Review Article:
Maternal Serum IgE, Cord Blood IgE, and Children’s Allergy: A Narrative Review

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Abstract
Context: Asthma is a chronic inflammatory disorder of the respiratory system in children. Immunoglobulin E (IgE) has an important role in allergic disorders like asthma. This study aimed to review the association between maternal serum IgE and the incidence of childhood asthma.

Evidence Acquisition: Three researchers searched all articles in PubMed, Scopus, Google, and Embase databases related to maternal serum IgE, cord blood IgE, childhood asthma, and its incidence. We used keywords such as “maternal IgE, cord blood IgE, relation, association, childhood asthma, and child allergy”.

Results: We found a few related articles on maternal IgE, cord blood IgE, and childhood asthma. In total, we reviewed 11 articles. Parental atopy and allergy are the most important predictive factors for children's allergies, like asthma. IgE levels were higher in children whose mothers had higher IgE levels. Total IgE level was significantly higher in boys, compared to girls.

Conclusions: Increased maternal and cord blood IgE may be a predictive factor for the development of childhood asthma. More data are required to clarify this relationship.

1. Context
Asthma is a chronic inflammatory disorder of the respiratory system in children. The worldwide incidence of asthma in children has been increasing over the last decades (1). Cough, wheezing, and dyspnea are the most common clinical manifestations of asthmatic patients. Etiology of asthma is unclear; however, genetic and environmental factors are involved. Reversible airflow obstruction, bronchial hyper-responsiveness, mucus hypersecretion, inflammatory cell migration into the airways, and structural airway remodeling due to cytokines and chemokines are the characteristics of asthma. Some of the cytokines and chemokines are related to the severity and prediction of asthma (2, 3). There is an association between parents’ anxiety and their child's asthma severity (4). Asthma imposes a high financial burden to the patient, family, and society (5). Immunoglobulin E (IgE) is synthesized by plasma cells that are transformed from B cells.
For this process, T helper cells have an essential role in the synthesis of cytokines like IL4 and IL13. IgE has a vital role in allergic disorders such as asthma, allergic rhinitis, atopic dermatitis, urticaria, and anaphylaxis. In addition, IgE has a defensive role against parasite infections. An atopic person is defined by an increased level of allergen-specific IgE. Approximately 50% of IgE positive individuals (by skin prick test or serum assay) suffer from an allergic disorder. Studies revealed that males have higher total and allergen-specific IgE levels than females. The IgE levels generally appear to decrease in adulthood (6).

There is evidence that factors associated with early life, such as cord serum and maternal IgE level affect the later development of allergic disorders. Serum IgE might be a predictive factor for allergic diseases. There is a strong relationship between specific IgE antibodies, or total IgE and asthma (7). This study aimed to review the literature on the association between maternal serum IgE, cord blood IgE, and the incidence of childhood asthma.

2. Evidence Acquisition

In this narrative review, PubMed, Scopus, Google Scholar, and Embase databases were searched using the following keywords: “maternal IgE, cord blood IgE, children asthma, prevalence and incidence, and relation or association”. Three researchers searched all articles related to maternal serum IgE, cord blood IgE, and the incidence of childhood asthma up to September 2018. There was no time limitation to this search. All of the articles in English; abstracts, brief reports, and full-texts were included. Irrelevant studies were excluded from the review process. We found a few relative articles, and the extracted data included maternal serum IgE, cord blood IgE, and allergy, which are discussed here.

3. Results

We found 11 articles related to the association between maternal IgE, cord blood IgE, and childhood asthma. Tables 1 and 2 present the data extracted from the reviewed articles. Allergic disorders usually appear in early life. Allergy sensitization may be possible in fetal life. The relevant predictive factors are more diverse and heterogeneous. The primary criteria for the prevalence and persistence of asthma are parental asthma or atopy, sensitization to aeroallergens, and personal eczema. The atopic or allergic history of parents has been used as an essential predictor for infant disorders. The minor criteria for the prevalence and persistence of asthma are sensitization to food, wheezing apart from cold, allergic rhinitis, and eosinophilia (more than 4%) (19).

IgE levels were higher in children whose mothers had higher IgE levels, whereas IgE levels were lower in children whose mothers’ IgE levels were lower; both groups of children were breastfed. There was no significant association between feeding and IgE levels in the studied children. Inheritance and environmental factors have essential roles in IgE production. The relationship between breastfeeding and IgE levels is unclear (13).

Table 1. Quantities of cord serum and maternal IgE, association with allergy

| Author | CS Ige | Maternal IgE | Allergy | PV |
|--------|--------|--------------|---------|----|
| Shah (8) | 0.55 IU/mL | 280 IU/mL | AR, AD, in wheezing at 1 y | <0.001 |
| Canfield (9) | >150 IU/mL | >150 IU/mL | Various | 0.04 |
| Nabavi (10) | Male 1.70 IU/mL Female 1.80 | <30y 1.80 IU/mL >30y 1.50 | - | 0.001 |
| Liu (11) | >0.5 KU/L | >150 // | Eczema | 0.000 |
| Scirica (12) | 5.1 IU/mL | >115 // | Eczema | 0.05 |
| Wright (13) | 0.10-0.12 IU/mL | 113.5-118.3 // | - | |
| Croner (14) | ≥0.9 kU/L | - | 5.3% asthma | |
| Bønnelykke (15) | 0.26 (<0.1-0.71) IU/mL | 47 (17-140) IU/mL | - | P<0.001 |
| Shirakawa (16) | 0.286 kU/L | 66.25 kU/L | - | 0.07 |
| Hicks (17) | 0.38 (0.27-0.53) IU/mL | 52.7 (40.9-68.0) IU/mL | Eczema at 2 y (OR 2.6; 95% CI 1.2-5.7) | |

a. CS: Cord Serum; b. AR: Allergic Rhinitis; c. Allergic Dermatitis
Total IgE level was significantly higher in boys, compared to girls. Boys’ total IgE levels were highly correlated with both mothers’ and fathers’ total IgE levels; however, no such correlation was found in girls. Higher IgE in male cord blood may have a more gender-related effect (9). Because IgE does not cross the placenta, the cord blood IgE is produced by fetus itself. Bønnelykke et al. believed that the transfer of IgE from maternal to fetal blood might be a common cause of high cord blood IgE levels (15).

There was an association between maternal IgE and cord blood IgE levels. This association is related to many factors such as maternal sensitization, socioeconomic class, smoking, maternal age, the season of birth, race/ethnicity, neonatal gender and delivery type (10, 12).

Antenatal sensitization, the elevation of Cord Blood IgE (CBIgE), as a predictor of asthma and other allergic diseases have been studied; however, the obtained results are controversial. There are a few studies that confirmed a relationship between cord blood IgE and asthma in children. Sadeghnejad et al. argued that increased cord serum IgE is a risk factor for asthma at ages 4 and 10 years (15.2% and 12.8%, respectively) and increased aeroallergen sensitizations. Childhood asthma was more common (5-fold) in children with high cord blood IgE (more than 0.9 kU/L) (7, 14).

Maternal total IgE level (>150 KU/L) correlates with elevated cord blood IgE levels (IgE >0.5 KU/L), infant IgE levels (>40 KU/L; 80th percentile) and infant atopy. Specificity and sensitivity for the prediction of infant atopy were 83% and 34%, respectively. Fetal allergic sensitization and increased infantile eczema were more commonly associated with higher maternal IgE level (specificity: 83%, sensitivity: 34%) (14). Cord serum IgE level (IgE >0.55 IU/mL), fails to predict the infants at-risk of allergies. However, children with sensitization to mite allergens are more at risk of developing asthma (8). Aeroallergen sensitization is more prevalent in infants with a history of higher cord blood IgE level (20). Two studies reported that recurrent wheezing and asthma are more frequent in children with higher cord blood IgE (7, 21).

| Author          | CB IgE Positive Relation Factors                                                                 | CB IgE No Relation Factors                                                                 | CB IgE Negative Relation Factors                                                                 | Publishing Year |
|-----------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------|
| Scirica (12)    | Maternal history of asthma or atopy, maternal total serum IgE level of greater than 36.0 IU/mL, and maternal allergen sensitization, black and Hispanic race/ethnicity, smoking during pregnancy, male gender, residence in areas | Maternal parity, mode of delivery, gestational age, and season of birth | Maternal age greater than 27.3 years | 2007 |
| Nabavi (10)     | delivery season, type of delivery, history of allergy during pregnancy, the number of previous pregnancies, maternal age | allergic disease and history of allergic disease before pregnancy, neonatal gender, family history, | | 2103 |
| Kaan (18)       | Increase maternal age,                                                                           | -                                                                                          | -                                                                                                 | 2000 |
| Shah (8)        | Allergic Mothers, γIFNa and HDMb allergens (CS Der p1 and CS Blo t5)                           | -                                                                                          | Lower maternal IgE                                                                               | 1999 |
| Wright (13)     | Higher maternal IgE                                                                          | feeding status                                                                           | -                                                                                                 | 2009 |
| Liu (11)        | Maternal IgE levels (>150 KU/L)                                                                | Paternal IgE                                                                             | -                                                                                                 | 2003 |
| Bønnelykke (15) | Maternal IgE, cord blood IgA                                                                  | Paternal IgE                                                                             | Paternal IgE                                                                                      | 2010 |
| Shirakawa (16)  | Mother (positive allergic history and IgE of more than 400 IU/mL, siblings.                      | Hereditary effects of fathers and grandparents                                          | -                                                                                                 | 1997 |

a. IFN: Interferon; b. HDM: House Dust Mite.
Increased maternal total IgE level, maternal allergen sensitization, and residence in low-income areas were associated with detectable or increased cord blood IgE levels. However, this study suggested that maternal atopy or asthma were not significantly associated with detectable cord blood IgE (12). Kaan et al. demonstrated that higher cord blood IgE is a significant risk factor for the development of urticaria at 12 months, but not for other allergic disorders (18).

Other studies indicated that allergic disorders in childhood were not related to increased cord blood IgE (22-24). Croner et al. believed that bronchial asthma was developing 5-fold in infant and children with a higher cord blood IgE (≥0.9 kU/L). The sensitivity of cord blood IgE with a cut-off point of 0.9 kU/L was only 26%. Therefore, cord blood IgE cannot be recommended as a single screening test (14). Types of evaluation of serum total IgE and specific IgE were different in the reviewed studies. Both quantities and cut-off points of IgE were different. It is not possible to conduct a meta-analysis with this data, because the studies were heterogeneous, and the results were different. Nasal eosinophilia and increased serum IgE levels are associated with an increased risk of children developing allergic disorders (25).

4. Conclusion

Parental atopy and allergy are the most important predictive factors for childhood allergies like asthma. Most researchers believed that IgE production and allergic sensitization begin at the fetal period. Cord blood IgE levels depend on many factors, such as parental atopy, parental IgE, smoking, and aeroallergen sensitization. A great body of studies believe that higher maternal IgE could increase cord blood IgE level. Increasing maternal and cord blood IgE may be a predictive factor for the development of children’s asthma. Further data are required to clarify such relation.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information; Moreover, They were allowed to leave the study whenever they wish, and if desired, the results of the research would be available to them.

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Author’s contributions

Read and approve the final manuscript: Zeinab Nazari, Abbas Dabbaghzadeh; Performed editing the final version: Negar Ghafari.

Conflict of interest

All authors certify that this manuscript has neither been published in whole nor part nor being considered for publication elsewhere. The authors declare no conflict of interest.

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