

## Maternal Alcohol Ingestion and Blood Cord IgE Concentrations

MARY GRZYBOWSKI, Ph.D.,<sup>1</sup> DENNIS R. OWNBY, M.D.,<sup>2</sup>  
CHRISTINE C. JOHNSON, Ph.D.,<sup>3</sup> and  
EDWARD L. PETERSON, Ph.D.<sup>3</sup>

### ABSTRACT

Previous reports have implicated maternal ethanol ingestion as a cause of immunoglobulin abnormalities in children. We investigated the relationship between self-reported alcohol ingestion in 98 women during pregnancy and serum cord Immunoglobulin E (IgE). We found that mean cord IgE concentrations were significantly lower among newborns born to drinking mothers (0.15 IU/ml) than nondrinking mothers (0.27 IU/ml),  $p \leq 0.05$ . The difference of serum cord IgE means remained significant among infants with a positive family history of allergic disease, 0.15 IU/ml for infants of drinking mothers and 0.40 IU/ml of nondrinking mothers. There was a significant trend for lower mean cord IgE with increasing ethanol ingestion ( $p \leq 0.05$ ). Maternal alcohol drinking should be considered a potential influence on cord blood IgE concentrations at birth.

### INTRODUCTION

MANY STUDIES HAVE REPORTED ADVERSE EFFECTS of maternal alcohol consumption on fetal growth and immunological development in animals.<sup>(1-3)</sup> However, few studies have explored the relationship between prenatal alcohol consumption and immune parameters in humans. Animal models have demonstrated that ethanol ingestion throughout fetal development critically impairs thymus development. A reduction in circulating lymphoid cells and a depletion of lymphocytes from the thymus and spleen have been shown in both animal and human studies.<sup>(1-5)</sup> The impact of these changes on host defenses has not yet been established.

Immunologic abnormalities have been reported in children with fetal alcohol syndrome (FAS). Johnson et al. reported decreased concentrations of IgG, IgA, or IgM in children with FAS.<sup>(4)</sup> Ammann et al. reported four infants with DiGeorge syndrome associated with maternal alcoholism.<sup>(5)</sup> To our knowledge, only one study investigated the association between maternal intake of alcohol during pregnancy and serum cord immunoglobulin E (IgE) concentrations.<sup>(6)</sup> A Denmark study found that maternal ethanol consumption during pregnancy was significantly associated with elevated IgE concentrations. A significant dose-related increase in the odds ratio was also demonstrated after controlling for the infants' sex, birth weight and length, month of birth, atopic family history, and the mothers' smoking habits during pregnancy. To fur-

---

<sup>1</sup>Department of Emergency Medicine and <sup>2</sup>Allergy Research Laboratory, Henry Ford Hospital, and <sup>3</sup>Division of Biostatistics and Research Epidemiology, Henry Ford Health Sciences Center, Detroit, Michigan 48202.

ther examine this potential association, we examined the relationship between ethanol ingestion during pregnancy and serum cord IgE concentrations in a prospective population-based study.

## MATERIALS AND METHODS

The current study population is derived from an ongoing prospective investigation following a cohort of children from birth to assess the relationship between environmental allergen exposure and childhood allergies and asthma. The details of recruitment for the Childhood Allergy Study have been previously described.<sup>(7)</sup> In brief, pregnant women residing within a suburban Detroit area defined by contiguous zip codes, whose expected dates of confinement were between April 15, 1987 and August 31, 1989, were recruited. Eligible women were also required to be at least 18 years of age and be members of a large health maintenance program (Health Alliance Plan). This research was approved by the Henry Ford Hospital Human Rights Committee.

Trained nurse interviewers contacted the women during midterm prenatal visits. One child per family was enrolled. Standardized questionnaires were completed regarding demographics, current smoking habits, and physician-diagnosed parental history of asthma, seasonal rhinitis, and allergies. Selected demographic characteristics included maternal age, race, and educational status. To obtain pilot data for another study, we added questions about alcohol consumption to the questionnaire on March 23, 1989. Therefore, alcohol consumption data were obtained from women with expected dates of delivery during the last 5 months of the 28 1/2-month enrollment period. Each woman was asked, "During this pregnancy, how often do you drink beer, wine or liquor?" Responses were classified as "about everyday," "3–5 times a week," "about once a week," "less than once a week," "less than once a month," or "never."

Infant delivery data, including date of birth, gender, and birth weight and length, were abstracted from medical records. At the time of delivery, serum cord specimens were collected, separated, and stored at  $-20^{\circ}\text{C}$  until assayed. Total IgE and IgA levels in the cord sera were quantitated as described previously using an enzyme-linked immunoassay.<sup>(7)</sup> Six serum samples with IgA levels above  $30\text{ }\mu\text{g/ml}$  were excluded because of probable contamination by maternal blood.<sup>(7–9)</sup> The routine sensitivity of the assay was 0.02 IU/ml of IgE and the average interassay coefficient of variation was 17.6%.<sup>(7)</sup>

### *Statistical methods*

For statistical analyses, the following variables were dichotomized: race (white/nonwhite), education (high school education or less/post high school education), and smoking status (yes/no). Parental allergic disease was defined as physician-diagnosed asthma, hay fever, or atopic dermatitis. The baby was classified as having a positive family allergy history if either parent reported having any form of allergic disease. Alcohol consumption was examined dichotomously (no ethanol consumption/any ethanol consumption) and by level of consumption (no ethanol ingestion/less than one drink per month/more than one drink per month).

Serum cord IgE levels were positively skewed; therefore, the IgE values were transformed via natural logarithm, and the geometric mean is reported throughout. Maternal demographic variables, infant delivery data, and IgE values were compared between drinkers and nondrinkers with chi-square and two-sided Student's *t* tests. Fishers exact test and Welch's *t* test were used when indicated by the data. Least-squares regression was used to evaluate the trend in mean cord blood IgE values with ethanol ingestion.

## RESULTS

Of 1,194 eligible women contacted for the study during the entire recruitment period, 953 (80%) consented to participate. Cord sera were obtained from infants of 740 (88%) of the 841 women enrolled during the first 23 1/2 months and from 101 (90%) of the 112 enrolled during the last five months.

Of the 101 women who were interviewed during the last 5 months of the enrollment period and for whom valid cord sera were available for the newborns, one woman refused to answer the question assessing alcohol consumption, and two women were inadvertently administered a questionnaire without the alcohol

# MATERNAL ALCOHOL AND SERUM CORD IgE

**TABLE 1. NEWBORN CHARACTERISTICS BY GENDER  
(MEAN AND STANDARD DEVIATION  $N = 98$ )**

|                               | <i>Males</i><br>( $N = 48$ ) | <i>Females</i><br>( $N = 50$ ) |
|-------------------------------|------------------------------|--------------------------------|
| Weight (kg) <sup>a</sup>      | $3.7 \pm 0.6$                | $3.5 \pm 0.5$                  |
| Length (cm) <sup>b</sup>      | $52.9 \pm 2.9$               | $52.0 \pm 2.6$                 |
| Log IgE <sup>c</sup>          | $-1.3 \pm 1.5$               | $-1.7 \pm 2.6$                 |
| IgE mean (IU/ml) <sup>d</sup> | 0.27                         | 0.19                           |

<sup>a</sup> $p \leq 0.05$  comparing males to females.

<sup>b</sup>Differences are not significant between males and females ( $p \geq 0.13$ ).

<sup>c</sup>The mean and standard deviations are the log-transformed values of IgE.

<sup>d</sup>Geometric mean;  $p = 0.20$  comparing males to females.

questions, yielding a sample size of 98. The 98 women averaged 1 year older (1.3 years,  $p \leq 0.01$ ) than the 740 women interviewed during earlier enrollment, but they did not differ significantly in terms of race ( $p = 0.35$ ), education ( $p = 0.07$ ), smoking status ( $p = 0.26$ ), and allergic disease history ( $p = 0.91$ ).

The newborns' mean IgE concentration in the serum cord was 0.23 IU/ml (range,  $\leq 0.01$  to 2.30 IU/ml). Forty-nine percent of the infants were males. Male infants weighed significantly more than the females ( $p \leq 0.05$ ), but differences in length and IgE concentrations between males and females were not significant (Table 1).

The mean age of the mothers in the present study was  $30 \pm 4.3$  years and for the fathers,  $32 \pm 4.9$  years. The mothers were 90% white, 70% had a post-high school education, 13% smoked, and 24% had a history of allergic disease. Paternal prevalence of allergic disease was 21%. None of the mothers reported drinking daily, 2.0% drank 2–5 times a week, 3.1% drank about once a week, 5.1% drank less than once a week, 22.5% drank less than once a month, and 67.3% stated they never drank during their pregnancy. Mean serum cord IgE levels were higher among newborns with positive parental allergy histories (0.30 IU/ml) than those infants without allergy histories (0.17 IU/ml),  $p \leq 0.05$  (Table 2).

Mothers who drank any alcohol during their pregnancy were older by almost 3 years than those who did not drink (32 versus 29 years,  $p \leq 0.01$ ). Fewer drinkers had histories of atopic disease (9.4 versus 30.3%,  $p \leq 0.05$ ). Drinking did not vary significantly by race, level of education, or current smoking status. Infant birth weight and length did not differ by maternal drinking status. However, infants of mothers who consumed ethanol during pregnancy had significantly lower cord IgE levels (0.15 IU/ml) than infants of mothers who did not consume ethanol at all (0.27 IU/ml),  $p \leq 0.01$  (Table 3).

Among the 44 babies with a family history of allergic disease, the mean serum cord IgE was significantly lower among newborns born to mothers who drank during their pregnancy (0.15 IU/ml) than those born to nondrinking mothers (0.40 IU/ml) ( $p \leq 0.05$ ). For the 54 babies without a family history of allergic disease,

**TABLE 2. COMPARISON OF MEAN CORD IgE BY PARENTAL HISTORY OF ALLERGY**

| <i>Allergy history status</i> | <i>Log IgE<sup>a</sup></i><br>( <i>mean <math>\pm</math> SD</i> ) | <i>IgE (IU/ml)<sup>b</sup></i><br>( <i>geometric mean</i> ) |
|-------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------|
| Positive history ( $N = 44$ ) | $-1.2 \pm 1.5$                                                    | 0.30                                                        |
| Negative history ( $N = 54$ ) | $-1.8 \pm 1.3$                                                    | 0.17                                                        |

<sup>a</sup>The mean and standard deviations are the log-transformed values of IgE.

<sup>b</sup> $p \leq 0.05$  for differences in log IgE between infants with positive and negative histories of parental allergies.

**TABLE 3. COMPARISON OF MEAN WEIGHT, LENGTH, AND CORD SERUM IgE BY DRINKING STATUS**

|                          | <i>Drinkers</i><br>( <i>N</i> = 32) | <i>Nondrinkers</i><br>( <i>N</i> = 66) |
|--------------------------|-------------------------------------|----------------------------------------|
| Weight (kg) <sup>a</sup> | 3.6 ± 0.6                           | 3.6 ± 0.6                              |
| Length (cm) <sup>a</sup> | 52.8 ± 2.6                          | 52.3 ± 2.9                             |
| Log IgE <sup>b</sup>     | -1.9 ± 1.0                          | -1.3 ± 1.5                             |
| IgE (IU/ml) <sup>c</sup> | 0.15                                | 0.27                                   |

<sup>a</sup>Differences are not significant between drinkers and nondrinkers ( $p \geq 0.34$ ).

<sup>b</sup>The mean and standard deviations are the log-transformed values of IgE.

<sup>c</sup> $p \leq 0.05$  for differences in geometric mean IgE concentrations between drinkers and nondrinkers.

the relationship of means was in the same direction, 0.14 IU/ml for children of drinking mothers versus 0.19 IU/ml for children of nondrinking mothers, but this difference was not statistically significant.

Least-squares regression revealed an overall significant trend for lower mean cord IgE with increasing ethanol ingestion (Table 4). We also tested for trend stratifying by history of allergy. The trend was marginally significant among infants with a positive family history of allergy ( $p = 0.052$ ). Those infants with a negative family history of atopic disease had decreasing mean serum cord IgE values, but the test was not significant.

## DISCUSSION

In 1994, Bjerke and co-authors reported from Denmark that maternal ethanol ingestion during pregnancy was associated with increased serum cord concentrations of IgE after controlling for potential confounders.<sup>(6)</sup> These findings were based on predelivery questionnaires collecting information on ethanol ingestion and serum cord samples among a prospective cohort of 2,631 infants. Their finding suggests that ethanol is one factor that may influence fetal IgE synthesis and subsequent development of allergic diseases.

In this present study, we found a significant trend for lower mean cord IgE with increasing ethanol ingestion, contrary to Bjerke's findings.<sup>(6)</sup> This trend suggests a biological effect. The seemingly more dramatic pattern in infants with a positive family history of allergies may reflect the greater range of IgE values within this group or a greater effect of ethanol on the developing infant predisposed toward higher IgE

**TABLE 4. TRENDS IN MEAN SERUM CORD IgE WITH INCREASING ETHANOL INGESTION**

| <i>Ethanol consumption</i>   | <i>Total population</i><br>( <i>N</i> = 98) |                        |               | <i>Positive parental allergy</i><br><i>history</i><br>( <i>N</i> = 44) |                        |               | <i>Negative parental allergy</i><br><i>history</i><br>( <i>N</i> = 54) |            |               |
|------------------------------|---------------------------------------------|------------------------|---------------|------------------------------------------------------------------------|------------------------|---------------|------------------------------------------------------------------------|------------|---------------|
|                              | <i>Geometric mean</i>                       |                        |               | <i>Geometric mean</i>                                                  |                        |               | <i>Geometric mean</i>                                                  |            |               |
|                              | <i>N</i>                                    | <i>IgE<sup>a</sup></i> | <i>95% CI</i> | <i>N</i>                                                               | <i>IgE<sup>a</sup></i> | <i>95% CI</i> | <i>N</i>                                                               | <i>IgE</i> | <i>95% CI</i> |
| Denied any ethanol ingestion | 66                                          | 0.27                   | 0.19, 0.40    | 33                                                                     | 0.40                   | 0.23, 0.70    | 33                                                                     | 0.19       | 0.12, 0.30    |
| Less than 1 drink per month  | 22                                          | 0.16                   | 0.11, 0.25    | 8                                                                      | 0.19                   | 0.12, 0.30    | 14                                                                     | 0.15       | 0.08, 0.29    |
| More than 1 drink per month  | 10                                          | 0.11                   | 0.06, 0.22    | 3                                                                      | 0.09                   | 0.03, 0.26    | 7                                                                      | 0.12       | 0.05, 0.29    |

<sup>a</sup>Least-squares regression trend for lower mean cord IgE with increasing ethanol ingestion for the total population ( $p \leq 0.05$ ) and among babies with a family history of allergic disease ( $p = 0.052$ ).

## MATERNAL ALCOHOL AND SERUM CORD IgE

concentration. However, genetic predisposition,<sup>(10–12)</sup> independent of alcohol consumption, may also influence umbilical serum cord IgE concentrations and atopic risk of infants.<sup>(10,13,14)</sup> Studies have shown that a child's risk of becoming allergic increases if both parents are allergic and increases further if both parents have the same form of allergic disease.<sup>(6,8)</sup> Therefore, it is possible that the high serum cord IgE concentrations of infants with positive parental histories of atopy may relate to the degree of IgE producing potential of the infant.

Several reports suggest that alcohol may affect the developing human fetal immune system.<sup>(1–5)</sup> Ammann et al. reported four infants with DiGeorge syndrome born to mothers who were described as chronic alcoholics.<sup>(5)</sup> Ammann et al. also noted the clinical similarities between FAS and DiGeorge syndrome in terms of facial changes, cardiac, renal, and CNS malformations, and immune defects.<sup>(5)</sup> Johnson et al. reported abnormally low levels of serum IgG, IgA, or IgM in 9 of 13 infants with FAS.<sup>(4)</sup> Serum IgE levels were not evaluated.<sup>(4)</sup> Children with FAS are also at increased risk of infection.<sup>(4,5)</sup>

Even though alcohol consumption was only assessed during the final 5 months of the study, there is no evidence that the 98 women meeting study criteria in the final 5 months differed significantly from the 740 previously enrolled women except that they were 1 year older. There was no significant correlation in the entire larger study population ( $n = 838$ ) between maternal age and serum cord IgE level (data not shown).

An obvious difference between the study group and the entire Childhood Allergy Study cohort is that the data for the former group were collected during a limited time period rather than over 29 months and all seasons. The mean IgE concentration of the current study sample was not significantly different from that of the 740 babies from earlier enrollment (data not shown); however, the mean cord IgE concentration was higher in all babies, including the study babies, born in the spring and summer compared to the fall and winter babies (0.25 versus 0.18 IU/ml,  $p \leq 0.001$ ). While the development of hypersensitivity to specific allergens or diagnosis of asthma has been related to season of birth in some studies,<sup>(10,15)</sup> serum cord IgE was not associated with season of birth in a Swedish study.<sup>(16)</sup> Since no maternal alcohol exposure data were collected on the previously enrolled infants to assess the association between maternal alcohol consumption and seasonality, we cannot exclude the possibility that the observed depression of cord IgE with maternal alcohol intake is conditional on time of year.

A strength of this study is that it is prospective and population-based. However, alcohol consumption was self-reported. A critical issue is the accuracy of the ethanol ingestion history. Pregnant women may under report alcohol consumption,<sup>(17,18)</sup> and there is no convenient, biologic marker to independently verify reported consumption. Previous case reports showing decreased immunoglobulin concentrations in children with FAS probably involved higher levels of *in utero* alcohol exposure since none of the children in this study had evidence of FAS. However, one would presume that the women are generally classified correctly relative to each other. Further, it is reasonable to assume that the classification error in drinking frequency is not systematically associated with serum cord IgE level.

Another limiting factor is the sample size in the current study, which may contribute to the discrepancy in study results concerning the association of ethanol and serum cord IgE concentrations. However, as in Bjerke's study,<sup>(6)</sup> males infants had higher IgE concentrations than female infants, although we found no statistically significant difference. Compared to Bjerke's study, the proportion of biparental atopic disease is significantly higher ( $p \leq 0.001$ ). This disparity may reflect a difference in the atopic diseases used to define parental atopic history.

We have found an association between maternal drinking and decreased mean cord serum IgE concentrations. Biologic mechanisms regarding the alcohol-induced decrease in serum cord IgE concentrations are unknown. This finding is consistent only with previous reports of decreased immunoglobulins in children with FAS. We do not know whether maternal drinking will affect the risk of allergic disease in children. These observations deserve further study.

## ACKNOWLEDGMENTS

We acknowledge Nonna Akkerman, Gerri Berg, Shirley Blocki, Judith McCullough, and Karen Wells for their assistance with this study. This work is supported by the National Institute for Allergy and Infectious

Diseases Grant AI24156, and by the Fund for Henry Ford Hospital. Presented at the 1992 Society of Epidemiologic Research Conference, Minneapolis, MN.

## REFERENCES

1. Monjan AA, Mandell W. Fetal alcohol and immunity: Depression of mitogen-induced lymphocyte blastogenesis. *Neurobehavior Technol* 1980;2:213–215.
2. Ewald SJ, Frost WW. Effect of prenatal exposure on development of the thymus. *Thymus* 1985;9:211–215.
3. Ewald SJ, Walden SM. Flow cytometric and histologic analysis of mouse thymus in fetal alcohol syndrome. *J Leukocyte Biol* 1988;44:434.
4. Johnson S, Knight R, Marmer D, Steele R. Immune deficiency in fetal alcohol syndrome. *Pediatr Res* 1981;15:908–911.
5. Ammann A, Wara D, Cowan M, Barrett D, Stiehm R. The DiGeorge syndrome and the fetal alcohol syndrome. *Am J Dis Child* 1982;136:906–908.
6. Bjerke T, Hedegaard M, Henriksen TN, Nielson BW, Schiotz PO. Several genetic and environmental factors influence cord blood IgE concentration. *Pediatr Allergy Immunol* 1994;5:88–94.
7. Ownby D, Johnson C, Peterson E. Maternal smoking does not influence cord serum IgE or IgD concentrations. *J Allergy Clin Immunol* 1991;88:555–560.
8. Kimpen J, Callaert H, Embrechts P, Bosmans E. Cord blood IgE and month of birth. *Arch Dis Child* 1987;62:478–482.
9. 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;78:127–128.
10. Kjellman NIM. Predictive value of high IgE levels in children. *Acta Paediatr Scand* 1976;65:465–471.
11. Marsh DG, Meyers DA, Bias WB. The epidemiology and genetics of atopic allergy. *N Engl J Med* 1981;305:1551–1559.
12. Halonen M, Stern D, Lyle S, Wright A, Taussig L, Martinez FD. Relationship of total serum IgE levels in cord and 9-month sera of infants. *Clin Exp Allergy* 1991;21:235–241.
13. Croner S, Kjellman NIM, Eriksson B, Roth A. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 1982;57:364–368.
14. 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;65:422–430.
15. Johnson CC, Ownby DR, McCullough J. Month of birth and risk of immediate hypersensitivity to seasonal and non-seasonal allergens. *Pediatr Asthma Allergy Immunol* 1989;3:111–121.
16. Croner S, Kjellman NIM. Predictors of atopic disease: Cord blood IgE and month of birth. *Allergy* 1986;41:68–70.
17. Ernhart CB, Morrow-Tlucak M, Sokol RJ, Martier S. Underreporting of alcohol use in pregnancy. *Alcoholism Clin Exp Res* 1988;12:506–511.
18. Verkerk PH. The impact of alcohol misclassification on the relationship between alcohol and pregnancy outcomes. *Int J Epidemiol* 1992;21 (suppl 1):S33–S37.

Address reprints to:  
*Mary Grzybowski, Ph.D.*  
*Department of Emergency Medicine*  
*Henry Ford Hospital*  
*2799 West Grand Blvd*  
*Detroit, MI 48202*