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Maternal Serum IgE, Cord Blood IgE and Children Allergy: A narrative review

Running Title: Maternal & Cord Blood IgE and Children Allergy …

Zeinab Nazari[1], Abbas Dabbaghzadeh[2*], Negar Ghaffari[3]

[1] Department of Gynecologist and Obstetrics, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[2*] Department of Allergy and clinical Immunology, Pediatric Infectious Diseases Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

[3] Medical student, Mazandaran University of Medical Sciences, Sari, Iran

2*- Corresponding author: Abbas Dabbaghzadeh, MD., Assistant Professor of Allergy and Clinical Immunology

Postal Address: Department of Allergy and clinical Immunology, Pediatric Infectious Diseases Research Center, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari, Mazandaran Province, Iran

Tel & Fax: +98 11 33344506

Email: siamakdabbaghzade@yahoo.com

ORCID IDs of all Authors (If any):

Dr. Zeinab Nazari: 0000-0002-4178-9373

Dr. Abbas Dabbaghzadeh:0000-0000-0000-0000

Dr. Negar Ghaffari: 0000-0000-0000-0000

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Abstract

Context: Asthma is chronic inflammatory disorder of the respiratory system in childhood. IgE has an important role in allergic disorders such as asthma. The aim of this study is to review the association between maternal serum IgE and 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 incidence using key words such as maternal IgE, cord blood IgE, relation, association, childhood asthma, child allergy.

Results: We found a few related articles on the topic of maternal IgE, cord blood IgE, and childhood asthma. We reviewed 11 articles for this study. Parental atopy and allergy are more important predictive factors for children's allergies such as asthma. IgE levels was higher in children whose mothers had higher IgE levels. Total IgE level was significantly higher in boys compared to girls.

Conclusions: Increasing maternal and cord blood IgE may be a predictive factor for development of children asthma. More data is needed to clearify this relation.

Key words: Cord blood IgE, Children Asthma, Maternal serum IgE

1. Context

Asthma is a chronic inflammatory disorder of the respiratory system in childhood. 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 not clear but 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 characteristics of asthma. Some of cytokines and/ or chemokines are related to the severity of asthma and prediction of asthma (2, 3). There is an association between anxiety in parents and the severity of their child's asthma (4). Asthma disease has high a financial burden for 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 important role in the synthesis of cytokines such as IL4 and IL13. IgE has an important 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. Reports showed that males have higher total and allergen-specific IgE levels than females. The IgE levels generally appear to decrease in adulthood (6).

There are evidence that factors early in life such as cord serum and/ or maternal IgE level have effects on 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). The aim of this study is to review the literature on the association between maternal serum IgE, cord blood IgE, and incidence of children asthma.

2. Evidence Acquisition

In this narrative review, the databases including PubMed, Scopus, Google 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 children asthma up to September 2018. There was no time limitation to this search. All of articles in English; abstract, brief and full text were included. Irrelevant studies were excluded from the review process. We found a few articles and the extracted data included maternal serum IgE, cord blood IgE, and allergy 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 show the data extracted from the reviewed articles.

Table 1. Quantities of Cord Serum and maternal IgE, association with allergy

Author	CS[a] IgE	Maternal IgE	Allergy	PV

Shah[8]	0.55 IU/ml	280 IU/ml	AR[b], AD[c], 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* < .0001
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;

Table 2. Relation of cord blood IgE with multiple factors

Author	CB[a] 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 sex, 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, γIFN and HDM allergens (CS Der p1 and CS Blo t5)	-	-	2009
Wright[13]	Higher maternal IgE	feeding status	Lower maternal IgE	1999
Liu[11]	Maternal IgE levels (>150 KU/L)	Paternal IgE	-	2003
Bønnelykke[15]	Maternal IgE , cord blood IgA,	Paternal IgE	-	2010
Shirakawa[16]	mother (positive allergic history and/or IgE of more than 400 IU/ml, siblings. Frequency of parity, gender of baby and mother's age at deli	Hereditary effects of fathers and/or grandparen	-	1997

a. CB: cord blood; b. IFN: Interferon; c. HDM: house dust mite

Allergic disorders usually appear in early life. Allergy sensitization may be possible in fetal life. The predictive factors are more diverse and heterogeneous. The major criteria for the prevalence and persistent 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 important predictor for infant disorders. The minor criteria for the prevalence and persistent of asthma are sensitization to food, wheezing apart from cold, allergic rhinitis and eosinophilia (more than 4 percent) (19).

IgE levels was higher in children whose mothers had higher IgE levels whereas IgE levels were lower in children whose mother's IgE levels were lower, although both groups of children were breastfed. In this study, there was no significant association between feeding and IgE levels in the child. Inheritance and environmental factors have important roles in IgE production. The relationship between breast-feeding and IgE levels is not yet clear (13).

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 but no such correlation was found in girls. Of course, higher IgE in male cord blood may be more sex- related effect (9). Because IgE does not cross the placenta, the cord blood IgE is produced by fetus itself. Of course, 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 is 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, season of birth, race/ethnicity, neonatal gender and type of delivery (10, 12).

Antenatal sensitization, elevation of cord blood serum IgE (CBIgE), as a predictor of asthma and other allergic diseases has been studied; however, the results are controversial. There are a few studies that confirmed a relationship between cord blood IgE and asthma in children. Sadeghnejad et al showed 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 was more commonly associated with higher maternal IgE level (specificity 83% and sensitivity 34%) (14). Cord serum IgE level (IgE> 0.55 IU/mL), cannot predict the infant at-risk of allergies. But children with sensitization to mite allergens are more at risk of developing asthma (8). Aeroallergen sensitization is more common in infants with a history of higher cord blood IgE level (20). Two studies showed that recurrent wheezing and asthma are more common in children with higher cord blood IgE (7, 21).
Increased maternal total IgE level, maternal allergen sensitization and residence in low-income areas were associated with detectable or increased cord blood IgE levels. But this study showed that maternal atopy or asthma was not significantly associated with detectable cord blood IgE (12).

Kaan et al showed 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 showed 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 cut-off of 0.9 kU/l was only 26%. Therefore, cord blood IgE cannot be recommend as a single screening test (14).

Types of evaluation of serum total IgE and specific IgE were different in studies. Both quantities and cutoffs of IgE were different. It is not possible for a meta-analysis 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. Conclusions

Parental atopy and allergy are the most important predictive factors for childhood allergies such as asthma. Most of researchers believed that IgE production and allergic sensitization begin at fetal period. Cord blood IgE levels depends on many factors such as parental atopy, parental IgE, smoking and aeroallergen sensitization. More studies believe that higher maternal IgE could increase cord blood IgE level. Increasing maternal and cord blood IgE may be a predictive factor for development of children asthma. We need more data to clarify this relation.

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

References

1. Ghaffari J, Aarabi M. The prevalence of pediatric asthma in the Islamic Republic of Iran: A systematic review and meta-analysis. J Pediatr Rev. 2013; 1(1):2-11.

2.Hatami H, Ghaffari N, Ghaffari J, Rafatpanah H. Role of Cytokines and Chemokines in the Outcome of Children With Severe Asthma. J Pediatr Rev. 2019; 7(1):17-28

3. Ghaffari J, Rafiei AR, Ajami A, Mahdavi M, Hoshiar B. Serum interleukins 6 and 8 in mild and severe asthmatic patients, is it difference. Caspian Journal of Internal Medicine. 2011; 2(2):226-8.

4. Ghaffari J, Shafaat A, Yazdani Charati J, Kheradmand A. The Relationship Between Intensity of Parental Anxiety and Severity of Asthma in 5- to 15-Year-Old Children, Iran J Psychiatry Behav Sci. 2018 ; 12(1):e9361. doi: 10.5812/ijpbs.9361.

5. Ghaffari J, Hadian A, Daneshpoor SMM, Khademloo M. Asthma Burden in the Hospitalized Patients in North of Iran. Int J Pediatr. 2014;2(4.1):257-66.

6. Leffler J, Stumbles PA, Strickland DH.Immunological Processes Driving IgE Sensitisation and Disease Development in Males and Females. Int J Mol Sci. 2018; 19(6): pii: E1554. doi: 10.3390/ijms19061554.

7. Sadeghnejad A, Karmaus W, Davis S, Kurukulaaratchy R, Matthews S, Arshad S. Raised cord serum immunoglobulin E increases the risk of allergic sensitisation at ages 4 and 10 and asthma at age 10. Thorax. 2004; 59(11):936-942. doi:10.1136/thx.2004.024224.

8. Shah S, Bapat M.Cord serum screening test and the newborns allergic status. Indian Pediatr. 2009; 46(4): 295-9.

9.Canfield SM, Jacobson JS, Perzanowski MS, Mellins RB, Zemble RM, Chew GL, Goldstein IF.Total and specific IgE associations between New York City Head Start children and their parents. J Allergy Clin Immunol. 2008 Jun;121(6):1422-7, 1427.e1-4. doi: 10.1016/j.jaci.2008.03.011. Epub 2008 May 12.

10.Nabavi M, Ghorbani R, Asadi AM, Faranoush M. Factors associated with cord blood IgE levels. Asian Pac J Allergy Immunol. 2013 Jun;31(2):157-62. doi: 10.12932/AP0234.31.2.2013.

11. Liu CA, Wang CL, Chuang H, Ou CY, Hsu TY, Yang KD. Prenatal prediction of infant atopy by maternal but not paternal total IgE levels.The Journal of Allergy and Clinical Immunology, vol. 112, no. 5, pp. 899–904, 2003.

12.Scirica CV, Gold DR, Ryan L, Abulkerim H, Celedón JC, Platts-Mills TA, Naccara LM, Weiss ST, Litonjua AA. Predictors of cord blood IgE levels in children at risk for asthma and atopy. J Allergy Clin Immunol. 2007 Jan; 119(1):81-8.

13.Wright AL, Sherrill D, Holberg CJ, et al. Breast-feeding, maternal IgE, and total serum IgE in childhood. J Allergy Clin Immunol 1999; 104:589–94.

14.Croner S , Kjellman NI. 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.

15.Bønnelykke K, Pipper CB, Bisgaard H.Transfer of maternal IgE can be a common cause of increased IgE levels in cord blood. J Allergy Clin Immunol. 2010 Sep;126(3):657-63. doi: 10.1016/j.jaci.2010.06.027.

16. Shirakawa T, Morimoto K, Sasaki S, Taniguchi K, Motonaga M, Akahori W, Akahori S, Akahori T, Ohmori H, Kuroda E, Okabe K, Yugari K, Yamana M. European Journal of Epidemiology. 1997; 13(4); 395-402.

17. Hicks WB, Nageotte CG, Wegienka G, Havstad S, Johnson CC, Ownby DR, Zoratti EM.The association of maternal prenatal IgE and eczema in offspring is restricted to nonatopic mothers. Pediatr Allergy Immunol. 2011 November ; 22(7): 684–687. doi:10.1111/j.1399-3038.2011.01160.x.

18.Kaan A, Dimich-Ward H, Manfreda J, Becker A, Watson W, Ferguson A, et al. Cord blood IgE: its determinants and prediction of development of asthma and other allergic disorders at 12 months. Ann Allergy Asthma Immunol. 2000; 84: 37-42.

19. Liu AH, Covar RA, Spahn JD, Sichere SH. Childhood asthma, Chapter 144. Pp ; 1095-1115. Robert M. Kliegman ,Bonita M.D. Stanton ,Joseph St. Geme ,Nina F Schor , Richard E. Behrman , Nelson Textbook of Pediatrics, 20th edition, 2016. Philadelphia, Elsevier.

20. Wu C-C, Chen R-F, Kuo H-C. Different Implications of Paternal and Maternal Atopy for Perinatal IgE Production and Asthma Development. Clinical and Developmental Immunology. 2012; 2012:132142. doi:10.1155/2012/132142.

21.Ferguson A, Dimich-Ward H, Becker A, et al.Elevated cord blood IgE is associated with recurrent wheeze and atopy at 7 yrs in a high risk cohort.Pediatric Allergy and Immunology. 2009; 20(8): 710–713.

22. Hansen LG, Host A, Halken S,et al.Cord blood IgE. II. Prediction of atopic disease. A follow-up at the age of 18 months. Allergy. 1992; 47(4 Part 2): 397–403.

23. Edenharter G, Bergmann RL, Bergmann KE, et al.Cord blood-IgE as risk factor and predictor for atopic diseases. Clinical and Experimental Allergy. 1998; 28(6): 671–678.

24. Hide DW, Arshad SH, Twiselton R, Stevens M.Cord serum IgE: an insensitive method for prediction of Atopy. Clinical and Experimental Allergy. 1991; 21(6): 739–743.

25.Wang QP ,Wu KM , Li ZQ , Xue F, Chen W, Ji H, Wang BL. Association between Maternal Allergic Rhinitis and Asthma on the Prevalence of Atopic Disease in Offspring. International Archives of Allergy and Immunology. 2011; 157(4): 379–386. doi:10.1159/000328789.