

# Evaluation of in utero sensitization by screening antigen-specific immunoglobulin E levels in umbilical cord blood

Tamay Gürbüz, Burcu Karakol, Zehra Esra Önal, Yonca Tabak, Çağatay Nuhoglu, Ömer Ceran

Department of Pediatrics, Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey  
Head of the Department: Çağatay Nuhoglu MD, Assoc. Prof.

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## Abstract

**Introduction:** The incidence of asthma and atopic reactions is increasing worldwide. Previous reports have suggested that maternal exposure to allergens during pregnancy may have potential effects on allergic sensitization in infants.

**Aim:** To evaluate the effects of maternal exposure to environmental allergens during pregnancy on in-utero sensitization.

**Material and methods:** Two hundred mothers and their infants were analyzed in this cross-sectional study. Mothers were given a questionnaire that had a series of questions to evaluate the maternal allergic status and environmental exposures during pregnancy. Plasma specific immunoglobulin E (IgE) levels to pets, grass, food (nuts) of all mothers and their infants were analyzed by an immune-enzymatic assay.

**Results:** There was no significant correlation between plasma specific IgE positivity in mothers, with regard to keeping indoor domestic pets, living in grass habitat, eating nuts in diet. A significant correlation was found between specific IgE presence in mothers and allergic reactions; however, there was no correlation between plasma specific IgE positivity of mothers and infants.

**Conclusions:** We concluded that prenatal maternal sensitivity to environmental allergens could not be evaluated as a predictive factor for in-utero sensitization.

**Key words:** in-utero sensitization, umbilical cord blood, maternal immunoglobulin E.

## Introduction

The incidence of asthma and atopic reactions is increasing worldwide. Previous reports have suggested that maternal exposure to allergens during pregnancy may have potential effects on allergic sensitization in infants. Over the last several years, fetal exposures to environmental determinants such as tobacco, air pollutants, house dust mites and domestic pets have been investigated as potentially critical factors in the development of allergic diseases [1–5].

## Aim

In this study, we analyzed maternal exposure to environmental factors, such as presence of domestic pets, living in the rural environment, eating allergenic foods (nuts) during pregnancy and history of allergic reactions.

Here, we evaluated plasma specific immunoglobulin E (IgE) levels of mothers and cord blood specific IgE levels of infants following delivery, to determine a potential relationship between environmental exposure and allergic sensitization early in life.

## Material and methods

This study was a prospective birth cohort study that was approved by the Local Ethics Committee. The study included 200 infants born in the Department of Obstetrics of the Haydarpaşa Numune Training and Research Hospital during 2012, along with their respective mothers. Mothers were divided into two groups of specific IgE positive and negative mothers. The criteria for positivity were defined as a level of more than 0.35 IU/ml. Additionally, mothers were given questionnaires to investi-

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**Address for correspondence:** Tamay Gürbüz, Department of Pediatrics, Haydarpaşa Numune Training and Research Hospital, Tıbbiye Cad. No:40 Üsküdar, 34668 Istanbul, Turkey, phone: +90 5326372550, e-mail: tamayoz1610@gmail.com

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gate family history of allergy, allergic rhinitis, asthma, while also inquiring about domestic pets kept, living in the rural area, and allergenic food (nuts) eaten during pregnancy.

Umbilical blood samples of infants were obtained by puncture of the umbilical veins; samples were then centrifuged, and plasma was frozen and stored at  $-70^{\circ}\text{C}$ . Total concentrations of maternal IgE were determined by measuring chemiluminescence with a sandwich-type assay, using an Elecsys 2010 analyzer. Allergen specific IgE of infants was also assessed by utilizing an antibody kit specific to cats, grass and nuts.

Specific IgE was assessed using a non-competitive immune-enzymatic assay. Specific IgE concentrations over a threshold level of 0.35 IU/ml were accepted as positive [6].

### Statistical analysis

All levels of significance were calculated by using tests for independence of two qualitative variables and the Mann-Whitney *U* test.

### Results

According to information about the infants in the study, no correlation between maternal specific IgE positivity and gender, birth weights, and gestational ages of infants was observed ( $p < 0.05$ ) (Table 1).

With regard to the presence of domestic pets, only 4.1% of mothers (4 of 97) who had positive maternal specific IgE levels kept domestic pets at home and likewise, only 5.8% of mothers (6 of 103) who had negative maternal specific IgE levels kept domestic pets as well (Table 2).

With regard to living in the rural area (grass habitat), only 34% of mothers (33 of 97) who had positive maternal specific IgE levels lived in the grass habitat and likewise, only 27.2% of mothers (28 of 103) who had negative maternal specific IgE levels lived in the rural areas as well (Table 2).

With regard to eating allergenic foods (nuts), only 61.9% of mothers (60 of 97) who had positive maternal

**Table 1.** Correlation of maternal specific IgE positivity with infant related factors

Parameter	Maternal specific IgE		Value of <i>p</i>
	Negative	Positive	
Gestational age, mean $\pm$ SD [weeks] <sup>a</sup>	38.87 $\pm$ 1.09	38.75 $\pm$ 1.27	0.472
Birth weight, mean $\pm$ SD [g] <sup>a</sup>	3298.80 $\pm$ 397.22	3372.06 $\pm$ 379.84	0.185
Gender, <i>n</i> (%) <sup>b</sup> :			
Male	52 (50.5)	49 (50.5)	0.997
Female	51 (49.5)	48 (49.5)	

<sup>a</sup>Student *t* test; <sup>b</sup> $\chi^2$  test. SD – standard deviation.

**Table 2.** Evaluation of environmental factors and maternal allergic reactions related with maternal specific IgE levels

Parameter		Maternal specific IgE		Value of <i>p</i>
		Positive	Negative	
Domestic pets, <i>n</i> (%)	Present	4 (4.1)	6 (5.8)	0.581
	Absent	93 (95.9)	97 (94.2)	
Tobacco smoke, <i>n</i> (%)	Present	33 (34)	28 (27.2)	0.294
	Absent	64 (66)	75 (72.8)	
Passive smoking, <i>n</i> (%)	Present	60 (61.9)	69 (67)	0.448
	Absent	37 (38.1)	34 (33)	
Maternal atopic dermatitis, <i>n</i> (%)	Present	12 (12.4)	7 (6.8)	0.179
	Absent	85 (87.6)	96 (93.2)	
Maternal conjunctivitis, <i>n</i> (%)	Present	13 (13.4)	6 (5.8)	0.068
	Absent	84 (86.6)	97 (94.2)	
Maternal allergic rhinitis, <i>n</i> (%)	Present	15 (15.5)	4 (3.9)	0.005 <sup>†</sup>
	Absent	82 (84.5)	99 (96.1)	
Maternal bronchial asthma, <i>n</i> (%)	Present	10 (10.3)	3 (2.9)	0.034 <sup>*</sup>
	Absent	87 (89.7)	100 (97.1)	

$\chi^2$  test was performed. <sup>\*</sup> $p < 0.05$ , <sup>†</sup> $p < 0.01$ .

**Table 3.** Correlation between neonatal specific IgE levels and maternal specific IgE positivity

Neonatal specific IgE	Maternal specific IgE		Value of <i>p</i>
	Positive	Negative	
Positive, <i>n</i> (%)	1 (0.5)	0	0.001 <sup>†</sup>
Negative, <i>n</i> (%)	96 (48)	103 (51.5)	

McNemar test was performed; <sup>†</sup>*p* < 0.01.

specific IgE levels had nuts in their diets and likewise, only 67% of mothers (69 of 103) who had negative maternal specific IgE levels had nuts in their diets as well (Table 2). There was no significant correlation between maternal plasma specific IgE positivity and keeping domestic pets, living in grass habitat, and eating allergenic foods (nuts) (*p* > 0.05) (Table 2).

Fifteen of 97 mothers (15.5%) with positive maternal specific IgE levels showed significantly higher percentages of allergic rhinitis. Furthermore, 10.3% (10 of 97) mothers with positive maternal specific IgE levels had higher percentages of asthma. There was a statistically significant correlation between positivity of maternal specific IgE levels and maternal asthma, maternal allergic rhinitis (*p* < 0.05) (Table 2). But there was no significant correlation between maternal specific IgE positivity and maternal conjunctivitis, maternal atopic dermatitis (*p* > 0.05) (Table 2).

Only one infant born from the mother with positive specific IgE levels (1 of 97) revealed a positive cord blood specific IgE level. All of infants born from mothers with negative maternal specific IgE levels showed negative neonatal plasma specific IgE levels. Only in 1 case, plasma specific IgE levels of the mother and infant seemed to match. There was no correlation between plasma specific IgE levels of mothers and infants (*p* > 0.05) (Table 3).

## Discussion

Currently, there is a high incidence of allergy worldwide, perhaps related to increasing environmental pollution, and changing life-styles with respect to hygienic and nutritional status [7, 8]. An infant is defined as a high-risk one if there is at least one first-degree relative (parent or sibling) with documented allergic disease. This definition is based on a consensus among several committees representing the European Society for Pediatric Allergology and Clinical Immunology (ESPACI) and the American Academy of Pediatrics [9].

In this study, we investigated whether life-style and maternal allergen sensitization status influenced in utero allergen sensitization. We analyzed allergen-specific IgE levels in cord blood samples of infants and in plasma of their mothers. Mothers were asked about their environmental exposure to grass, eating allergenic

foods (nuts), indoor pet keeping and presence of allergic reactions. Based on these environmental factors during pregnancy, we evaluated potential effects on intrauterine sensitization.

The most common immunologic abnormalities detected early in life among children who went on to have asthma included diminished interferon  $\gamma$  (IFN- $\gamma$ ) production and reduced T Helper 2 responses [10].

Sybilski *et al.* analyzed 173 newborns and mothers to evaluate the effects of environmental factors on their total IgE levels and on the presence of selected antigen specific IgE in umbilical cord blood plasma. In this study, 519 assays (173  $\times$  3) for antigen specific IgE were performed [11]. Most previous reports point to the presence of maternal atopic diseases in causing elevated levels of IgE in umbilical cord blood. In this study, total cord blood IgE levels were significantly higher in male infants, compared with females. Additionally, the number of siblings (family size) correlated with a decrease in cord blood IgE levels. Maternal contact with a domestic cat during pregnancy resulted in increased levels of IgE against grass, cereals and food. Sybilski *et al.* found a significant association between the level of antigen specific IgE against domestic dust mites and maternal tobacco smoking in which they detected specific IgE in 34 newborns (6.6% with a positive test). Of the 40 positive tests, 20 were positive to grass, 11 to house dust mites and 9 to food. No correlations were noted between family history of allergy and the presence of a specific immunoglobulin. There was no statistically significant correlation between antigen-specific IgE in umbilical cord plasma and pregnancy associated factors [11]. The results of this study were similar to ours because they showed no correlation between pregnancy, environmental factors and the presence of IgE in umbilical cord plasma.

In a study conducted in the USA, Peters *et al.* examined 301 mother-infant pairs to evaluate the effects of prenatal and early life social and physical environmental exposures. Elevated prenatal dust mite levels increased cord blood IgE levels by 29%. Continuous dust mite concentrations were associated with a significant increase in cord blood IgE levels. These results demonstrated that maternal prenatal exposure to household allergens might affect cord blood IgE levels [12]. However, in our study, we did not find a correlation between maternal plasma specific IgE and cord blood IgE levels of infants. Maternal sensitization did not affect in utero sensitization.

Keil *et al.* examined the interaction of passive smoking and allergic sensitization during the first ten years of life. In their study, 18% of the children were exposed to regular maternal smoking since pregnancy and 43% to paternal smoking and irregular maternal smoking. They concluded that maternal smoking was a strong risk factor for allergic sensitization and asthma symptoms during the first 10 years of life, but only in children with allergic parents [13]. Our study did not show that mater-

nal environmental factors influenced in utero sensitization of infants, but we could not follow the infants for a long time.

Lannerö *et al.* analyzed 4089 families with children for environmental factors and symptoms of allergic disease. They found no evident association between maternal smoking during pregnancy and risk of IgE sensitization. However, a different study showed that there was an increased risk of sensitization to inhalant and/or food allergens among children exposed to environmental tobacco smoke [14]. We could not analyze the effect of smoking on in utero sensitization, because none of mothers in this study smoked during pregnancy.

Aichbhaumik *et al.* investigated whether maternal exposure to pets affected the cord blood IgE level. A total of 1258 mothers were evaluated by demographic and allergic history characteristics. Cord IgE data were also available from 1049 infants. The presence of indoor cats or dogs, maternal smoking during pregnancy, maternal atopy, birth weight and gestational age were analyzed. When they investigated for any effect of indoor pet exposure on umbilical cord IgE levels, they found that maternal exposure to indoor dogs or cats during pregnancy was associated with lower cord blood IgE levels [15]. Their findings were similar to those of Kerkhof *et al.*, who measured IgE levels by heel prick from 1027 infants in the Netherlands during the first week of life to assess IgE to specific prenatal exposures, including pets. They determined that when dogs or cats were present in the home during pregnancy, there was a lower likelihood of having a detectable level of total IgE at birth. In addition to the effects of pet keeping on attenuating total and allergen specific IgE, there are many reports suggesting that pets decrease the risk of clinical atopy-related disorders. A predictor of the elevated cord blood IgE level in their study, as well as in others, was positive for family history of atopy and allergic disease [15]. In this study, the presence of indoor cats did not affect in utero sensitization. Infants did not reveal higher specific IgE levels, although pets were kept indoors, mothers lived in rural areas or ate allergenic foods (nuts) during the intrauterine period. This study showed no correlation between infants cord blood levels of specific IgE and maternal specific IgE positivity.

Bønnelykke *et al.* examined the relevance of allergen-specific IgE in cord blood to sensitization in early infancy. Inhalant and food allergen specific IgE in cord blood was analyzed and compared with specific IgE in infant blood at 6 months of age. Allergen specific IgE levels against inhalant allergens were detected in 14% of cord blood samples. Specific IgE in cord blood completely matched specific IgE in maternal blood, with respect to allergen specificity. Allergen specific IgE in cord blood did not reflect intrauterine sensitization but seemed to be a result of maternal-fetal transfer of IgE [16]. Our study

was supported by this study which did not confirm intrauterine sensitization.

Rowe *et al.* suggested that the development of atopic sensitization to peanut occurs in the postnatal period rather than in utero. T-cell cytokine responses and antibody assays of peanut-specific IgE and IgG were investigated in a cohort of 200 high-risk infants at birth and 6, 12 and 24 months of age. No association was found between cord blood T-cell reactivity and subsequent postnatal IgE sensitization at birth, whereas an increasingly strong association developed between these parameters at 6 months of age [17]. In our study, maternal atopic sensitization did not reveal IgE sensitization in the cord blood of infants, but we could not perform a subsequent analysis of the infants' IgE levels at the 6-month follow-up.

A 2008 report sponsored by the American Academy of Pediatrics concluded that there was insufficient evidence to recommend that a woman whose child is at high-risk of allergic disease because of documented parental allergic disease should avoid environmental allergens for the purpose of preventing allergic disease [18].

Depner *et al.* investigated whether allergen specific memory was primed prenatally and whether it would cause persistent immunologic sensitization. The Protection against Allergy: Study in Rural Environments (PASTURE) birth control study included 793 children from rural regions of 5 European countries. Specific IgE levels for 6 food and 13 common inhalant allergens were analyzed from cord blood samples and compared with blood samples collected once the children turned 1 year old. Sensitization was more common in the 1-year-old children than at birth for nearly all specificities. Persistent sensitization to the same allergen was rare (1%), whereas transient sensitization (only at birth, 11%) and specific incidents of sensitization (only at 12 months, 34%) were more common. Associations of transient sensitization with maternal sensitization differed with the allergen specificities, IgE sensitization pattern, change between birth and 12 months and were related to maternal and environmental influences [19]. Our study did not confirm in utero sensitization because antigen specific IgE was not determined in the cord blood samples of infants.

Fusaro *et al.* demonstrated that maternal allergen intake during pregnancy could induce a tolerance state in the offspring. The results revealed that early antigen exposure in utero could induce fetal tolerance, whereas antigen exposure following birth facilitated neonatal allergen sensitization [20]. The data of our study demonstrated that maternal sensitization during pregnancy did not affect in utero sensitization.

Kamemura *et al.* investigated food and inhalant allergen specific IgE antibodies in 92 paired cord blood samples of neonates and mothers in order to determine if allergic sensitization starts in utero. They found that food allergen specific IgE antibodies were detected more

often than inhalant allergen specific IgE antibodies in cord blood [21]. Our study did not support the presence of in utero sensitization affected by the maternal environmental factors.

Illi *et al.* examined the effects of early environmental exposures on the development of asthma and atopy. Allergens in house dust were measured at 3 months. Atopic sensitization was assessed at 1 and 5 years. 526 German children were followed from 1 to 5 years of age. They concluded that factors affecting in utero environment, such as maternal atopy and bacterial exposure in pregnancy or early life may immunomodulate or inhibit the development of asthma and atopy in childhood [22].

Here, we observed that infants born from allergic mothers who had high specific IgE levels showed no allergic sensitization. One limitation of this study was that we could not evaluate whether the sensitization patterns of infants would change during a 1-year follow up. In this study, we wanted to evaluate the immunological responses of neonates at risk of atopy, in relation to specific intrauterine exposures to environmental allergens; however, we did not find a relationship between maternal allergic status and environmental factors on intrauterine sensitization. We feel that future comprehensive studies that include more subjects can help to evaluate the influence of maternal exposure to allergens on intrauterine sensitization.

### Conflict of interest

The authors declare no conflict of interest.

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