

Evaluation of cord blood immunoglobulin E and its association with maternal factors in a group of Iranian newborns

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Abstract

Allergic disorders are among the most common diseases around the world especially in children. Many factors contribute to the pathogenesis of atopic disorders, but early events during the pregnancy are very important. The aim of this study was to evaluate the level of cord blood immunoglobulin E (CB-IgE) and its association with maternal in a group of Iranian newborns. In a cross-sectional study, 163 pregnant women randomly selected and information about pregnancy and atopy were taken by questionnaire. Blood samples of mothers and matched cord blood were collected and total serum IgE levels were measured by enzyme-linked immunosorbent assay (ELISA) method. To rolling out the possibility of contamination with maternal blood, total IgA was checked for all the cord blood samples. Sixteen percent of mothers had the history of atopic diseases and the mean IgE level was significantly higher in an atopic than nonatopic mothers (241 vs 102, $P < 0.001$). About 73.9% of cord blood samples, had high IgE level (>0.9 IU/mL). The level of cord blood IgE (CB-IgE) was not significantly different in male and female newborns (2.14 vs 2.15 IU/mL). There was no significant correlation between maternal factors such as age, pregnancy variables, allergens exposure, smoking, and maternal IgE with cord blood IgE. The results of this study showed that CB-IgE is high in a remarkable number of samples; independent of maternal or fetal factors. Further studies need to evaluate the reasons for the high level of IgE in cord blood in our area.

KEYWORDS

allergic predisposition, cord blood immunoglobulin E, Iranian newborns, maternal exposure, sensitization

1 | INTRODUCTION

Allergic diseases are among the most common chronic diseases in children and adolescent and the prevalence of allergic disorders have been increasing in recent decades.¹ In addition to high prevalence, allergic disorders have profound negative effects on patients'

quality of life. To prevent these common disorders and reduce the economic burden, much attention has been paid for finding a reliable predictor of allergies, particularly in early life, when the sensitization to different allergens may occur.²

Manifestations of some allergic symptoms during early life, suggest that the development of atopic immune

response may begin early after birth or even during the fetal period. In this regard, the first allergen encountered is very important, and therefore, there is a great interest in the detection of allergen-specific immune response, as well as any other contributing factor, as early as possible to control the exposures and later consequences. Up to date, many variables, including genetic, epigenetic, and environmental factors have been studied, concerning their possible role in developing an allergy and to find a suitable predicting factor.³⁻⁵ Genetic and epigenetic factors are difficult to control, but environmental variables are easier to manipulate and evaluate. In the absence of a valid biomarker, especially in early age, evaluation of predisposing factors, and considering proper strategies for prevention and treatment will be abortive. During recent decades, cord blood IgE (CB-IgE) has gained much attention, as a potential predictor of allergic diseases.² In addition, it is available and easy to access, with existing methods; however, there are many controversies about its predicting value for allergic disorders in infants, and children. Some reports have shown that the fetus is able to produce IgE, therefore, measuring CB-IgE can predict the development of atopic disorders.^{2,6} In contrast, other studies found that it is not useful in predicting the outcome of the early childhood allergic reaction.

The CB-IgE level is influenced by many factors including, fetal and maternal factors, such as the month of birth, maternal diet, and smoking,⁷ during pregnancy.⁷ Considering the influence of genetics, and environmental factors on the CB-IgE and to overcome the controversies, more studies need to be performed on different population and situation, to evaluate the value of CB-IgE.⁸ Regarding the scarcity of studies about CB-IgE in Iranian newborns, the aim of the present study was to evaluate the level of CB-IgE, as well as the affecting maternal and environmental factors in a group of newborns in the city of Birjand, in Iran.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

In this study, 163 pregnant women who had delivered at the Vali-Asr Hospital of Birjand, between November 2014 and August 2016, were enrolled. The study was approved by the Ethics Committee of the Birjand University of Medical Sciences, and all participants provided written consent form before enrolling in the study. A questionnaire was used to obtain information about demographic variables, delivery characteristics, diet, history of any atopic or other diseases, as well as allergic symptoms, and history of exposure to allergens. Cases with any malformation, Apgar score less than 7, pre-eclampsia,

addiction or any serious health problem among mothers, were excluded from the study.

2.2 | Cord blood and maternal total immunoglobulin E

Before delivery, 5 mL of venous blood was taken from mothers. After successful delivery, the umbilical cord was clamped and cut. Cord blood was collected by aspirating blood from the umbilical vein and processed immediately. After separation of serums by centrifugation at 3000 rpm for 20 minutes, the level of total IgE in maternal, and cord blood was measured by a commercial ELISA Kit (Radim Diagnostics, Freiburg, Germany), in duplicate. The kit's detection limit was 0.2 IU/mL, and IgE level higher than 150 and 0.9 IU/mL were considered as a high IgE level for mothers and newborns, respectively. To check the contamination with maternal blood, total IgA was determined by a commercial Nephelometry Kit (Nephstar, Shenzhen, China), and all samples with detectable IgA were excluded from the study.

2.3 | Statistical consideration and analysis

Data were analyzed, using SPSS software package version 16 (SPSS Inc, Chicago). The χ^2 test or Fisher's exact test was used to compare frequencies. Total IgE is presented as geometric mean with 95% confidence interval. $P < 0.05$ was considered significant.

3 | RESULTS

Umbilical cord serum IgE, and maternal IgE level were examined as a possible predictor of the subsequent incidence of allergic disorders. All infants were full-term. This study was performed on 119 newborns and 163 pregnant mothers. The mean age of mothers was 28.7 ± 5.8 (range, 16-42) years. About 56.2% of babies were female. The mean of cord blood and maternal IgE level was 2.33 and 126.1 IU/mL, respectively. Almost 22.2% of mothers and 73.9% of neonates have high IgE (Figure 1), according to the kit manual. No significant correlation was found between maternal IgE and CB-IgE (Spearman's $r = 0.101$, $P > 0.5$).

There was no significant association between neither mothers' factors, nor infant variables, including weight, head circumference, and the type of delivery with CB-IgE value (Tables 1,2). About 16% of the mothers suffered from atopic disorders, and the prevalence of asthma, eczema, and allergic rhinitis was 1.2%, 9.9%, and 9.1%, respectively. The mean serum IgE was significantly

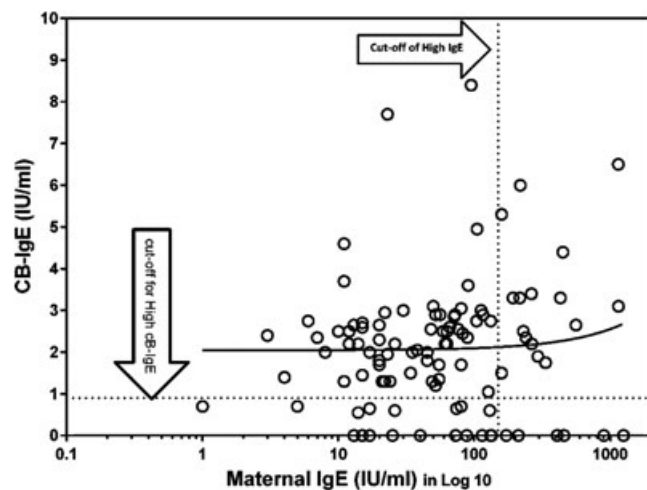


FIGURE 1 Distribution of maternal and cord blood immunoglobulin (IgE) (dotted lines are cutoff of normal Cord blood and adult IgE). CB-IgE, immunoglobulin IgE

TABLE 1 Effect of different variables on cord blood immunoglobulin E level

Variables	N (%)	Cord blood IgE level, IU/mL	P value
Neonatal sex			
Male	52 (43.80)	2.14 ± 1.55	0.92
Female	66 (56.20)	2.15 ± 2.19	
Type of delivery			
Cesarean	4 (3.30)	3.07 ± 3.36	0.25
Vaginal	115 (96.70)	2.11 ± 1.87	
Mother smoking			
Yes	2 (1.20)	1.75 ± 1.06	0.44
No	117 (98.80)	2.40 ± 2.20	
Family income (Iranian Rial)			
<5 000 000	105 (89.70)	2.02 ± 1.90	0.58
>5 000 000	12 (10.30)	1.75 ± 1.60	
Allergic disorders during pregnancies			
Present	19 (11.70)	1.70 ± 1.79	0.31
Absent	99 (60.70)	2.24 ± 1.94	
Contact pets			
Yes	18 (11.04)	2.80 ± 2.30	0.28
No	93 (57.05)	2.10 ± 2.10	
Father smoking			
Yes	10 (8.60)	1.65 ± 1.18	0.26
No	106 (91.40)	2.21 ± 1.99	

higher in atopic mothers (271 vs 102, $P < 0.001$), but not in mothers with asthma, eczema, or rhinitis, separately. Table 3 shows the effect of different variables on the mother's serum IgE.

4 | DISCUSSION

In this cross-sectional study, we evaluated the CB-IgE and the risk factors for its elevation in a group of

TABLE 2 Variables of pregnant mothers and their correlation with cord blood immunoglobulin E

Pregnancy variables	Mean ± SD	P value
Maternal age, y	27.8 ± 5.8	0.24
Pregnancy duration, wk	38.7 ± 4.5	0.68
Number of previous pregnancies	1.3 ± 1.5	0.38
Number of previous deliveries	1.2 ± 1.4	0.37
Maternal weight before pregnancy, kg	56.2 ± 1.0	0.40
Neonate weight, g	3058 ± 414	0.71
Neonate height, cm	50.2 ± 2.5	0.80
Level of maternal education, y	7.9 ± 4.7	0.85

newborns. Some studies uniformly supported the usefulness of elevated CB-IgE (>0.5 kU/L), as the indicator of atopic disease,⁹ while several other studies have shown poor predictive value for CB-IgE,¹⁰⁻¹² so these conflicting results complicate the validity of CB-IgE, in predicting the development of allergy.

Our analysis demonstrated that the majority of neonates had a detectable level of IgE in their cord blood, and for about two-thirds of the CB-IgE was higher than 0.9 IU/mL cut-off value. Considering the major production of IgE antibody, which occurs after birth, it was expected that CB-IgE was undetectable, or very low in the majority of cases. One possible explanation is lower cut-off value. There are at least two cut-off values of 0.5 and 0.9 IU/mL, but there are some controversies about

TABLE 3 Influence of different factors on mothers' mean serum immunoglobulin E

Variables	N (%)	Serum IgE level, IU/mL	P value
Eczema			
Yes	16 (9.9)	218 ± 325	0.33
No	146 (90.1)	121 ± 203	
Asthma			
Yes	2 (1.2)	711 ± 754	<0.001
No	161 (98.8)	121 ± 193	
Allergic rhinitis			
Yes	13 (9.1)	233 ± 277	0.24
No	150 (90.9)	121 ± 211	
Family income (Iranian Rial)			
<5 000 000	142 (87.1)	141 ± 232	0.25
>5 000 000	18 (11)	72 ± 88	
Any allergy during pregnancies			
Yes	26 (16)	271 ± 382	0.001
No	136 (83.4)	102 ± 154	
Contact pets			
Yes	24 (14.7)	160 ± 261	0.51
No	134 (82.2)	118 ± 209	

the optimal cut-off for CB-IgE.¹³ In this study, and similar to the study of Corner et al.,¹⁴ higher cut-off value of 0.9 IU/mL was chosen to cover the possible insensitivity of an ELISA method around its lower limit of detection.

Similar to our results, some other studies¹⁵ have reported high CB-IgE level. Bønnelykke et al.¹⁵ showed that among 184 cord blood samples, 74% and more than 30% had an IgE level more than 0.01, and 0.05 kU/L, respectively. In Hernández study, 56.1% of Mexican newborns had detectable IgE,¹⁶ but inconsistent with this study, a correlation between maternal IgE levels and CB-IgE has been found.¹⁷ One-third of newborns in Liu et al.¹⁷ study had detectable IgE (≥ 0.35 kU/L by the CAP system) in their cord blood.

As far as the reason for high CB-IgE is concerned, some researchers, such as Bønnelykke et al.¹⁵ and Nabavi et al.¹⁸ suggested that maternofetal transfer might be a common cause of increased CB-IgE level.⁹ In contrast, Heinrich et al.¹⁹ believed that the fetus is able to produce IgE as early as 11 weeks.

In the present study, to prohibit error arisen from possible contamination with maternal samples, CB-IgE, and IgA were measured simultaneously, and all samples with detectable IgA were excluded. It is worth to mention that several studies have shown that no correlation exists between the concentrations of CB-IgE and IgA,²⁰ therefore, it is unlikely that maternal blood contamination can be the reason of high CB-IgE. There are several explanations for the high percentage of detectable and elevated CB-IgE in our cord blood samples. Firstly, despite the fact that there is no data about the level of CB-IgE in Iran, it might be an indicator of developing allergic disorders in the future, because of modern lifestyle, less exposure to microbes, infections, higher level of allergen exposure during pregnancy, and higher prevalence of allergic disorders in developed countries.^{21–23} Another possible reason is the epigenetic changes in Th2 activation and Th1 silencing that depends on the gene, environment, and their interactions, which may induce long-lasting altered gene expression.^{22,24} In the murine model, these changes may be transferred to the second generation by the epigenetic alteration in the germline.^{22,25} Therefore, newborns with high IgE level can be a sign for increasing prevalence of the allergic disorder in the future, but further studies are needed to evaluate its value for the prediction of atopy in children. Genetic changes in population would be too slow to account for the abrupt rising prevalence, so other factors should be considered. Interactions between genes and environment, or environment-environment intervention in the pre or postnatal period, are associated with altered gene expression or suppression, and the consequent development of allergic disease. Regardless of the genetic and

environmental effects, high CB-IgE can be a temporary phenomenon as a result of stress²⁶ or increase in the level of proinflammatory cytokines.¹⁶

In this study, no correlation was found between CB-IgE, and maternal factors, which is consistent with Wang et al. study.¹⁷ Although, there are some studies, showing the association between CB-IgE levels, and some socioeconomic factors.¹¹ This discrepancy might arise from genetic, and ethnic differences or simply because the people may not like to reveal correctly their economic, or educational status.

In the present study, there was no correlation between the level of IgE in mothers and cord blood, which is consistent with the study of Yu et al.²⁷, suggesting that because of the low level of IgE in neonates, CB-IgE may be a fetal origin, and maternal IgE cannot be transferred to the child in the uterus. In contrast, Nabavi et al.¹⁸ reported a positive correlation between mother and CB-IgE. In an agreement with Nabavi et al.,¹⁸ De Amici et al.²⁸ believed that the transfer of cytokines and chemokine through the placenta, and gaining access to the gut-associated lymphoid tissue can lead to overproduction of maternal IgE. As mentioned previously, different inclusion criteria influence different results; therefore, these conclusions are not completely consistent.

Similar to Nabavi et al.,¹⁸ and two other studies no gender differences in CB-IgE was detected, but several studies, showing higher levels of CB-IgE in males, possibly because of interaction between interleukin-13 (IL-13) and CB-IgE, which is modified by male sex.²⁹ In the current study, no significant correlation between maternal age, and total IgE, or CB-IgE has been found, which is consistent with other studies.¹⁸ Although, an insignificant decrease in CB-IgE is observed as maternal age increases.³⁰ Kaan et al.³¹ showed that an increase in maternal age was associated with an increase in neonatal CB-IgE levels.

Data about the correlation between the type of delivery and CB-IgE are controversial. Consistent with our study, no association was found in another study,³² while Nabavi et al.¹⁸ showed a positive correlation between the cesarean and elevated CB-IgE. It has reported that cesarean section increases the risk of the allergic development by 20%, through changes in gastrointestinal microbiota, which is deficient in *Lactobacillus* species.³³ In our study, the mean CB-IgE was higher in cesarean groups, but the difference was not significant, possibly because of the low number of cesarean cases, as the majority of mothers had the vaginal delivery.

In case of allergic disorders, the prevalence of different allergic disorders in pregnant mothers is consistent with our previous surveys,^{34,35} and for asthma is in line with another study in Sabzevar, which is a city in the vicinity of Khorasan.³⁶

The current study has some limitations. First, our sample size was not so large and second, some information was obtained by questionnaire, which has its own limitations, but we believe that careful planning and analysis reduce the impact of limitations.

In conclusion, the result of this study showed that CB-IgE is high in a remarkable number of samples; independent of maternal or fetal factors. This can be an alarming sign that warns the development of allergic disorders in the future, but further studies, especially cohort studies needed to reveal the exact reasons and possible factors for this increase.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHORS CONTRIBUTION

MF conceived and designed the analysis and edited the manuscript. FAN collected the data and performed the laboratory experiments. ES performed the analysis, wrote and submitted the paper. MA reviewed and edited the manuscript.

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