cord blood IgE levels were included as independent variables: gender and gestational age of the infant, and parental history of atopy and serum IgE levels. One-way analysis of variance test was used for comparison of the sum among groups. The association in 2-dimensional contingency tables between cord blood IgE levels and other variables was assessed using Pearson's chi-square test. Multivariate analy-
ses of dichotomous effects were carried out by multiple logistic regression to analyze which factors, if any, were better predictors for babies with elevated cord blood IgE levels. The odds ratio is presented with the 95% confidence interval (95% CI). A p value of less than 0.05 was regarded as statistically significant.

RESULTS

Distribution of cord blood IgE levels

In total, 437 cord blood samples were collected. The range of cord blood IgE levels was between 0.01 and 5.87 KU/L with a mean value of 0.450±0.748 KU/L (95% CI 0.382–0.519 KU/L). One-third of newborns in this study revealed detectable IgE (≥ 0.35 KU/L by the CAP system) in cord blood. Frequencies of elevated cord blood IgE levels greater than 0.5, 0.7, and 1.0 KU/L were 23.7%, 16.5%, and 10.7%, respectively. Only 4 of 437 babies had detectable specific IgE antibodies to egg white or milk.

Correlations of gender, gestational age, and season with cord blood IgE levels

Boys had higher cord blood IgE levels than did girls (Fig. 1A) (0.535±0.898 vs. 0.369±0.565 KU/L, p = 0.021), and a higher proportion of boys had elevated cord blood IgE levels ≥ 1.0 KU/L than did girls (Table 1) (14.5% vs. 7.2%, respectively, p = 0.018). Comparing the gestational age of these babies, it was found that premature babies born before 37 weeks of gestational age had lower cord blood IgE levels than did babies born after 37 weeks of gestational age (p = 0.006) (Fig. 1B). A relatively higher proportion of elevated cord blood IgE levels was also found in babies born after 37 weeks of gestational age (Table 1). The 4 babies positive for specific IgE to egg or milk were male babies born between 39 and 41 weeks of gestational age. Among

Fig. 1 Distribution of mean cord blood IgE levels according to gender (A), gestational age (B), and month of birth (C).
the 48 babies with cord blood IgE levels \( \geq 1.0 \text{ KU/L} \),
only 2 babies were delivered prematurely at the gestational age of 36 weeks. 
Comparing the delivery seasons of the babies, we found a cyclic trend in both mean cord blood IgE levels (Fig. 1C) and frequency of higher cord blood IgE levels in babies born in different seasons with peaks in early summer and early winter.

**Correlation of maternal allergic history with cord blood IgE levels**

The mean value of cord blood IgE levels in babies from mothers with a history of atopy was higher than that in those without a history of atopy, but the difference was not statistically significant (0.506 \( \pm \) 0.744 vs. 0.392 \( \pm \) 0.776 KU/L, \( p = 0.116 \)).

Of those babies from mothers with a history of atopy, 28% had elevated cord blood IgE levels (\( \geq 0.5 \text{ KU/L} \)), whereas 18% of the other babies from mothers without a history of atopy had elevated cord blood IgE levels (OR=1.74, 95% CI 1.157~2.608, \( p = 0.009 \)) (Fig. 2A). In contrast, there was no difference in the frequency of elevated cord blood IgE levels (\( \geq 0.5 \text{ KU/L} \)) (OR=0.72, 95% CI 0.483~1.072, \( p = 0.105 \)), or mean values of cord blood IgE levels between babies from fathers with and those without a history of atopy (0.417 \( \pm \) 0.697 vs. 0.483 \( \pm \) 0.809 KU/L, \( p = 0.363 \)).

**Correlation of maternal IgE levels with cord blood IgE levels**

To explore the relationship between cord blood IgE levels and parental total IgE levels, we simultaneously assayed both parents' total serum IgE levels. Elevation of IgE levels in mothers and fathers was determined at a cut-off value of \( \geq 100 \text{ KU/L} \), based on the level of the \( \geq 70\text{th} \) percentile of the population in which 30% people may have atopic features. We found that babies from mothers with elevated IgE

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**Table 1. Number and Percentage of Babies with Higher Cord Blood IgE Levels according to Gender and Gestational Age**

<table>
<thead>
<tr>
<th>Cord blood IgE levels (KU/L)</th>
<th>( \geq 0.5 )</th>
<th>( \geq 0.7 )</th>
<th>( \geq 1.0 )</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>male</td>
<td>56 (24.5%)</td>
<td>45 (19.7%)</td>
<td>33 (14.5%)*</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>53 (25.3%)</td>
<td>31 (14.8%)</td>
<td>15 ( 7.2%)*</td>
</tr>
<tr>
<td>Gestational age</td>
<td>( \leq 37 )</td>
<td>17 (24.2%)</td>
<td>9 (12.9%)</td>
<td>4 ( 5.7%)</td>
</tr>
<tr>
<td></td>
<td>&gt; 37</td>
<td>93 (25.3%)</td>
<td>65 (17.7%)</td>
<td>44 (12%)</td>
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</tbody>
</table>

\( * p = 0.018 \) (Chi-square test) between boys and girls with IgE \( \geq 1.0 \text{ KU/L} \).

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**Fig. 2** Correlations between higher cord blood IgE levels and parental history of atopy (A), total IgE levels (B), and the presence of Der p-specific IgE (C).
levels (≥100 KU/L) had a significantly higher relative risk of having elevated cord blood IgE levels (OR=5.71, 95% CI 3.649–8.944, \( p = 0.000 \)) (Fig. 2B). Babies from fathers with elevated IgE levels revealed no higher relative risk for elevated cord blood IgE levels (OR=0.86, \( p = 0.489 \)) (Fig. 2B). The mean value of cord blood IgE levels was significantly higher in babies from mothers with elevated IgE levels than from those without elevated IgE levels (0.813±0.869 vs. 0.328±0.610 KU/L, \( p = 0.000 \)). Babies from fathers with and those without elevated IgE levels did not have significantly different cord blood IgE levels (0.486±0.745 vs. 0.443±0.669 KU/L, \( p = 0.674 \)). More interestingly, babies from mothers with detectable specific IgE for the Der \( p \) antigen also had a higher frequency of elevated cord blood IgE levels (\( p = 0.000 \)) (Fig. 2C).

In contrast, paternal atopic features such as elevated total IgE levels or the presence of specific IgE for Der \( p \) were not correlated with and were unable to predict elevated cord blood IgE levels in babies.

### Multiple logistic regression analysis of the relative risks of perinatal features

Multiple logistic regression analysis was carried out to examine which perinatal factors were important in determining cord blood IgE levels when these variables were considered together. Higher maternal IgE levels of ≥100 KU/L had the highest relative risk at 6.35 (\( p = 0.000 \)), followed by male baby gender with a relative risk of 2.31 (\( p = 0.021 \)), and

<table>
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<th>Variable</th>
<th>OR</th>
<th>95% CI for OR</th>
<th>( p )</th>
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<td>No</td>
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<td>1.38</td>
<td>0.67-2.84</td>
<td>0.380</td>
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<td>No</td>
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<td>Yes</td>
<td>1.68</td>
<td>0.82-3.46</td>
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<td>Maternal IgE ≥ 100 KU/L</td>
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<td>No</td>
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<td>Yes</td>
<td>6.35</td>
<td>3.06-13.91</td>
<td>0.000</td>
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<td>Paternal IgE ≥ 100 KU/L</td>
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<tr>
<td>Yes</td>
<td>1.05</td>
<td>0.52-2.12</td>
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<tr>
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<tr>
<td>Male</td>
<td>2.31</td>
<td>1.13-4.71</td>
<td>0.021</td>
</tr>
<tr>
<td>Gestational age</td>
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<td></td>
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</tr>
<tr>
<td>1.34*</td>
<td>1.01-1.77</td>
<td>0.039</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** OR, odds ratio.

* Represents the odds of elevated cord blood IgE levels in babies with weekly increases in gestational age.
increases in gestational age by 1 week with a relative risk of 1.34 ($p=0.039$) (Table 3). Again, neither paternal history of atopy nor elevated total IgE levels was significantly correlated with elevated cord blood IgE levels ($p>0.05$).

**DISCUSSION**

Elevation of cord blood IgE levels and a family history of atopy are the most important factors in predicting childhood atopy.\(^{10-12}\) Screening of cord blood IgE levels has been widely used as a predictor of asthma and other IgE-mediated allergic diseases for years, but the sensitivity and specificity of this method are controversial.\(^{10-14}\) In order to identify the optimal cut-off value of cord blood IgE levels for further prospective studies, it is important to establish references of cord blood IgE levels in different races. In the present study, we establish reference values for cord blood IgE levels in Taiwan. We found that cord blood IgE levels were not normally distributed, and that most cord blood IgE levels were below 0.5 KU/L, as was found in previous reports by Kimpem et al.\(^{(18)}\) and Bergmann et al.\(^{(21)}\) We further discovered that male babies had higher mean cord blood IgE concentrations than did female babies, and that male babies had a higher proportion of elevated cord blood IgE levels greater than 1.0 KU/L. The influence of gender on cord blood IgE levels may have resulted from a genetic predisposition or from the presence of sex hormone. Because boys have a higher incidence of childhood atopy than do girls, we suggest that male and female babies should have different cut-off points for elevated cord blood IgE levels for predicting childhood atopy.

Seasonal variations in cord blood IgE levels have been previously reported, and have been referred to as a clue for intrauterine allergen sensitization.\(^{13,16,20}\) The climate in Taiwan is subtropical, and in southern Taiwan, the temperature can be warm and humid throughout the year. In this study, we found that cord blood IgE levels fluctuated in a cyclic trend with peaks near early summer (June) and early winter (December). The mean cord blood IgE values also fluctuated from month to month. Seasonal variations in cord blood IgE levels in Taiwanese are compatible with seasonal variations of Der p concentrations previously published by Li et al.\(^{(26)}\) showing the highest concentrations in June and December. Szepfalusi et al. recently reported that allergens can be actively transferred across the placenta.\(^{(27)}\) Taken together, maternal allergen exposure during pregnancy may cause fetal sensitization and augment cord blood IgE production.

Contamination by maternal IgE in the measurement of cord blood IgE levels is an unsolved issue. Some studies have measured both cord blood IgE and IgA levels to exclude contaminated samples when elevated IgA levels were detected. However, several studies have shown that no correlation exists between the concentrations of cord blood IgE and IgA.\(^{19-21}\) Thus, IgA might not be a truly specific marker for maternal blood contamination. In fact, results from this study revealed that babies of different gender or different gestational age had significantly different cord blood IgE levels, indicating that contamination of maternal IgE in the measurement of cord blood IgE levels was not important. If maternal blood contamination in the cord blood is important, male and female babies should have had relatively equal cord blood IgE levels since adult blood IgE concentrations are 100 times greater than cord blood IgE levels. Similarly, if contamination of maternal IgE existed in cord blood, the correlation of elevated cord blood IgE levels with increased gestational age by week would also not have been present. In support of the idea that fetal IgE levels represent the immunological status of the fetus, Szepfalusi et al.\(^{(27)}\) showed direct evidence for transplancental allergen transfer, and we have shown that seasonal variations of cord blood IgE levels (Fig. 1C) are compatible with seasonal variations of common allergen (Der p) concentrations.\(^{(26)}\) The Der p allergen is the most common allergen in Taiwan.\(^{22,23}\)

We also confirmed that a maternal history of atopy but not paternal history was correlated with babies having elevated cord blood IgE levels, as has previously been reported.\(^{13,16,21,24}\) However, researchers have frequently argued about bias from questionnaires of allergic history since most allergy questionnaires are completed by mothers who possibly misinterpret the paternal allergic history. In order to explore whether maternal atopy but not paternal atopy is truly correlated to elevation of cord blood IgE levels, we simultaneously correlated parental total IgE levels and Der p-specific IgE levels to cord blood IgE levels. It was found that elevated maternal, but not paternal, total IgE levels had
the best positive predictive power for babies with elevated cord blood IgE levels. These results suggest that gender-linked inheritance and the maternal environment including placental factors may affect fetal allergy sensitization and IgE production. Cookson et al.\(^6\) reported that the transmission of atopy at chromosome 11q was detectable only through the maternal line. Piccinni et al.\(^7\) showed that sensitization to aeroallergens can occur in utero. Similarly, there is also evidence showing that placental factors tend to deviate the fetal immune reaction toward an allergic reaction. Thus, avoiding allergens during pregnancy and decreasing allergic activities in pregnant women may be the most important means of preventing infants and children from developing allergic diseases. Further studies should be done to identify allergic gene(s) and ways to control fetal sensitization in pregnancy, as these are the most important issues in the prevention of childhood atopic disorders. Moreover, male and female babies should be assigned different cut-off points for cord blood IgE values when they are used to predict childhood atopy.

**REFERENCES**

利用媽媽血中的IgE值與新生兒性別以及懷孕週數可預測
臍帶血會有較高的IgE值

劉健安 王志祿 莊 好 歐家佑 許德耀 楊春德

背景：新生兒臍帶血IgE值可用來預測兒童過敏症，我們希望藉由分析父母親的過敏症以及
懷孕週數、男女性別與出生季節對新生兒臍帶血IgE值的影響，找出影響臍帶血IgE
值的相關因子。

方法：懷孕過程收集父母親過敏史，並於懷孕第三期收集父母親的血，臍帶血則是在新生
兒出生時收集。血中IgE以及特殊過敏原IgE的值是利用Phamacia CAP系統來檢測。

結果：總共收集了437個家庭，分析發現男嬰比女嬰有較高的臍帶血IgE值 (0.535±0.898 vs.
0.369±0.565 KU/L, p=0.021) 以及有較高比例的臍帶血IgE值大於1.0 KU/L (14.6% vs.
7.5%, p=0.018)。在初夏以及早冬季節出生的嬰兒有較高的臍帶血IgE值。多變數
迴歸分析顯示若媽媽血中有較高的IgE值 (OR=6.35; p=0.000) 、性別為男嬰 (OR=2.31;
p=0.021) 、以及懷孕週數較大者 (OR=1.34; p=0.039) 可預測新生兒會有較高的臍帶
血IgE值。相反的，父母親的過敏史或者爸爸的血中IgE值則與新生兒臍帶血的IgE值
無相關。

結論：嬰兒的性別、懷孕週數、以及母親血中IgE的值會影響臍帶血IgE值。因此在懷孕期
間避免過敏原的接觸以及降低過敏反應對於防止胎兒致敏是很重要的。
(長庚醫誌 2003;26:561-9)

關鍵字：臍帶血，IgE，家族過敏史，男女性別，懷孕週數。