

Transfer of maternal IgE can be a common cause of increased IgE levels in cord blood

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Background: IgE in cord blood is thought to be a product of the fetus. A high level of total IgE is therefore used as a measure of atopic propensity in the newborn. We recently found strong evidence that allergen-specific IgE in cord blood was the result of transfer of maternal IgE to fetal blood or cord blood (maternofetal transfer) rather than fetal production. This also suggests that total IgE in cord blood might primarily be a maternal product.

Objective: We sought to determine to what extent increased levels of total IgE in cord blood is the result of maternofetal transfer of IgE.

Methods: Total IgE in cord blood was analyzed in a prospective birth cohort study. Maternofetal transfer of IgE was detected by means of high-sensitivity analyses of cord blood IgA and allergen-specific IgE and comparison with parental IgE levels and levels at 6 months of age.

Results: Forty-six percent of cord blood samples with increased IgE levels (≥ 0.5 IU/mL) showed indication of maternofetal transfer of IgE. Maternal origin of IgE in these samples was validated by showing reduced levels of IgE at 6 months of age compared with samples with no indication of maternofetal transfer (geometric mean, 9.4 vs 5.4 IU/mL; $P = .01$).

Maternofetal transfer was not appropriately accounted for by the conventional method of cord blood IgA measurement.

Conclusions: Maternofetal transfer might be a common cause of increased cord blood IgE levels. Future studies should take potential maternofetal transfer into account or use other markers of atopy. (*J Allergy Clin Immunol* 2010;126:657-63.)

Key words: IgE, cord blood, infant, intrauterine, atopy

IgE in cord blood is thought to be a product of the fetus. A high level of total IgE has therefore often been used as a measure of atopic propensity in the newborn.¹⁻⁷ Such early markers of atopy are of major interest in light of the hypothesis of fetal programming of atopic diseases⁸ and might help in identification of

Abbreviation used

COPSAC: Copenhagen Prospective Study of Asthma in Childhood

prenatal risk factors. However, it is essential that such markers are valid to avoid noneffective or harmful recommendations about environmental exposures during pregnancy.

In a recent study we found strong evidence that allergen-specific IgE in cord blood was the result of transfer of maternal IgE to fetal blood or cord blood rather than fetal production.⁹ This suggests that also total IgE in cord blood might primarily be a maternal product, and hence the validity of total IgE as a measure of fetal atopic propensity might be biased and instead reflect maternal atopic status.

On the other hand, levels of total IgE in cord blood (of which the majority is nonspecific IgE) are generally much higher than allergen-specific levels and can be detected in the majority of cord blood samples in contrast to allergen-specific IgE, which is rarely detected. Furthermore, the fetus is capable of producing nonspecific IgE.^{10,11} It is therefore possible that the fetus produces significant amounts of nonspecific IgE and that transfer from maternal blood is less of a problem in studies of total IgE.

The aim of this study was to determine to what extent increased levels of total IgE in cord blood are the result of transfer of maternal IgE to cord blood (ie, maternofetal transfer of IgE) rather than fetal production. We studied this in the Copenhagen Prospective Study of Asthma in Childhood (COPSAC) birth cohort using high-sensitivity analyses of cord blood IgA and total and allergen-specific IgE levels and comparison with IgE levels at 6 months of age and parental levels.

METHODS

COPSAC is a prospective birth cohort study of 411 children born to mothers with verified asthma, the recruitment of whom was previously described in detail.¹² 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 (2008-41-1754). Before enrollment, informed consent was obtained from parents. Data validity was ensured by compliance with Good Clinical Practice guidelines and quality control procedures.

Midwives received written information instructing them to collect cord blood by means of 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°C until analysis.

IgE antibody levels were determined by using the ImmunoCAP assay (Phadia AB, Uppsala, Sweden).¹³ Cord blood and blood at 6 months of age were analyzed for milk and egg allergens and cumulative levels of specific IgE against a panel of common inhalant and food allergens (Phadiatop Infant). 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), as previously described.⁹ IgE levels in parental blood were analyzed similarly after screening with Phadiatop. The detection limit for IgE was 0.1 IU/mL in

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TABLE I. Serum levels of IgE and IgA in parents and offspring

	No.	Median (25th-75th percentile)
Total IgE (IU/mL)		
Cord blood	243	0.26 (<0.1-0.71)
Infants at 6 mo	219	4.2 (2.3-8.6)
Mothers	243	47 (17-140)
Fathers	220	32 (13-70)
IgA (μ g/L)		
Cord blood	243	10.8 (6.1-19.2)

cord blood and at age 6 months.¹⁴ In parental blood detection limits for total and specific IgE were 2 and 0.35 IU/mL, respectively.

Cord blood samples were analyzed for total IgA by using a sensitive ELIA assay designed to measure low levels of IgA (detection limit, 0.1 μ g/L; analyzed by Phadia AB).

We modeled the underlying association between total IgE and IgA levels in cord blood by means of linear regression and by assuming an underlying normal distribution. From this, we extracted a model for the observed values, accounting for detection limits. Similar models were analyzed for the association between total IgE levels in cord blood and maternal blood for each level of cord blood IgA and for the association between total IgE levels in cord blood and paternal blood. Maximum likelihood estimates with asymptotic 95% Wald CIs were calculated, and likelihood ratio tests for hypotheses were performed. A smoothing curve (Lowess) was calculated based on levels greater than the detection limit for the association between total IgE and IgA to visually determine a relevant cutoff level for association. The degree of association beyond this cutoff was quantified by using Spearman rank correlation. The association between predicted and observed levels of total IgE in cord blood was analyzed by using simple linear regression methods. IgE levels at 6 months of age in children of different cord blood categories were compared by means of ANOVA with adjustment for maternal IgE levels. All values were transformed to a logarithmic scale.

RESULTS

Paired samples of cord blood–maternal blood, cord blood–paternal blood, and cord blood–6-month blood samples were available for 243, 220, and 219 children, respectively. Detectable levels of total IgE (≥ 0.1 IU/mL) were found in 184 (74%) cord blood samples, and increased levels (>0.5 IU/mL) were found in 74 (30%) samples. Levels of IgE and IgA in parents and offspring are shown in Table I.

Total IgE in cord blood and parental blood

There was a highly significant correlation between cord blood and maternal levels of total IgE ($P < .0001$; Fig 1, A). This correlation was related to cord blood IgA levels and was significant for all levels of cord blood IgA. IgE was always detected in cord blood if the maternal level was greater than 145 IU/mL (55 samples), and all cord blood samples had increased levels if the maternal level was greater than 516 IU/mL (17 samples). None of the 21 cord blood samples in which the maternal level was less than 6.7 IU/mL had increased IgE levels. In contrast, there was no association between cord blood and paternal levels of total IgE ($P = .70$; Fig 1, B).

IgA in cord blood as an indicator of maternal transfer of total IgE

The level of total IgE in cord blood was positively correlated to the level of cord blood IgA ($P < .001$, Fig 2). The correlation was

not linear but driven by the samples with the highest IgA levels, as shown by the smoothing curve of average values (Fig 2). The correlation was significant in restricted analyses of samples with IgA levels of greater than 25 μ g/L ($P < .001$, $n = 41$) and IgA levels of greater than 50 μ g/L ($P = .02$, $n = 21$). Average cord blood IgE levels were clearly increased for IgA levels of greater than 50 μ g/L (by means of visual inspection of Fig 2), and this was supported by IgA-stratified analyses of cord blood and maternal IgE levels showing an upward shift of the association line for IgA levels of greater than 50 μ g/mL and a further shift for IgA levels of greater than 100 μ g/L (Fig 1, A). These results are in accordance with our previous findings for allergen-specific IgE levels in cord blood⁹ and suggest that cord blood samples with IgA levels of greater than 50 μ g/L should be suspected to have falsely increased IgE levels. This level was used as an indicator of maternofetal transfer of IgE in the following analyses.

Allergen-specific IgE levels in cord blood as an indicator of maternofetal transfer of total IgE

We previously found strong evidence that allergen-specific IgE in cord blood was the result of maternofetal transfer of IgE.⁹ If such transfer is the only source of IgE, then the total level of IgE can be predicted on the basis of total/allergen-specific IgE levels in maternal blood and allergen-specific IgE levels in cord blood. We therefore calculated the predicted level for cord blood samples with detectable IgE against single allergens ($n = 22$) and compared this with the actual observed level of total IgE in cord blood. The predicted and observed levels of total IgE in cord blood were highly significantly correlated ($P < .001$), with an approximately 1:1 relationship between them (Fig 3, A). Accordingly, the observed level of cord blood IgE was generally close to 100% of the predicted level (mean, 105% [SD 34%]; Fig 3, B). This strongly suggests that total IgE is mainly a product of the mother in samples with detectable allergen-specific IgE. Detection of allergen-specific IgE was therefore used, together with cord blood IgA, as an indicator of maternal transfer of IgE in the following analyses.

Frequency of maternofetal transfer of IgE

There was indication of maternofetal transfer of IgE in 34 (46%) of 74 cord blood samples with increased total IgE levels (>0.5 IU/mL). Of these, 35% were suspected to be “contaminated” on the basis of both increased IgA levels and detectable allergen-specific IgE levels, 47% on the basis of allergen-specific IgE levels only, and 18% on the basis of increased IgA levels only.

Cord blood IgE levels and IgE levels at 6 months of age

Children with increased cord blood IgE levels and indication of contamination ($n = 32$) had significantly lower IgE levels at 6 months of age compared with children with increased IgE levels and no indication of contamination ($n = 35$; geometric mean, 5.4 vs 9.4 IU/mL; $P = .01$; Table II). Furthermore, increased cord blood IgE levels were not significantly associated with IgE levels at 6 months of age in samples with indication of maternofetal transfer of IgE after adjustment for maternal IgE levels ($P = .07$), which is in contrast to a highly significant independent association for samples without indication of transfer ($P < .0001$, Table II).

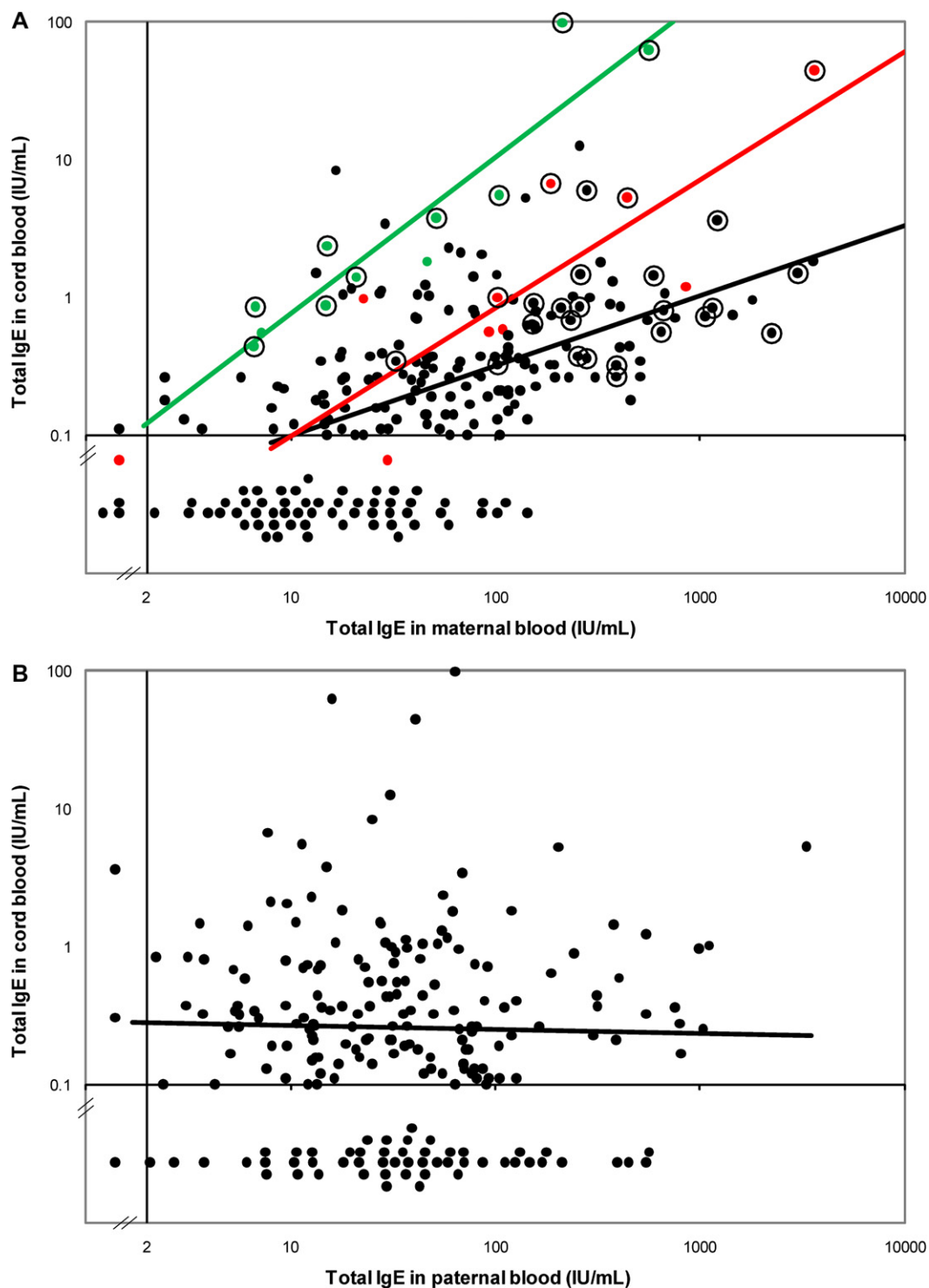


FIG 1. A, Relation between total IgE levels in cord blood and maternal blood stratified for level of IgA in cord blood. Regression lines are shown for each level of cord blood IgA. *Green lines and circles*, Cord blood IgA level of greater than 100 µg/L; *red lines and circles*, cord blood IgA level of 50 to 100 µg/L; *black lines and circles*, cord blood IgA level of less than 50 µg/L. *Circles*, Detectable allergen-specific IgE in cord blood. B, Relation between total IgE levels in cord blood and paternal blood. Regression line is shown.

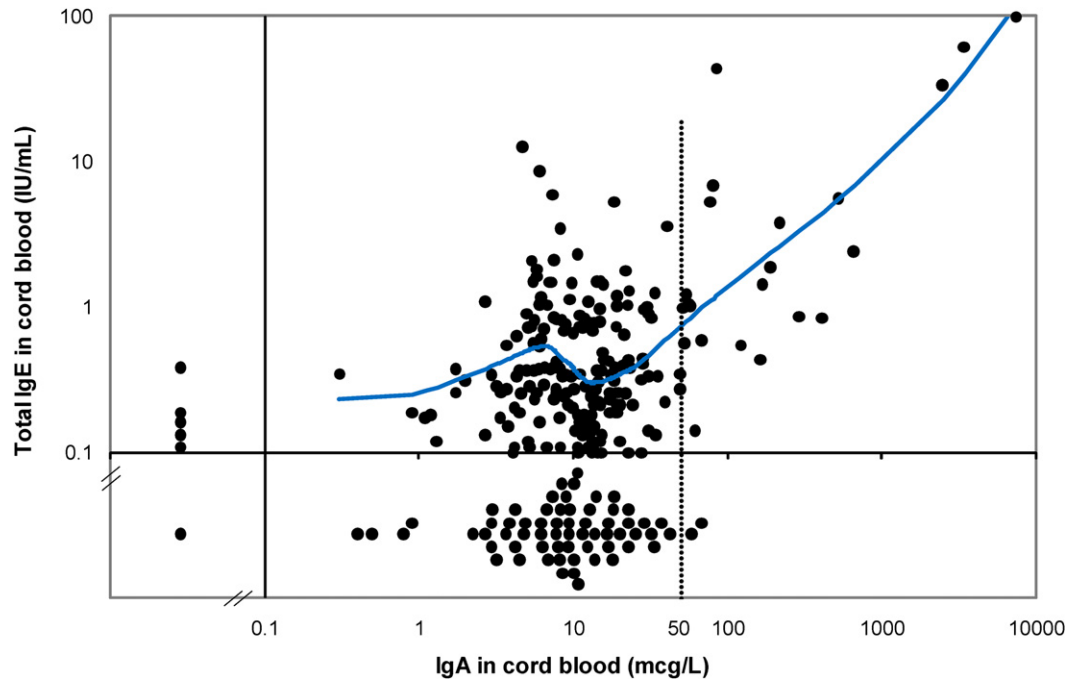


FIG 2. Relation between IgA and total IgE levels in cord blood. Smoothing curve (Lowess) is shown.

DISCUSSION

Main findings

Approximately half of cord blood samples with increased IgE levels showed indications of transfer of maternal IgE to fetal blood or cord blood (ie, maternofetal transfer of IgE). This frequency of suspected “contamination” with maternal IgE is much higher than expected from previous studies, with important implications for the value of increased cord blood IgE levels as a marker of atopy in the newborn.

Potential maternofetal transfer was indicated by a strong association between maternal and cord blood IgE levels where IgE was always detected in cord blood if the maternal level was high. In contrast, there was no association between paternal IgE levels and cord blood IgE levels. We then used 2 different methods to detect maternofetal transfer of IgE in individual samples. The first method was based on increased levels of IgA in cord blood. Because IgA does not cross the placental barrier and is not produced *in utero* in significant amounts,¹⁵ increased levels are supposed to reflect maternal blood contamination. We confirmed this by showing an association between IgA and IgE levels in cord blood above a certain IgA level.

The second method was based on the detection of allergen-specific IgE in cord blood. We previously provided strong evidence that such IgE is the result of maternofetal transfer of IgE, as demonstrated by a perfect allergen-specific match between specific IgE levels in maternal blood and cord blood and the disappearance of cord blood specific IgE levels before 6 months of age.⁹ In the present study we further demonstrated that in samples with detectable allergen-specific IgE, total IgE levels seem to be the result of transfer from the mother. We hypothesized that if both total and allergen-specific IgE was the result of transfer, then total IgE levels in cord blood could be predicted by the maternal total IgE/specific IgE ratio and the level of specific IgE in cord blood, which our data subsequently confirmed. This means that

in these samples the fetus does not seem to produce significant amounts of unspecific IgE in addition to the amount transferred from the mother, and therefore detection of allergen-specific IgE could be used as a marker of maternofetal transfer of IgE.

Finally, we validated the hypothesis of maternal origin of IgE in samples with suspected maternofetal transfer of IgE by analyzing the association with the child's IgE level at 6 months of age. Children with increased cord blood IgE levels had significantly lower IgE levels at 6 months of age if the cord blood sample showed indications of maternofetal transfer. Also, cord blood IgE levels were not independently associated with IgE at 6 months of age in samples with indications of maternofetal transfer of IgE in contrast to a highly significant independent association in samples without such indications.

Meaning of the study

Together, our results suggest that increased IgE levels in cord blood were the result of maternofetal transfer in almost half of the cases. This frequency of suspected maternal origin of increased IgE levels is much higher than suspected in previous studies. Some have reported frequencies of contamination as low as 1% of cord blood samples with increased total IgE levels¹⁶ or did not test for falsely increased IgE levels.^{1,2} This suggests that previous studies with increased IgE levels in cord blood as a marker of atopic status included a number of cord blood samples with falsely increased total IgE levels because of maternofetal transfer of IgE. A number of prenatal factors, including allergen exposure during pregnancy,^{2,3} parity,⁴ maternal age,¹ and sex of the infant,^{1,6} have been associated with increased levels of IgE in cord blood and have therefore been interpreted as risk factors for atopy in the child. Because all of these prenatal factors are also associated with maternal IgE levels,^{1,2,17} the associations with cord blood IgE might be caused by maternofetal transfer of IgE and therefore not reflect an effect on atopic development

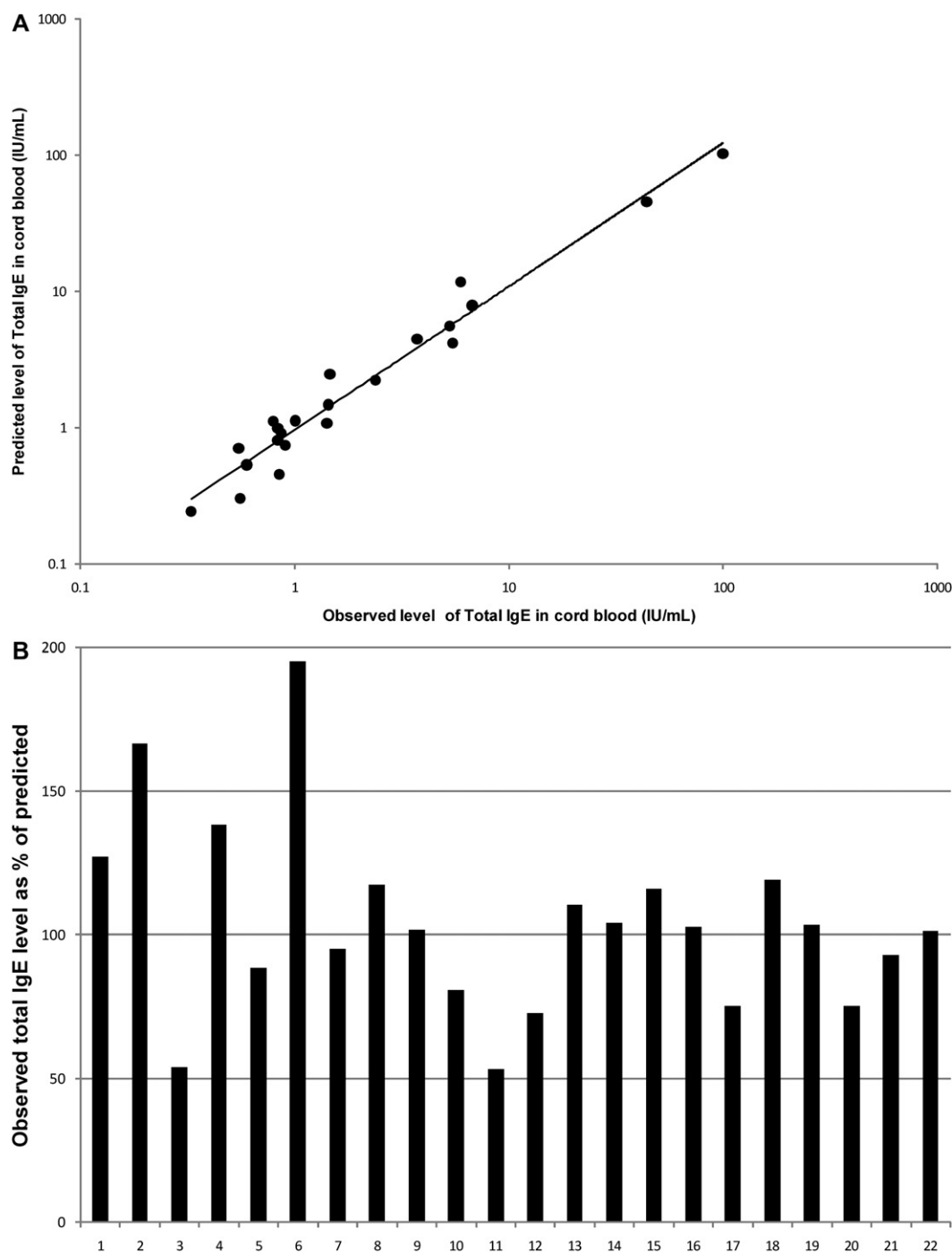


FIG 3. **A**, Relation between observed total IgE levels in cord blood and predicted (calculated) levels in samples with detectable allergen-specific IgE against single allergens. Regression line is shown. **B**, Observed level of total IgE in cord blood as a percentage of predicted level. Values are listed in order of increasing level of cord blood IgA. Each number represents 1 cord blood sample.

in the offspring but only an effect on maternal IgE levels. In accordance with this, a path analysis suggested that the effect of parity on cord blood IgE is mediated through maternal levels of IgE,¹⁷ and similarly, other suggested risk factors were no longer significantly associated with cord blood IgE levels after adjustment for maternal IgE.^{1,2} The results of previous studies using total IgE level as the outcome should therefore be interpreted with caution, and future studies must take potential maternofetal transfer of IgE

into account to ensure that findings are related to fetal and not maternal IgE production. A conservative approach could be adjustment for maternal IgE level, which has been done in some studies.^{1,2}

Our findings suggest 3 different causes of increased IgE levels in cord blood. First, maternal blood contamination of cord blood is one possible cause and seemed responsible for 25% of samples with increased IgE levels, as demonstrated by association with

TABLE II. Association of categories of cord blood IgE with IgE levels at 6 months of age

Cord blood IgE category	No.	IgE level at 6 mo of age		
		Geometric mean (IU/mL)	RR* (P value)†	
IgE <0.5	152	3.5	—	1 (reference)
IgE >0.5 with indication of maternofetal transfer	32	5.4	1 (reference)	1.5 (.07)
IgE >0.5 without indication of maternofetal transfer	35	9.4	1.8 (.01)	2.7 (<.0001)

*Relative risk estimate adjusted for maternal level of IgE.

†Tested by using ANOVA statistics adjusted for maternal level of IgE.

IgA levels. Because IgE levels in maternal blood are often more than 1,000-fold higher than in cord blood, even a low level of contamination with maternal blood is sufficient to cause increased levels in cord blood. Maternal blood contamination can occur during cord blood sampling or through small placental bleedings during late pregnancy or delivery. Demonstration of increased IgA levels in cord blood is the conventional method to detect falsely increased IgE levels. However, our study suggests that the level of IgA considered indicative of a falsely increased IgE level might be too high. The cutoff level used has been 10 mg/L or higher,¹⁸ and the proportion of samples discarded as contaminated on this basis has been very low, as low as 1% of samples with increased IgE levels.¹⁶ Interestingly, none of our samples had levels of greater than the 10 mg/L limit, but by associating IgA and IgE in cord blood, we found a strong indication of significant transfer of IgE together with IgA (maternal blood contamination) already from IgA levels of 0.05 mg/mL. IgA levels of greater than this were found in 9% of all cord blood samples and in 24% of samples with increased levels of IgE. Previous studies have not usually established an internally relevant cutoff level of IgA but have relied on cutoff levels from previous older studies, and this might not be appropriate because of differences in analytic methods and improvement of anti-IgA antibody specificity during recent years.

Maternal blood contamination of cord blood might be prevented by strict sampling procedures if it takes place during cord blood sampling but not if it is caused by small placental bleedings.

Second, transplacental transfer of IgE is another potential mechanism, and we found indications of this in 22% of samples with increased IgE levels. This was demonstrated by normal IgA levels but the presence of allergen-specific IgE levels completely matching maternal specific IgE levels and disappearance before 6 months of age. Our previous study on allergen-specific IgE, as well as the present study, suggest a cord blood/maternal transfer ratio of approximately 1 to 1,000 through a non-IgA-associated mechanism. This is consistent with our finding that all cord blood samples had detectable IgE if the maternal level was high. We cannot rule out that this correlation is not the result of fetal production influenced by maternal IgE status, such as intrauterine sensitization facilitated by fetal swallowing of IgE and subsequent binding to IgE receptors on antigen-presenting cells in the fetal gastrointestinal tract.¹⁹ However, the consistency and allergen specificity of this correlation seems more likely explained by a mechanism of transfer than a never-failing mechanism of fetal production. It is generally supposed that IgE does not cross the

placental barrier,²⁰ but this has never been proved. On the contrary, an older study reported that human IgE injected into the blood of a pregnant monkey can be detected in the blood of the offspring in a ratio similar to albumin.²¹ Such transfer of IgE would not be prevented by strict sampling procedures and is not accounted for by IgA measuring. A previous study by Lilja et al²² supports that the IgA method does not control sufficiently for maternofetal transfer of IgE.

Third, we found strong evidence that some cord blood samples had increased IgE levels as a result of fetal production of IgE. Increased cord blood IgE levels in samples without indications of maternofetal transfer (approximately half of samples) was highly significantly associated with IgE levels at 6 months of age independent of maternal IgE levels. This supports that the fetus is capable of producing nonspecific IgE and that this tendency to produce high levels at birth tracks into infancy. This is in line with previous studies documenting the fetal capacity of IgE production.^{10,11}

The association between IgE levels in cord blood and maternal, but not paternal, blood was also evident in samples without indications of maternofetal transfer. This might be due to the limited sensitivity of our method not allowing detection of maternofetal transfer of IgE in all cases. However, it is also likely that in addition to maternofetal transfer of IgE, maternal factors might affect IgE production in the offspring, as demonstrated for infant eczema and IgE levels.²³ Involved mechanisms could be maternal influence through the intrauterine environment, shared environment by the mother and fetus, or maternal inheritance.²⁴

This study specifically addresses the origin of IgE in cord blood, which has important implications for studies using cord blood IgE level as the outcome, because these are based on the assumption of cord blood IgE being a fetal product. However, it does not address the capacity of increased IgE levels in cord blood as a predictor of atopic disease. Also, IgE is characterized by a very low cord blood/maternal blood ratio (often <1:1,000). Maternofetal transfer might be a smaller problem in studies of other substances with a higher cord blood/maternal blood ratio or studies of cord blood cells. This study therefore does not address or question putative prenatal priming of lymphocytes. Also, these results should not be taken as evidence against the hypothesis of fetal programming of atopic diseases and importance of the intrauterine environment.

Limitations

Midwives were instructed to sample cord blood by means of 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.²⁵ The frequency of cord blood IgE against inhalant allergens was similar to a previous report of cord blood IgE against inhalant allergens in infants of atopic mothers.²² However, since cord blood sampling was not performed by research personal we can not be sure that all samples were collected by needle puncture. Furthermore, this study is limited by only including children of asthmatic mothers. Mothers with asthma have higher IgE levels, and the number of cord blood samples with increased IgE levels would have been smaller in an unselected population.

For these reasons, this study should be replicated in a cohort of unselected women and preferably with cord blood sampling performed by research personal.

Conclusions

In conclusion, our study highlights several potential problems with cord blood IgE as an indicator of atopy in the newborn. First, a considerable fraction of samples with increased IgE levels seems to be the result of transfer of IgE from the mother rather than fetal production. Second, the traditional method of IgA measurement might not appropriately account for such transfer; the IgA level currently considered indicative of falsely increased IgE levels seems too high, and non-IgA-associated maternofetal transfer of IgE might take place. This suggests that previous studies with cord blood IgE as the outcome might have included samples with falsely increased IgE levels and therefore should be interpreted with caution. On the other hand, we found strong evidence of fetal IgE production in samples without indication of maternofetal transfer. We recommend that future studies take into account potential maternofetal transfer of IgE or use other markers of atopy.

We thank the parents and children who took part in the study, the COPSAC research team, and Bjarne Kristensen and Inger Pedersen for their dedicated work with the IgE analyses.

Key messages

- An increased IgE level in cord blood can frequently be the result of transfer of maternal IgE to fetal blood or cord blood (maternofetal transfer) rather than fetal production and thereby is not a valid marker of atopic propensity in the newborn.
- Future studies must take potential maternofetal transfer of IgE into account or use other markers of atopy.
- The traditional method of cord blood IgA measurement seems not to account appropriately for maternofetal transfer of IgE.

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