

Maternal smoking does not influence cord serum IgE or IgD concentrations

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Increased cord blood IgE concentrations have been related to atopic risk in children, and a previous study reported increased cord blood IgE concentrations in smoking mothers. These associations suggest a relationship between maternal smoking during pregnancy and atopic risk. To evaluate this question, we prospectively studied parental smoking and cord blood IgE and IgD concentrations in a geographically defined group of women belonging to a health maintenance organization. Cord blood samples were obtained from 847 infants born to these women. Cotinine concentrations were measured in 114 cord blood samples to evaluate the veracity of the maternal smoking histories. Smoking during the prenatal period was reported by 144 mothers (17%) and 204 fathers (25%). Decreased birth weight and length were associated with maternal smoking ($p < 0.001$ for both), confirming previous studies. Neither maternal nor paternal smoking was found to be associated with IgE level in univariate or multivariate analyses. Maternal and paternal smoking was associated with IgD ($p = 0.03$ and $p = 0.06$, respectively) in univariate analysis. In multiple regression analysis controlling for potentially confounding variables, the association between paternal, but not maternal, smoking and IgD was sustained ($p = 0.05$ and $p > 0.20$, respectively). Our data do not demonstrate that maternal or paternal smoking increases cord blood IgE. (J ALLERGY CLIN IMMUNOL 1991;88:555-60)

Key words: Cord serum, IgE, IgD, parental smoking, newborn infants

Exposure to passive cigarette smoking has been associated with an increased occurrence in children of respiratory illness, including bronchitis, pneumonia, otitis media, and wheezing.¹⁻³ An Israeli study of 80 atopic wheezing babies suggested that parental smoking leads to persistence of wheezing, although there was no correlation between passive exposure to smoke and an increase in IgE levels.⁴ Other studies have failed to demonstrate a relationship between parental smoking and childhood asthma.⁵ Serum IgE and IgD have been demonstrated to be higher in adult

smokers versus that in nonsmokers,⁶⁻⁸ and animal studies indicate that exposure to tobacco smoke increases serum IgE levels in rats.⁹

As cord blood IgE has been demonstrated to be directly related to increased incidence of atopic disease in childhood,^{10, 11} a Swedish study investigated the influence of parental smoking on cord blood levels of both IgE and IgD.¹² Univariate and stratified analyses indicated that maternal smoking was related to higher IgE and IgD, especially in babies with a negative parental history of allergy. Paternal smoking did not influence cord blood IgE, but was associated with higher IgD among newborn infants with a negative family history of disease. However, in a French study, maternal smoking did not appear to influence the level of cord serum IgE.¹³ This study examined the association of parental smoking during pregnancy and cord blood IgE and IgD in a large, population-based, prospective study of newborn infants.

MATERIAL AND METHODS

This investigation is part of an ongoing prospective study evaluating environmental determinants of childhood allergies. All women scheduled for a prenatal appointment at

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one of seven medical facilities in Macomb and Oakland Counties north of Detroit, Mich., were potentially eligible for recruitment into the study. To be eligible, subjects had to reside within an area defined by contiguous zip codes, have an estimated date of confinement between April 15, 1987, and August 31, 1989, and plan to deliver at one of three hospitals. Study subjects were also required to belong to a health maintenance organization (Health Alliance Plan) to increase the probability of continued care and to facilitate access to medical records.

Nurses recruited eligible subjects during midterm prenatal visits. During these prenatal contacts, standardized questionnaires were completed concerning demographics, parental allergies, and smoking habits. Women younger than 18 years were excluded, as were subjects who anticipated placing their baby with adoptive parents and parents who knew they were moving out of the study area. Only one child was enrolled per family. All facets of this research have been approved by the Henry Ford Health System Human Rights Committee.

At the time of delivery, a cord blood sample was obtained. The serum was separated as soon as possible and stored at -20°C until assay. Total IgE levels were quantitated as previously described with an enzyme-linked immunoassay.¹⁴ Briefly, this assay is a biotin-avidin amplified ELISA with a fluorescent substrate. The antibody used in both the capture and detecting steps was affinity-purified antihuman IgE (Kirkegaard & Perry Laboratories, Gaithersburg, Md.). When the anti-IgE was used as the detecting antibody, it was biotin labeled.

Standard curves were constructed from appropriate dilutions of a patient serum that had been standardized against the U.S. reference standard. The average net fluorescent units produced by unknown samples were converted to units of IgE (international units) by calculation from the computer-fitted standard curve. Six internal standards were included with each assay run. The routine sensitivity of the assay was 0.02 IU/ml of IgE, and the average interassay coefficient of variation was 17.6%.

IgD was assayed in an analogous ELISA, except that antihuman IgD (Calbiochem, San Diego, Calif.) was substituted for the anti-IgE. The standard curve for the IgD was constructed from appropriate dilutions of a commercial standard (Calbiochem). The calibration of the commercial standard had been confirmed in this assay by comparison to World Health Organization standard 67/37.¹⁵ The results of IgD are expressed in international units per milliliter, consistent with the World Health Organization standard (1 IU equals 1.42 μg of IgD).¹⁵ Similarly, the concentration of IgA was measured by ELISA to evaluate possible contamination of the cord sera with maternal blood. Sera with IgA values of $>30\text{ }\mu\text{g/ml}$ were considered potentially contaminated and excluded from analyses.^{16, 17}

A previous pilot study of 200 cord bloods yielded a distribution of IgE in which the highest 25% were ≥ 0.56 IU/ml (unpublished data). This cut point was selected to define high versus low IgE categories. Samples with initial IgE values of >0.3 IU/ml were retested once or twice and classified as high if two of the three results were ≥ 0.56 IU/ml.

To assess the validity of the smoking histories obtained from the mothers, cotinine was measured with a commercial assay (Coti-Traq Assay, Serex, Inc., Tenaflly, N.J.) in 114 of the cord blood samples. The 114 samples were a stratified sample chosen to assure nearly equal proportions of samples from nonsmokers, light smokers, and heavy smokers. The cotinine assay was performed according to the manufacturer's instructions, and sensitivity was 0.01 $\mu\text{g/ml}$ of cotinine.

Statistical methods

The variable for IgE was treated in two ways: first, as a continuous variable, and second, as a binary variable, classifying samples into high and low IgE categories. The two definitions result in analyses that address slightly different questions. If there is a linear relationship between smoking and cord blood IgE, the continuous variable is more appropriate. If, in contrast, a threshold effect is present, the binary variable is appropriate. Both effects were considered possible, and hence, IgE was analyzed with both approaches. There was no natural cut point for the IgD values; thus, IgD was analyzed only as a continuous variable. Since IgE and IgD distributions were highly positively skewed, these variables were transformed with a natural logarithm. The exponentiated mean value of log-transformed data is, by definition, the geometric mean, and this value is reported throughout.

Parents' and babies' demographic, delivery, and smoking data (nonsmoker or smoker) and IgD values were compared with standard univariate tests. The log-transformed values of IgE and IgD were approximately normal; therefore parametric procedures were used. We used 0.05 throughout as the level of significance. All *p* values are two-sided. Mean values are presented plus or minus the standard deviation of the mean.

To assess the relationship of IgD and IgE to parental smoking status, multiple linear and logistic regression techniques were used. Adjustments were made for covariates believed to be important a priori. Various models both adjusting and not adjusting for the other parents' smoking status were examined.

It is likely that an inverse relationship exists between a history of allergic diseases and smoking. For this reason, it is possible that adjusting for a history of allergic diseases might mask the effect of smoking. The regression models were run both with and without an adjustment for parental history of allergic disease variables. A model was also examined with only those infants with negative biparental allergic histories.

RESULTS

The study nurses approached 1194 eligible women, and 953 consented to participate in the study. Cord bloods were not obtained from 106 deliveries for a variety of reasons, including miscarriage, stillbirth, delivery or medical complications, change of physician or hospital, or loss of a specimen. The mothers refusing to participate and mothers for whom cord blood samples were not obtained did not differ from

TABLE I. Birth weight and length of infants studied

	Smoking mothers			Nonsmoking mothers			<i>p</i> Value
	N	Mean	SD	N	Mean	SD	
Birth weight* (kg)	139	3.20	0.50	668	3.52	0.52	<0.001
Birth length* (cm)	118	51.60	2.69	626	52.90	2.52	<0.001

*The numbers do not total 841 because data were missing for some infants.

the 847 women for whom cord blood was obtained at delivery with respect to age, race, and estimated date of confinement. Of the 847 cord blood samples, the IgE level was ≥ 0.56 IU/ml in 147 blood samples. Six samples with IgE ≥ 0.56 IU/ml also had elevated IgA concentrations (≥ 39 μ g/ml) and were excluded because of the possibility of contamination with maternal blood, yielding a total sample size of 841.

The demographics of the childrens' parents revealed that the average age of the mothers was 28 years $\pm$ 4 years and that of the fathers was 31 years $\pm$ 6 years. Considering maternal race, 92% of the women were white, 2% black, and 6% were classified as "other," mostly subjects of Middle Eastern and Asian Indian descent. More than 90% of the parents had high school degrees, with a third of the mothers and nearly half the fathers having a college degree.

Twenty-five percent of the fathers were current smokers and 75% were nonsmokers. Seventeen percent of the mothers were current smokers and 83% were nonsmokers. There were 417 male and 424 female births, resulting in a ratio of 1:1. The average gestational age was 39.6 weeks (range, 36 to 43 weeks).

The cord serum cotinine measurements were compared to the maternal smoking histories. In 90% of the self-reported, nonsmoking mothers, no cotinine was detected in the cord serum, whereas cotinine was detectable in 78% of the cord blood samples of the self-reported smoking mothers. The cord serum cotinine levels were also significantly correlated with the number of cigarettes smoked per day ($r = 0.47$; $p < 0.0001$).

The geometric mean cord serum IgE level in the 841 subjects was 0.21 IU/ml (range, <0.01 to 7.4 IU/ml). Approximately 95% of the cord serum IgE values lay in the range 0.02 to 2.08 IU/ml. The use of the cut point of 0.56 IU/ml results in classifying 141 subjects (17%) as having high IgE and 700 (83%) subjects as having low IgE values.

The geometric mean cord serum IgD level was 0.14 IU/ml (range, <0.01 to 2.2 IU/ml) with 95% of the observations lying between 0.03 and 0.72 IU/ml. IgD

levels were associated with IgE levels with a correlation between the two of 0.18 ($p < 0.001$).

Maternal and paternal age and education, maternal marital status, mean gestation, American Pediatric Gross Assessment Record scores at 1, 5, and 10 minutes, birth weight and length, hospital of birth, birth order of baby, and number of previous pregnancies did not differ between those babies with high versus low IgE. Considering IgE in the continuous scale (log-transformed) also resulted in no statistically significant associations with any of the variables listed above.

IgE was not significantly related to the child's sex with 17% of both male and female infants having high IgE levels ($p = 0.99$). The results were the same comparing the geometric means, with male (0.22 IU/ml) and female (0.20 IU/ml) infants having similar results.

A difference in IgE was found when the ethnic distributions of babies with low versus high IgE were compared. White babies had 16% high IgE values compared to 32% for babies classified as black and other ($p = 0.01$). This result held when the geometric mean of IgE was compared for white babies, 0.20 IU/ml, to the geometric mean for babies classified as black or other, 0.36 IU/ml ($p = 0.01$).

The analyses of IgD demonstrated no statistically significant results for the variables listed previously for IgE. As with IgE, there was no relationship between the child's sex and IgD levels. The geometric mean for male and for female infants was 0.14 IU/ml ($p = 0.75$). There was also no relationship between IgD levels and the child's race. Those children classified as white had a geometric mean IgD of 0.14 IU/ml, whereas the children classified as black or other had a geometric mean of 0.15 IU/ml ($p = 0.58$).

Birth weight and length were assessed by the reported smoking status (yes/no) of the mother during pregnancy. Babies of smokers were of statistically significant lower weight and shorter in length than babies of nonsmoking mothers (Table I).

The frequency of high cord serum IgE concentrations was not significantly related to paternal smoking, 16% in smoking and 17% in nonsmoking fathers. The

TABLE II. Comparison of mean cord serum IgE and IgD (units per millimeter) by parent and smoking status*

Variable	Smoking mother (N = 144)			Nonsmoking mother (N = 696)			<i>p</i> Value
	Geometric mean	Log		Geometric mean	Log		
		Mean	SD		Mean	SD	
IgE	0.202	−1.60	1.20	0.210	−1.56	1.17	0.70
IgD	0.162	−1.82	0.89	0.138	−1.98	0.89	0.03

Variable	Smoking father (N = 204)			Nonsmoking father (N = 623)			<i>p</i> Value
	Geometric mean	Log		Geometric mean	Log		
		Mean	SD		Mean	SD	
IgE	0.205	−1.59	1.09	0.209	−1.57	1.20	0.85
IgD	0.155	−1.87	0.80	0.136	−1.99	0.82	0.06

*Means and standard deviations are of the log-transformed values of IgE and IgD.

same was true comparing the geometric mean cord serum IgE concentrations between smoking fathers, 0.21 IU/ml, and nonsmoking fathers, 0.21 IU/ml ($p = 0.85$) (Table II). Sixteen percent of the infants of mothers who smoked had high cord blood IgE levels compared to 17% for infants of nonsmoking mothers ($p = 0.77$). The geometric mean cord serum IgE concentrations are 0.20 IU/ml and 0.21 IU/ml for smokers and nonsmokers, respectively, and these values are not statistically different with $p = 0.70$. Repeating these analyses with only the children of nonatopic parents again demonstrated no significant differences ($N = 348$, $p = 0.78$ and $p = 0.99$ for maternal and paternal smoking, respectively).

Maternal smoking was significantly associated with cord serum IgD levels. Infants of mothers who smoked had a higher geometric mean IgD of 0.16 IU/ml, compared to nonsmoking mothers, 0.14 IU/ml; $p = 0.03$. Paternal smoking was marginally related to IgD. Fathers that smoked had infants with higher geometric mean IgD levels than nonsmoking fathers (0.15 IU/ml versus 0.14 IU/ml; $p = 0.06$).

The following potentially confounding variables were included in multiple regression models of parental smoking versus IgE and IgD levels: child's sex, birth weight, birth length, paternal history of allergies or asthma, maternal history of allergies or asthma, maternal visit to an allergist, history of skin testing, or immunotherapy.

The test for significance of maternal smoking and IgE level in the linear regression model was not significant, adjusting for the covariates listed above and either adjusting for or not adjusting for paternal smoking (p values are 0.37 and 0.23, respectively). Similarly, there are no statistically significant effects for paternal smoking either adjusting for maternal smoking ($p = 0.85$) or not adjusting for maternal smoking,

and IgE ($p = 0.90$). The results of the logistic regression (with the classification scheme for IgE levels) were similar. The regression model, fit without adjusting for parental history of allergies, demonstrated no significant association of IgE with either maternal ($p = 0.26$) or paternal smoking ($p = 0.33$) adjusting for one another.

Multiple regression analysis of IgD levels indicated a statistically significant relationship with paternal smoking. The p values for paternal smoking were 0.05 adjusting for, and 0.03 not adjusting for, maternal smoking. Considering only parents without any history of allergies, the association between IgD and paternal smoking was marginally significant with $p = 0.07$ (adjusting for maternal smoking). No similar relationship was found relating maternal smoking to cord serum IgD levels, with p values >0.20 level for all comparisons.

DISCUSSION

In 1986, Magnusson¹² reported from Sweden that maternal smoking was associated with increased cord blood concentrations of IgE and IgD. More importantly, infants born with elevated cord blood IgE were at increased risk of developing allergic disease. These findings were based on 186 cord blood samples and a retrospective survey collecting information on smoking. Magnusson's findings suggest that smoking cessation during pregnancy would result in a reduced prevalence of childhood allergic disease. Other investigators have failed to find an association between cord blood IgE and maternal smoking.¹³

In this present study, we did not find a significant association between maternal smoking and cord blood IgE concentration or IgD when we were controlling for other variables. Our prospectively studied population consists of 841 subjects, representative of mid-

dle-class women from suburban Detroit. We do not believe that we are missing a significant association, since we have used both univariate and multivariate statistical strategies in this large population. We also repeated the analysis with only infants of nonatopic parents, as described by Magnusson,¹² and again found no evidence for elevated cord blood IgE from maternal smoking. In the multivariate analysis, we considered the same variables that Magnusson reported to influence the effect of smoking on IgE and IgD: maternal and paternal histories of allergy, parental smoking, and the child's sex. We also evaluated the possible influence of birth length and weight, since these were reduced in infants of smoking mothers. A major strength of our study is that the sample size was sufficient to support multivariate analysis of the data.

We do not believe that the different results are because of different analytical methods for measuring the immunoglobulin concentrations for several reasons. The geometric mean IgE and IgD values are similar in both studies. Both IgE assays were evaluated in a blinded study designed to test the ability of assays to measure the small quantities of IgE present in cell cultures (assay numbers 15 and 19 in the reference).¹⁸ The observed sensitivity of our ELISA was slightly greater than that of the particle counting immunoassay used by Magnusson, 0.05 versus 0.10 ng/ml, and the accuracy of the assays, when duplicate samples were measured containing 0.5 ng/ml of IgE was similar, 0.19 and 0.49 ng/ml for the ELISA compared to 0.23 and 0.22 ng/ml for the particle counting immunoassay.

A critical issue is the accuracy of the smoking histories. In the present study, the smoking histories were obtained prospectively, and the histories were validated in a subset of 114 cord blood samples by use of a cotinine assay. The presence or absence of detectable cotinine was highly associated with the mothers' self-reported smoking behavior. The discrepancies between cotinine measurements and smoking histories were mostly the lack of detectable cotinine in 21 of 94 smoking mothers. This may be due to insufficient assay sensitivity or an absence of smoking before or during labor. The magnitude of the correlation between the serum cotinine levels and the number of cigarettes reportedly smoked is similar to that found by other investigators.¹⁹ As in Magnusson's study, we detected a highly significant association between smoking and a lower birth weight, and in addition, we found decreased birth length. The cotinine results and the differences in birth weights and lengths support the accuracy of the self-reported smoking behavior.

We also observed significantly higher cord blood IgE concentrations in nonwhite compared to white infants. In one limited study, no racial differences were detected in cord blood IgE concentrations,²⁰ whereas other studies are consistent with our observation of higher cord blood IgE concentrations in nonwhite infants.^{21, 22} This finding suggests that if cord blood IgE levels are to be used to predict the risk of allergy, racial differences will need to be considered.

In agreement with Magnusson's study, we found a weak but consistent association between paternal smoking and cord blood IgD concentration; however, we could not find a plausible explanation for this observation. This observation in two studies is intriguing and perhaps results from a relationship between paternal smoking and another variable related to cord blood IgD.

This lack of association between maternal smoking and cord blood IgE is in agreement with our previous study demonstrating no association between parental smoking and allergen-specific IgE concentrations in older children.²³ It is also in agreement with other prospective studies that failed to find an association between maternal smoking and allergic disease.⁵

We plan to follow this cohort of children until they are 4 years of age to learn if there is an association between parental smoking and the onset of allergic sensitization and respiratory disease.

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REFERENCES

1. Ferris BG, Ware JH, Berkey CS, Dockery DW, Spiro A, Speizer FE. Effects of passive smoking on health of children. *Environ Health Perspect* 1985;63:289-95.
2. Ware JH, Dockery DW, Spiro A, Speizer FE, Ferris BG. Passive smoking, gas cooking, and respiratory health of children living in six cities. *Am Rev Respir Dis* 1984;129:366-74.
3. Angione AM, Fanciulli G, Corchia C. Frequency of and risk factors for allergy in primary school children: results of a population survey. *Paediatr Perinat Epidemiol* 1989;3:248-55.
4. Geller-Bernstein G, Kennett R, Weisglass L, Tsur S, Lahav M, Levin S. Atopic babies with wheezy bronchitis. *Allergy* 1987;42:85-91.
5. Horwood LJ, Fergusson DM, Hons BA, Shannon FT. Social and familial factors in the development of early childhood asthma. *Pediatrics* 1985;75:859-68.
6. Zetterstrom O, Osterman K, Machado L, Johansson SGO. Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. *Br Med J* 1981;283:1215-7.
7. Bahna SL, Heiner DC, Myhre BA. Immunoglobulin E pattern in cigarette smokers. *Allergy* 1983;38:57-64.

8. Bahna SL, Heiner DC, Myhre BA. Changes in serum IgD in cigarette smokers. *Clin Exp Immunol* 1983;51:624-30.
9. Zetterstrom O, Nordvall SL, Bjorksten B, Ahlstedt S, Stelander M. Increased IgE antibody responses in rats exposed to tobacco smoke. *J ALLERGY CLIN IMMUNOL* 1985;75:594-8.
10. Kjellman NIM, Croner S. Cord blood IgE determination for allergy prediction - a follow up to seven years of age in 1651 children. *Annals Allergy* 1984;53:167-71.
11. Businco L, Marchetti F, Pellegrini G, Perlini R. Predictive value of cord blood IgE levels in "at risk" newborn babies and influence of type of feeding. *Clin Allergy* 1983;13:503-8.
12. Magnusson CGM. Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. *J ALLERGY CLIN IMMUNOL* 1986;78:898-904.
13. 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.
14. Rowe MS, Bailey J, Ownby DR. Evaluation of the cause of nasal and ocular symptoms associated with lawn mowing. *J ALLERGY CLIN IMMUNOL* 1986;77:714-9.
15. Rowe DS, Anderson SG, Tackett L. A research standard for human serum immunoglobulin D. *Bull WHO* 1970;43:607-9.
16. Kimpen J, Callaert H, Embrechts P, Bosmans E. Cord blood IgE and month of birth. *Arch Dis Child* 1987;62:478-82.
17. Tseng RYM, Lam CWK, Loong EPL, Ho DWY, Davies DP. Lower incidence of elevated umbilical cord serum IgE concentration in infants of hepatitis B carrier mothers. *Acta Paediatr Scand* 1989;78:127-8.
18. Helm RM, Buckley RH, Adkinson NF Jr, Squillace DL, Gleich GJ, Yunginger JW. Variability of IgE protein measurement in cell-culture supernatants: results from a multicenter collaborative study. *J ALLERGY CLIN IMMUNOL* 1986;77:880-90.
19. Patteshall EN, Strope GL, Etzel RA, Helms RW, Haley NJ, Denny FW. Serum cotinine as a measure of tobacco smoke exposure in children. *Am J Dis Child* 1985;139:1101-4.
20. Thomas J, Abrishami MA, Chehreh MN, Walters CS. Neonatal IgE values in the black population. *Ann Allergy* 1979;43:144-5.
21. Magnusson CGM, Masson PL. Immunoglobulin E assayed after pepsin digestion by an automated and highly sensitive particle-counting immunoassay: application to human cord blood. *J ALLERGY CLIN IMMUNOL* 1985;75:513-24.
22. Haus M, Heese HDeV, Weinberg EG, Potter PC, Hall JM, Malherbe D. The influence of ethnicity, an atopic family history, and maternal ascariasis on cord blood serum IgE concentrations. *J ALLERGY CLIN IMMUNOL* 1988;82:179-89.
23. Ownby DR, McCullough J. Passive exposure to cigarette smoke does not increase allergic sensitization in children. *J ALLERGY CLIN IMMUNOL* 1988;82:634-8.

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