

# Sensitization does not develop *in utero*

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**Background:** Intrauterine sensitization has been suggested to play a role in the development of atopic disease in children, and this has led to current guidelines recommending allergen avoidance during pregnancy.

**Objective:** To investigate the relevance of allergen-specific IgE in cord blood to sensitization in early infancy and the origin of such IgE.

**Methods:** Inhalant and food allergen-specific IgE in cord blood was analyzed and compared with specific IgE in infant blood at 6 months of age and in parental blood. Cord blood IgA was measured to detect maternal blood contamination of cord blood.

**Results:** Allergen-specific IgE, primarily against inhalant allergens, was detected in 14% of cord blood samples. However, corresponding specific IgE was not found in infant blood at 6 months of age. Specific IgE in cord blood completely matched specific IgE in maternal blood with respect to allergen specificity, level of specific IgE, and ratio of total IgE/specific IgE. Finally, there was a correlation between specific IgE and IgA in cord blood.

**Conclusion:** Allergen-specific IgE in cord blood does not reflect intrauterine sensitization but seems to be the result of transfer of maternal IgE to the fetus. (*J Allergy Clin Immunol* 2008;121:646-51.)

**Key words:** Sensitization, cord blood, infant, intrauterine, atopy

It has been suggested that atopic sensitization may occur *in utero*.<sup>1</sup> This idea finds some support from reports of fetal cells being capable of producing IgE from the second trimester<sup>2</sup> and some association between total IgE levels in cord blood and the development of atopic disease in children.<sup>3-5</sup> Likewise, allergen-specific IgE<sup>6</sup> and allergen-specific T-cell memory<sup>7,8</sup> in

cord blood have been reported to predict atopic disease. Intrauterine allergen exposure has been documented in cord blood and amniotic fluid, making intrauterine sensitization a theoretical possibility.<sup>9</sup>

The concept of intrauterine sensitization has led to current guidelines recommending peanut avoidance during pregnancy by atopic women,<sup>10,11</sup> although studies of inhalant<sup>12</sup> and food allergen<sup>13,14</sup> avoidance during pregnancy have shown no effect on sensitization in infancy.

The aim of this study was to investigate intrauterine sensitization measured by allergen-specific IgE in cord blood. We studied the clinical relevance of allergen-specific IgE in cord blood by comparing with allergen-specific IgE in the 6-month old infant. We then studied its origin hypothesizing materno-fetal transfer as the source of specific IgE in cord blood. Evidence in favor of this hypothesis would be present if fetal specific IgE closely matched maternal specific IgE with respect to allergen specificity, level of IgE, and ratio of total/specific IgE, and if there was a correlation between specific IgE and IgA in cord blood indicating maternal blood contamination.

## METHODS

The Copenhagen Prospective Study on Asthma in Childhood (COPSAC) is a prospective birth cohort study of 411 children born of mothers with verified asthma, the recruitment of whom was previously described in detail.<sup>15</sup> The study was conducted in accordance with the guiding principles of the Declaration of Helsinki and approved by the Ethics Committee for Copenhagen (KF 02-118/98) and the Danish Data Protection Agency (1998-1200-359). Before enrollment, informed consent was obtained from parents. Data validity was assured by compliance with Good Clinical Practice guidelines and quality control procedures.

Midwives received written information instructing them to collect cord blood by needle puncture of the umbilical cord vein. Blood was further collected from the infants at 6 months of age and from parents after recruitment to the study. Serum and plasma were stored at  $-80^{\circ}\text{C}$  until analysis.

IgE antibody levels were determined via the ImmunoCAP assay<sup>16</sup> (Phadia AB, Uppsala, Sweden). Cord blood samples and infant blood at 6 months of age were analyzed for level of total IgE, specific IgE against milk and egg allergens, and cumulative level of specific IgE against a panel of common inhalant and food allergens (Phadia AB, Uppsala, Sweden).<sup>17</sup> Samples positive for Phadiatop Infant were further analyzed for specific IgE against relevant single allergens from this panel (*Dermatophagoides pteronyssinus*, cat dander, dog dander, birch, timothy, mugwort, and peanut). The detection limit for total and specific IgE was 0.1 IU/mL.<sup>18</sup> Specific IgE results in cord blood were double-tested. IgE levels in parental blood were analyzed similarly after screening with Phadiatop. Detection limits for total and specific IgE in parental blood were 2 IU/mL and 0.35 IU/mL, respectively.

Cord blood samples were analyzed for total IgA by using a sensitive ELIA assay designed to measure very low levels of IgA (detection limit, 0.1  $\mu\text{g/L}$ , analyzed by Phadia AB).

## Statistical analyses

We modeled the underlying association between specific IgE and IgA in cord blood by linear regression and by assuming an underlying normal distribution. From this we extracted a model for the observed values

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accounting for detection limits. Similar models were analyzed for the association between specific IgE in cord blood and maternal blood for each level of cord blood IgA and for the association between specific IgE in cord blood and paternal blood. Maximum likelihood estimates with asymptotic 95% Wald CIs were calculated, and likelihood ratio tests for hypotheses were performed. The association between ratios of total/specific IgE in cord blood and maternal blood was analyzed by simple linear regression analysis. All values were transformed on a logarithmic scale.

## RESULTS

Corresponding cord blood and maternal samples were available for 243 children. A paternal blood sample was available in 220 of these. Sixty-three percent of mothers and 36% of fathers were sensitized to inhalant allergens.

Specific IgE against mixed allergens (Phadiatop Infant) was found in 34 (14%) of all cord blood samples. Twenty-two samples (2 had insufficient plasma for further analyses) had detectable levels of specific IgE against single allergens. Together these 22 samples had 36 positive single-allergen tests, of which 35 were against inhalant allergens and 1 was against peanut. Specific IgE against milk or egg was not detectable in any of the 243 cord blood samples.

IgA was detectable in 239 (98%) of cord blood samples, and the median level (range) was 10.8 (0-7267)  $\mu\text{g/L}$ .

### Specific IgE in infant blood at 6 months of age

Twenty-one of 22 infants with specific IgE against single allergens in cord blood also had a blood sample taken at 6 months of age. None of the specific IgE against single allergens found in cord blood was reproduced in the infant's blood at 6 months of age.

### Specific IgE in cord blood and mother's blood

Cord blood IgE against mixed allergens was found only in offspring of mothers with corresponding specific IgE and not in any of the 92 infants of nonsensitized mothers. Similarly, all 36 positive single-allergen tests in cord blood corresponded to a positive test in maternal blood.

Comparing patterns of specific IgE against single allergens in the 22 individual pairs of cord blood and mother's blood showed that the cord blood pattern perfectly matched the maternal pattern with respect to both allergen specificity and relative levels of specific IgE (Fig 1). The specific IgE with highest levels in maternal blood was consistently found in cord blood. Complementary to this, specific IgE with lower maternal levels was not always detectable in cord blood as would be expected because of the detection limit in cord blood.

The level of specific IgE in cord blood (IgE against mixed allergens or sum of specific IgE against single allergens) was positively correlated to the level of cord blood IgA ( $P < .0001$ ; Figs 2 and 3, respectively). However, with IgA levels below 25  $\mu\text{g/L}$ , there seemed to be no such correlation (by visual inspection of Figs 2 and 3, respectively). Forty-four percent and 35% of cord blood samples with detectable specific IgE had IgA levels below 25  $\mu\text{g/L}$  and median level (10.8  $\mu\text{g/L}$ ), respectively.

The level of specific IgE in cord blood (IgE against mixed allergens or sum of specific IgE against single allergens) was also positively correlated to the maternal level of specific IgE. This correlation was related to cord blood IgA levels ( $P < .0001$ ; Figs 4

and 5, respectively) but was highly significant for all levels of cord blood IgA ( $P < .001$ ). With high levels of cord blood IgA, there was a strong correlation between cord blood and maternal specific IgE for all maternal levels. With low levels of cord blood IgA, specific IgE was only found in cord blood if mothers had high levels of such specific IgE. The maternal/cord blood specific IgE ratio was approximately 1/10, 1/100, and 1/1000 in infants with high, intermediate, and low levels of cord blood IgA, respectively.

The ratios of total/specific IgE in cord blood and maternal blood were highly significantly correlated ( $P < .001$ ), with an approximately 1:1 relationship between the 2 (Fig 6).

There was no correlation between specific IgE in cord blood and paternal blood ( $P = .19$ ).

## DISCUSSION

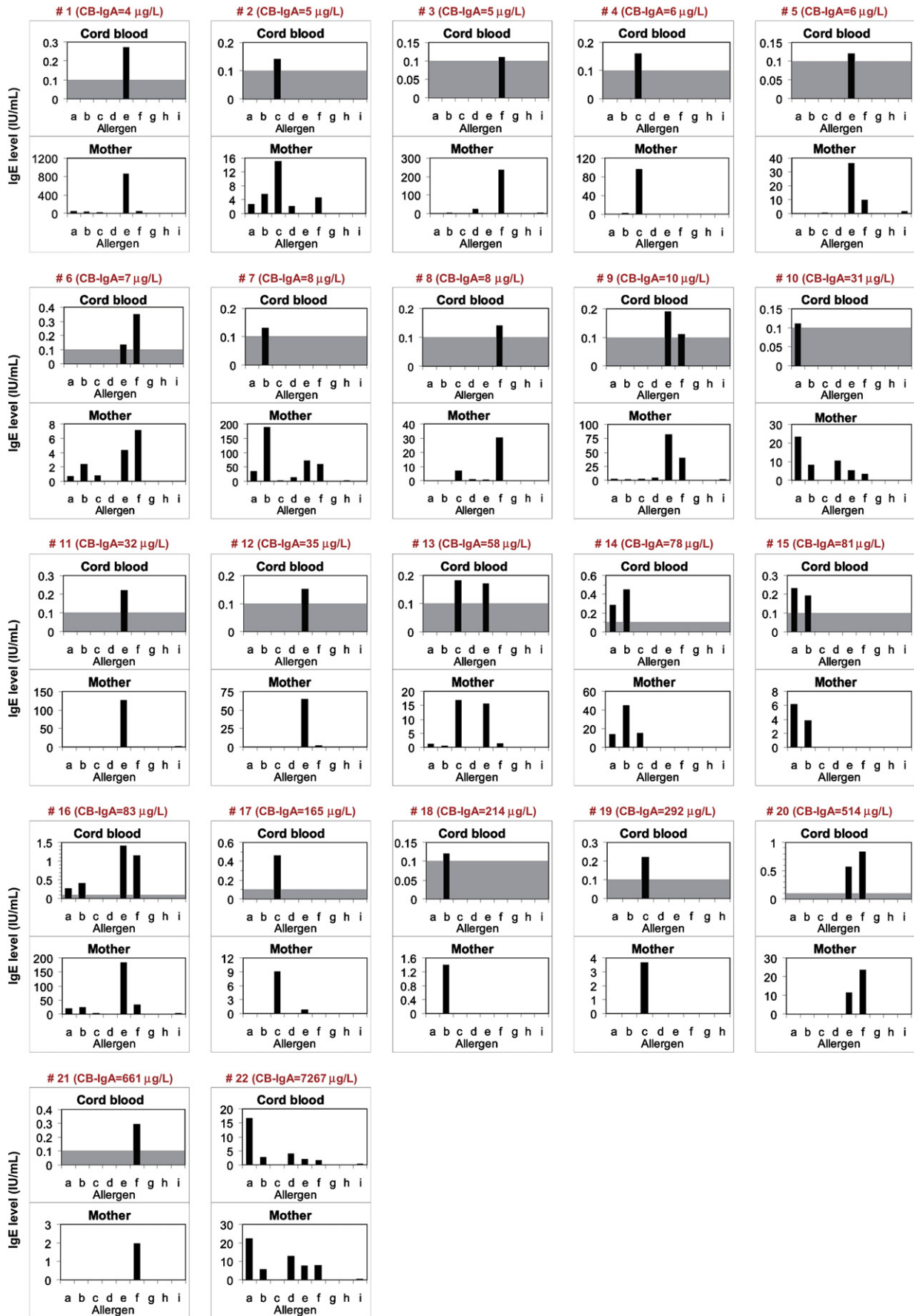
Allergen-specific IgE was found in 14% of cord blood samples. However, this allergen-specific IgE was no longer detectable in infant blood at 6 months of age, showing that it was not clinically relevant and did not indicate sensitization of the newborn. Furthermore, this suggests that specific IgE in cord blood is not a product of the fetus but rather the result of transfer of maternal IgE to cord blood or fetal blood.

We found a close match between specific IgE in mother's blood and in cord blood: (1) specific IgE was found only in newborns where the mother had the same specific IgE and never in mothers without specific IgE, (2) the pattern of specific IgE in cord blood consistently exhibited a fingerprint match of the maternal pattern, (3) the level of specific IgE in cord blood was closely correlated with the maternal level, and (4) the ratio of total/specific IgE in cord blood showed approximately 1:1 correlation with the maternal ratio. In contrast, there was no association between specific IgE in cord blood and paternal blood. Such close cord blood-mother match is in perfect agreement with materno-fetal transfer of IgE.

Specific IgE in cord blood correlated with cord blood-IgA. Because IgA does not cross the placental barrier and is not produced *in utero* in significant amounts, this indicates maternal blood contamination of cord blood samples.<sup>19</sup> Furthermore, cord blood IgA interacted with the relationship between cord blood and maternal specific IgE, as would be expected if maternal blood contamination was the causative mechanism. However, allergen specific IgE was also found in cord blood with low levels of IgA if the mother had very high levels of such IgE, indicating both an IgA-associated and a non-IgA-associated mechanism behind specific IgE in cord blood. Importantly, the close mother-cord blood match with respect to allergen specificity of IgE, level of specific IgE, and total/specific IgE ratio and the disappearance of specific IgE before 6 months of age was similar with high and low levels of IgA, suggesting a passive mechanism as a source of specific IgE in cord blood in both groups.

Together, this evidence strongly suggests that allergen-specific IgE in cord blood is passively acquired from the mother and is not the result of intrauterine sensitization. A single case of specific IgE in cord blood without corresponding IgE in the mother or a correlation between cord blood and father's specific IgE would have indicated at least some intrauterine sensitization, but this was not found.

Our data do not support fetal production of allergen-specific IgE and show that no matter the source of such IgE, it does not reflect clinically relevant lasting sensitization, which questions the existence of intrauterine sensitization and thereby the



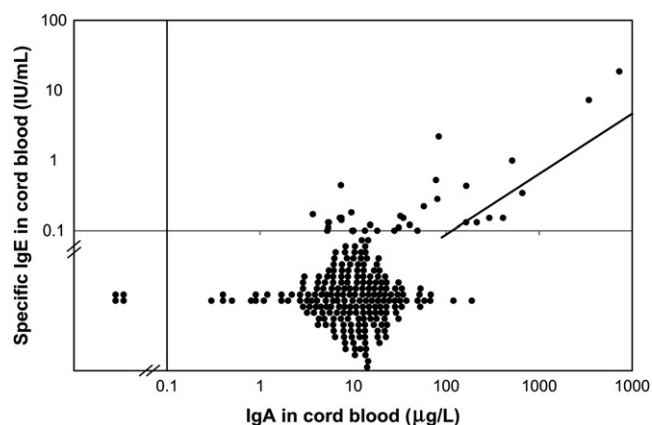


**FIG 2.** Relation between IgA and specific IgE (against mixed allergens) in cord blood. Regression line is shown.

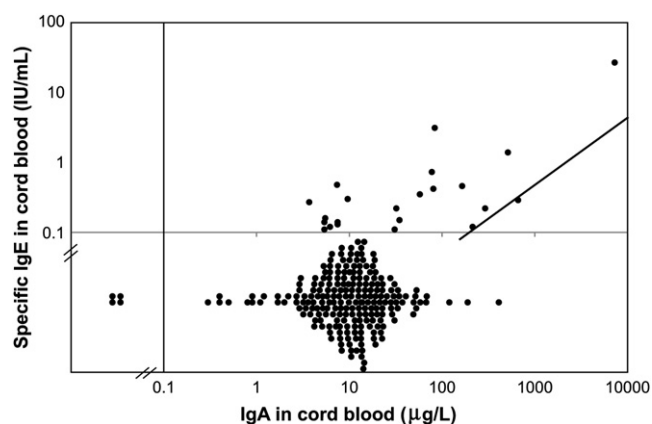


**FIG 3.** Relation between IgA and specific IgE (sum of specific IgE against single allergens) in cord blood. Regression line is shown.

rationale for current recommendations on allergen avoidance during pregnancy. This is consistent with the lack of protective effect from allergen avoidance, both of inhalant<sup>12</sup> and food<sup>13</sup> allergens, during pregnancy on sensitization in infants.

These results are in keeping with recent studies of cord blood mononuclear cells suggesting that putative  $T_H$  memory responses are not the result of allergen-specific priming but rather nonspecific reactions<sup>20</sup> and that development of  $T_H2$ -polarized allergen specific memory occurs postnatally rather than *in utero*.<sup>21</sup>

Because of the low levels of specific IgE against inhalants in cord blood, this has rarely been detectable with the methods of analysis used in previous studies. One previous study supports that cord blood specific IgE against inhalant allergens is caused by materno-fetal transfer of IgE because 2/3 of cord blood samples with such IgE showed markedly decreasing total IgE values from birth to 4 to 5 days of age.<sup>22</sup> Another earlier study contrasts with the current study in also detecting house dust mite specific IgE in cord blood in the absence of such IgE in maternal blood and

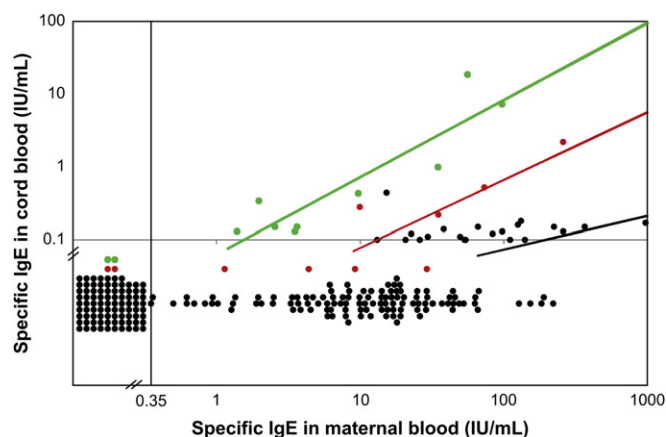


**FIG 4.** Relation between specific IgE (against mixed allergens) in cord blood and specific IgE in maternal blood, stratified for level of IgA in cord blood. Regression lines are shown for each level of cord blood IgA. — and ● Cord blood IgA > 100  $\mu$ g/L, — and ● Cord blood IgA = 50-100  $\mu$ g/L, — and ● Cord blood IgA < 50  $\mu$ g/L.

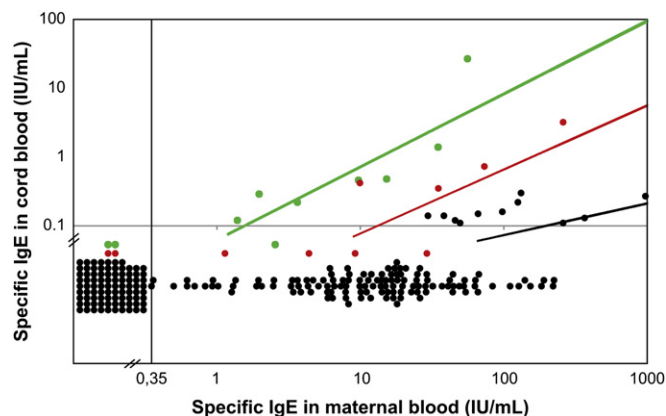


**FIG 5.** Relation between specific IgE in cord blood (sum of specific IgE against single allergens) and specific IgE in maternal blood, stratified for level of IgA in cord blood. Regression lines are shown for each level of cord blood IgA. — and ● Cord blood IgA > 100  $\mu$ g/L, — and ● Cord blood IgA = 50-100  $\mu$ g/L, — and ● Cord blood IgA < 50  $\mu$ g/L.

finding no correlation between cord blood and maternal levels of specific IgE.<sup>6</sup> However, our results question the validity of those findings. The prevalence of house dust mite specific IgE in cord blood was 10 times higher in the previous study of unselected infants than in the current study of high-risk infants (20% vs 2%  $\geq 0.1$  IU/mL), suggesting that methodological differences may explain the different results.

We did not detect any specific IgE against milk or egg allergens in cord blood in the current study. A recent study reported low levels of specific IgE against cow milk proteins in 37% of cord blood samples by using a sensitive chemiluminescence method.<sup>23</sup> Interestingly, that study demonstrated a similar close match between maternal and cord blood specific IgE, in accordance

**FIG 1.** Patterns of specific IgE in individual mother-cord blood pairs. The gray rectangle in the cord blood diagrams represents lower limit of IgE detection (0.1 IU/mL). CB, Cord blood. Allergen abbreviations: a, cat dander; b, dog dander; c, *D pteronyssinus*; d, mugwort; e, birch; f, grass; g, egg white; h, milk; i, peanut. Pairs are listed in order of increasing level of cord blood IgA.

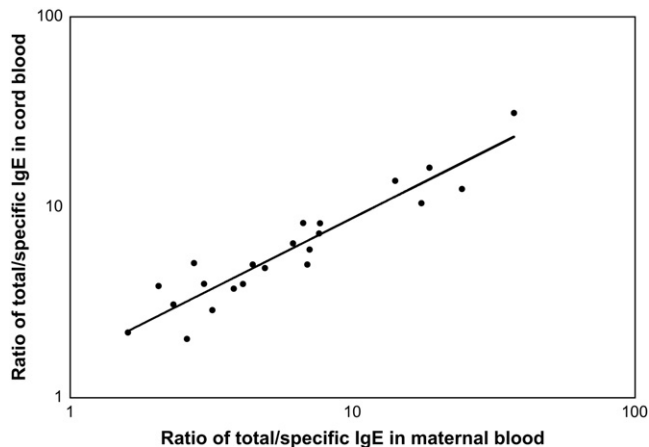


**FIG 6.** Relation between ratios of total/specific IgE in maternal blood and cord blood.

with materno-fetal transfer of IgE also being the responsible mechanism behind those findings.

Specific IgE against infectious agents such as parasites and HIV has also been found in cord blood.<sup>24,25</sup> It has been suggested that HIV-specific IgE in cord blood could be used as an indicator of infection in the infant under the assumption that such IgE is the result of intrauterine production.<sup>25</sup> However, the current study shows that such IgE is likely to be the result of materno-fetal transfer, and we suggest that future studies on specific IgE in cord blood should focus on studying and excluding such materno-fetal transfer of IgE.

We did not exclude samples with high IgA levels from the analysis. First, it is an important point of this study that materno-fetal transfer of specific IgE takes place at all levels of IgA, but to different degrees. Second, no samples had IgA levels higher than 10 mg/L, which has previously been the lowest cutoff level used to exclude contaminated cord blood samples.<sup>26</sup>

The mechanism behind materno-fetal transfer of IgE is not clear from this study. Because maternal IgE levels are often more than a 1000-fold higher than IgE levels in cord blood, even low levels of contamination with maternal IgE are sufficient to cause elevated levels in cord blood. Maternal blood contamination during cord blood sampling is one possible mechanism, although the method of needle puncture of the umbilical cord vein used in the current study probably causes a minimal amount of contamination. Small placental bleedings during late pregnancy or delivery may be a more plausible mechanism. Finally, transplacental transfer of IgE is another potential mechanism and may be responsible in samples with low levels of IgA. It is generally supposed that IgE does not cross the placental barrier,<sup>27</sup> but human IgE has been shown to pass through the placenta of monkeys in a ratio similar to albumin.<sup>28</sup>

There is no reason to believe that the frequency of contamination was higher in our study than in earlier studies of cord blood IgE. Midwives were instructed to sample cord blood by needle puncture of the umbilical vein, a method that has been shown to cause less contamination than collecting blood by letting it drip from the cut umbilical cord.<sup>29</sup> Furthermore, the frequency of cord blood IgE against inhalant allergens is similar to a previous report of cord blood IgE against inhalant allergens in infants of atopic mothers.<sup>22</sup>

This study included children of mothers with asthma. Because cord blood specific IgE is dependent on maternal specific IgE, the frequency of cord blood specific IgE would be lower in an unselected population. However, it seems unlikely that the origin of such IgE should be different in an unselected population.

## Conclusion

Allergen-specific IgE in cord blood does not reflect sensitization *in utero* but seems to be the result of materno-fetal transfer of IgE. This challenges the concept of intrauterine sensitization and thereby the rationale behind allergen avoidance during pregnancy. Our results together with previous clinical studies give no support to recommendations about allergen avoidance during pregnancy, which should be withdrawn.

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**Clinical implications: These findings refute the concept of intrauterine sensitization and thereby the rationale behind allergen avoidance during pregnancy.**

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