

## EDITORIAL

# Clinical & Experimental Allergy

## Cord blood IgE: fetal or maternal?

This editorial discusses the findings of the paper in this issue by Bundhoo et al. [26], pp. 1085–1098.

L. A. P. M. Meulenbroek<sup>1</sup> and L. M. J. Knippels<sup>1,2</sup>

<sup>1</sup>Department of Immunology, Nutricia Research, Utrecht and <sup>2</sup>Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, The Netherlands

Since 1970s, cord blood IgE (CB-IgE) has been investigated as a predictive marker for allergic diseases [1–15]. Whereas most studies found an association between elevated CB-IgE levels and the risk for allergic symptoms later in life [1–10], others only showed a correlation with elevated IgE levels [11–14] or no correlation at all [15]. Even if there was an association between CB-IgE and allergic symptoms, the predictive value of CB-IgE was often low [2–4, 6, 10].

In addition to its role as predictive marker, also the origin of CB-IgE has been intensively discussed during the years. In many studies, a strong association between total maternal IgE levels and CB-IgE levels was shown [16–21]. However, it is debated whether this is due to maternofetal transfer of IgE or due to fetal IgE production, which may be influenced by maternal factors.

Previous studies have indicated that the fetus may produce IgE [22, 23]. In 1973, Miller et al. [22] showed that cultured embryonic and fetal tissues were able to synthesize IgE. This synthesis could already be observed after 11 weeks of gestation. These data were confirmed by Lima et al. [23] who found VDJC $\epsilon$  transcripts, which are indicative for IgE production, in fetal cells of second- and third-trimester samples, although they indicated that these IgE-producing cells were rare until 9 months after birth. Moreover, two studies have shown that the association between maternal IgE and CB-IgE depends on the specificity of the antibody [24, 25]. Whereas food allergen-specific CB-IgE levels were highly associated with maternal food allergen-specific IgE levels, there was no association for IgE specific for

inhalant allergens. This scenario is more likely in case of fetal IgE production than with maternofetal transfer. In addition, Pfefferle et al. [24] found allergen-specific IgE in newborns while that specificity was not detected in their mothers, which also suggests *in utero* IgE production.

On the other hand, Bonnelykke et al. and Bertino et al. [18, 20] indicated that the sensitization profile in maternal and cord blood serum is highly comparable. Moreover, in a second study, Bonnelykke et al. [19] showed that the ratio between allergen-specific and total IgE in the mother is highly correlated with the ratio in cord blood. Based on this ratio and allergen-specific CB-IgE levels, the total CB-IgE levels could be correctly estimated. Furthermore, in these infants, CB-IgE levels did not correlate with IgE levels at an age of 6 months. Although these data suggest that IgE may be obtained by maternofetal transfer, the mechanism of this transfer is still unclear. So far, it is generally believed that only IgG is able to pass the placental barrier, and therefore, it is suggested that maternal IgE is obtained by the fetus due to contamination, either during sampling or during late pregnancy by small placental bleedings [18].

In contrast to this belief, Bundhoo et al. [26] show in an interesting article in this issue of *Clin Exp Allergy* that IgE can be transported across the placenta. This transport is mediated by IgG autoantibodies directed against IgE. The autoantibodies form complexes with IgE and bind to the FcRn receptor, which facilitates the transport of the complexes across the placenta to the fetus. The authors included 152 allergic and non-allergic pregnant women and their full-term infants and determined the levels of IgE, IgG anti-IgE and anti-IgE/IgE complexes in maternal and cord blood serum. They found that IgG autoantibodies are present in both allergic and non-allergic pregnant women, but the levels are only correlated to IgE levels in pregnant women with a history of allergic disease. Regardless of the allergic status, the level of anti-IgE/IgE complexes in

### Correspondence:

L. A. P. M. Meulenbroek, Department of Immunology, Nutricia Research, PO Box 80141, 3508 TC Utrecht, The Netherlands.  
E-mail: laura.meulenbroek@danone.com

Cite this as: L. A. P. M. Meulenbroek, L. M. J. Knippels, *Clinical & Experimental Allergy*, 2015 (45) 1012–1014.

 This logo highlights the Editorial article on the cover and the first page of the article.

maternal serum was highly correlated with the level in cord blood. In addition to the levels of IgG autoantibodies and anti-IgE/IgE complexes, the authors analysed the isotypes of the anti-IgE antibodies in the complexes. These data showed that the levels of IgG1-containing complexes were significantly higher in allergic mothers compared with non-allergic mothers. A similar trend was seen for the infants.

Interestingly, Bundhoo et al. showed that when depleting IgG from cord blood serum with protein A, almost all IgE antibodies were removed indicating that most of the IgE antibodies found in cord blood serum were bound to anti-IgE. Only 6% of total CB-IgE antibodies was free. The authors suggest that this residual fraction may be produced by the fetus. In addition, Bundhoo et al. showed in an *in vitro* binding assay that anti-IgE/IgE complexes were still able to bind to FcεRIα. Moreover, in the samples of a small group of infants, both from allergic and non-allergic mothers, they determined the percentage of cord blood basophils with surface-bound IgE. While in infants from allergic

mothers, CB-IgE levels were correlated with the percentage of basophils with bound IgE, the authors found no correlation in infants from non-allergic mothers. The clinical implications of the binding to cord blood basophils need to be further investigated.

In conclusion, Bundhoo et al. show for the first time that IgE can be transported over the placental barrier as anti-IgE/IgE complexes. These findings may have great implications as in previous studies it was often suggested that specific maternofetal transport of IgE was not possible. Moreover, the authors found differences in complex composition and complex binding to basophils in infants from allergic and non-allergic mothers. Therefore, the predictive value of anti-IgE/IgE complexes or free IgE antibodies should be investigated to determine whether these factors might be suitable to use as predictive markers for allergic diseases.

**Conflict of interest:** The authors declare no conflict of interest.

## References

- Wen H-J, Wang Y-J, Lin Y-C et al. Prediction of atopic dermatitis in 2-yr-old children by cord blood IgE, genetic polymorphisms in cytokine genes, and maternal mentality during pregnancy. *Pediatr Allergy Immunol* 2011; 22:695–703.
- Vogt H, Bråbäck L, Zetterström O et al. Asthma heredity, cord blood IgE and asthma-related symptoms and medication in adulthood: a long-term follow-up in a Swedish birth cohort. *PLoS ONE* 2013; 8:e66777.
- Pesonen M, Kallio MJT, Siimes MA et al. Cord serum immunoglobulin E as a risk factor for allergic symptoms and sensitization in children and young adults. *Pediatr Allergy Immunol* 2009; 20:12–8.
- Nissen SP, Kjaer HF, Høst A, Nielsen J, Halken S. Can family history and cord blood IgE predict sensitization and allergic diseases up to adulthood? *Pediatr Allergy Immunol* 2014; 26:42–8.
- 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. *Pediatr Allergy Immunol* 2009; 20:710–3.
- Croner S, Kjellman NI, Eriksson B, Roth A. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 1982; 57:364–8.
- Orgel HA, Hamburger RN, Bazalal M et al. Development of IgE and allergy in infancy. *J Allergy Clin Immunol* 1975; 56:296–307.
- Duchateau J, Casimir G. Neonatal serum IgE concentration as predictor of atopy. *Lancet* 1983; 1:413–4.
- Michel FB, Bousquet J, Greillier P, Robinet-Levy M, Coulomb Y. Comparison of cord blood immunoglobulin E concentrations and maternal allergy for the prediction of atopic diseases in infancy. *J Allergy Clin Immunol* 1980; 65:422–30.
- Hansen LG, Halken S, Høst A, Møller K, Osterballe O. Prediction of allergy from family history and cord blood IgE levels. A follow-up at the age of 5 years. Cord blood IgE. IV. *Pediatr Allergy Immunol* 1993; 4:34–40.
- Shah PS, Wegienka G, Havstad S et al. The relationship between cord blood immunoglobulin E levels and allergy-related outcomes in young adults. *Ann Allergy Asthma Immunol* 2011; 106:245–51.
- Tariq SM, Arshad SH, Matthews SM, Hakim EA. Elevated cord serum IgE increases the risk of aeroallergen sensitization without increasing respiratory allergic symptoms in early childhood. *Clin Exp Allergy* 1999; 29:1042–8.
- Edenharter G, Bergmann RL, Bergmann KE et al. Cord blood-IgE as risk factor and predictor for atopic diseases. *Clin Exp Allergy* 1998; 28:671–8.
- Bergmann RL, Edenharter G, Bergmann KE et al. Predictability of early atopy by cord blood-IgE and parental history. *Clin Exp Allergy* 1997; 27:752–60.
- Sybilski AJ, Doboszynska A, Samolinski B. Prediction of atopy in the first year of life using cord blood IgE levels and family history. *Eur J Med Res* 2009; 14(Suppl 4):227–32.
- Liu C-A, Wang C-L, Chuang H et al. Prenatal prediction of infant atopy by maternal but not paternal total IgE levels. *J Allergy Clin Immunol* 2003; 112:899–904.
- Cederqvist LL, Caprio RE, Rappaport I et al. Correlation between maternal and fetal immunoglobulin E levels. *Obstet Gynecol* 1984; 63:674–6.
- Bønnelykke K, Pipper CB, Bisgaard H. Sensitization does not develop in utero. *J Allergy Clin Immunol* 2008; 121:646–51.
- 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; 126:657–63.
- Bertino E, Bisson C, Martano C et al. Relationship between maternal- and

- fetal-specific IgE. *Pediatr Allergy Immunol* 2006; **17**:484–8.
- 21 Sverremark Ekstrom E, Nilsson C, Holmlund U et al. IgE is expressed on, but not produced by, fetal cells in the human placenta irrespective of maternal atopy. *Clin Exp Immunol* 2002; **127**:274–82.
- 22 Miller DL, Hiravonen T, Gitlin D. Synthesis of IgE by the human conceptus. *J Allergy Clin Immunol* 1973; **52**:182–8.
- 23 Lima JO, Zhang L, Atkinson TP et al. Early expression of iepsilon, CD23 (FepsilonRII), IL-4Ralpha, and IgE in the human fetus. *J Allergy Clin Immunol* 2000; **106**:911–7.
- 24 Pfefferle PI, Sel S, Ege MJ et al. Cord blood allergen-specific IgE is associated with reduced IFN-gamma production by cord blood cells: the Protection against Allergy-Study in Rural Environments (PASTURE) Study. *J Allergy Clin Immunol* 2008; **122**:711–6.
- 25 Kamemura N, Tada H, Shimojo N et al. Intrauterine sensitization of allergen-specific IgE analyzed by a highly sensitive new allergen microarray. *J Allergy Clin Immunol* 2012; **130**: 113–21.e2.
- 26 Bundhoo A, Pavaglio S, Rafti E et al. Evidence that FcRn mediates the transplacental passage of maternal IgE in the form of IgG anti-IgE/IgE immune complexes. *Clin Exp Allergy* 2015; **45**:1085–1098.