OBSTETRICS

Maternal Rh D status, anti-D immune globulin exposure during pregnancy, and risk of autism spectrum disorders

Lisa A. Croen, PhD; Marilyn Matevia, MA; Cathleen K. Yoshida, MS; Judith K. Grether, PhD

OBJECTIVE: The objective of the study was to investigate the association between maternal Rh D status, prenatal exposure to anti-D immune globulin, and the risk of autism in the offspring.

STUDY DESIGN: Case-control study among children born from 1995 to 1999 at Kaiser Permanente Northern California hospitals. Cases (n = 400) were children with an autism diagnosis; controls (n = 410) were children without autism, randomly sampled and frequency matched to cases on sex, birth year, and birth hospital. Maternal Rh D status and anti-D immune globulin exposure were ascertained from prenatal medical records.

RESULTS: No case-control differences were observed for maternal Rh negative status (11.5% vs 10.0%, $P = .5$) or prenatal anti-D immune globulin exposure (10.0% vs. 9.3%, $P = .7$). Risk of autism remained unassociated with maternal Rh status or prenatal exposure to anti-D immune globulins after adjustment for covariates.

CONCLUSION: These data support previous findings that prenatal exposure to thimerosal-containing anti-D immune globulins does not increase the risk of autism.

Key words: autism spectrum disorders, perinatal risk factors, RhoGam, thimerosal

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Autism spectrum disorders (ASD) encompass a range of neurodevelopmental disorders with varying degrees of severity. As a group, individuals with ASD are characterized by impairments in social interaction and communication and often have restricted, stereotyped interests and behaviors.[1] Although the causes of ASD are unknown, a significant body of research provides evidence for a strong genetic contribution, although to date, no specific autism genes have been identified.[2]

The reported prevalence of ASD has increased dramatically since the early 1980s,[3] and although some have attributed this trend only to an expansion of the diagnosis and/or increased awareness, others believe that the increased rates also represent a true increase in incidence (occurrence), suggesting a role for environmental factors.[4]

The environmental factor that has received the most attention is thimerosal, which is 49.6% ethyl mercury by weight and has been used as a preservative in multidose vials of vaccines since the 1930s. Over the time period during which autism prevalence initially increased, the number of recommended childhood vaccines also increased, resulting in higher levels of exposure to ethyl mercury from thimerosal among infants following the recommended immunization schedule.[5] This, coupled with the known neurotoxic effects of methylmercury,[6,7] led to widespread speculation regarding a possible association between early exposure to thimerosal and autism risk.[8-10] However, subsequent analyses have demonstrated that the prevalence of autism has continued to increase following removal of thimerosal from most childhood vaccines.[11-14] Nonetheless, concern about thimerosal as a contributor to autism continues.

Beginning in the 1970s, recommendations for the administration of anti-D immune globulin (RhIg) were introduced for prophylaxis against hemolytic disease of the newborn, which can result from rhesus (D) alloimmunization. The current recommendation stipulates that all Rh-negative woman who are not Rh D alloimmunized should receive a single 300-μg dose of RhIg at approximately 28 weeks of gestation and again within 72 hours after the delivery of a Rh-positive infant.[15] The predominant RhIg product used in the United States is RhoGam (Ortho-Clinical Diagnostics, Inc, Raritan, NJ). Until 2001, RhoGam contained thimerosal at a concentration of 0.003% (10.5 μg of ethyl mercury on average).[16]

From the Division of Research, Kaiser Permanente Northern California, Oakland (Dr Croen, Ms Matevia, and Ms Yoshida), and the Environmental Health Investigations Branch, California Department of Public Health, Richmond (Dr Grether), CA.

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Reprints: Lisa A. Croen, PhD, Division of Research, Kaiser Permanente, 2000 Broadway, Oakland, CA 94612. lisa.a.croen@kp.org.

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See Journal Club, page 322

The purpose of this study was to investigate the relationship between maternal Rh status, prenatal exposure to thimerosal from Rh immune globulins, and autism risk using a large, population-based case-control design. We further examined risk within demographically and phenotypically defined groups of children in an attempt to identify particular subgroups that may have increased vulnerability to these exposures.

Materials and Methods

Our study was part of a larger case-control study examining pre-, peri-, and neonatal risk factors for autism spectrum disorders. The study population was identified from the membership of Kaiser Permanente Northern California (KPNC), a group model, integrated health plan that provides care for more than 3.2 million northern California residents. The KPNC membership represents approximately 30% of the insured population in the region and is demographically similar to the residents of the counties served by KPNC, except that the very poor and very wealthy are underrepresented.[17] Cases and controls were identified from the cohort of infants born at a KPNC facility between January 1995 and December 1999 who remained KPNC members for at least 2 years following birth.

Cases (n = 420) were defined as children with at least 1 diagnosis of an ASD, including autism (*International Classification of Diseases, 9th Revision, Clinical Modification*[18] [ICD-9-CM] code 299.0) and Asperger disorder or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) (ICD-9-CM code 299.8) recorded anytime between January 1995 and December 2002. Diagnoses were identified by electronically scanning the KPNC outpatient clinical databases, which contain all diagnoses made at outpatient visits occurring at plan facilities and outside approved facilities. All children were between 4 and 7 years of age at the time the databases were scanned.

Children with ASD were further classified according to the number of ASD affected children in the siblingship (simplex [1] vs multiplex [2 or more]), and the severity of the diagnosis (autistic disorder [ICD-9-CM code 299.0] vs Asperger disorder or PDD-NOS [ICD-9-CM code 299.8]).

Initially, we randomly selected 5 controls per case from the cohort of births without an ASD diagnosis. Controls (n = 2100) were frequency matched to cases on sex, birth year, and hospital of birth. This entire control group was used in previous analyses of other perinatal risk factors ascertained from information recorded in the KPNC automated clinical databases.[19-21] For the current analysis, which relied on the review and abstraction of maternal medical records, we included only 1 randomly sampled control per case.

There were 13 case mothers and 5 control mothers who each had 2 children included in the original study cohort. To ensure independence of observations with respect to characteristics of the mother, we randomly sampled 1 child for each woman for inclusion in the final analytic file. Furthermore, children for whom maternal medical charts could not be located and abstracted (3 cases, 1 control) and children with missing data on any of the covariates (4 cases, 4 controls) were dropped from the final study file.

Information on maternal Rh status and Rh immunoglobulin exposure during pregnancy (date, dose, manufacturer, and product name) was abstracted from prenatal medical records using a standardized form. Information on receipt of the influenza vaccine during pregnancy was also recorded because it contained the preservative thimerosal (25 μg of ethyl mercury) during this time period.

Information on several maternal characteristics (age at delivery, race/ethnicity, educational attainment at delivery, parity) and infant characteristics (sex, birthweight, gestational age, plurality [ie, singleton or multiple]) was obtained from medical records and health plan and vital statistics databases.

Differences between cases and controls in the frequency of maternal Rh-negative status and Rh immunoglobulin exposure were compared with a χ^2 statistic. Relative risks were estimated by crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression. Maternal and infant characteristics that were associated with maternal Rh status or Rh immunoglobulin exposure and infant case status were included as covariates in multivariate analyses. This study had 80% power to detect a minimum odds ratio of 1.9 given a background exposure prevalence of 10%.

All study procedures were approved by the KPNC Institutional Review Board and the California State Committee for the Protection of Human Subjects.

Results

Characteristics of the 400 cases and the 410 controls in the final study population are shown in Table 1. Males outnumbered females by 4 to 1, with a similar distribution among cases and controls because of matching. The distribution of gestational age, birthweight, and plurality was similar for cases and controls; the percentage of children with third or higher birth order was greater among controls. Mothers of case children were somewhat older and had more years of education than the control mothers, but the race/ethnic distribution was similar between the 2 study groups.

Overall, 10.7% (n = 87) of the study population had a Rh-negative mother. The frequency of Rh-negative status varied by race/ethnicity (16% in whites, 6% in Hispanics, 7% in blacks, and 3% in Asians) and was similar to published rates (15% in whites, 5-8% in blacks, and 1-2% in Asians).[22] The proportion of Rh-negative mothers did not differ between cases and controls (11.5% vs 10.0%, $P = .49$; OR, 1.17, 95% CI, 0.75 to 1.82).

Single and multiple variable adjustment for sex, maternal age, maternal race/ethnicity, maternal education, parity, and plurality did not alter the results (Table 2). Furthermore, no association between maternal Rh status and autism risk was observed for subgroups of children defined by sex, plurality, autism severity, birth order, or number of ASD-

TABLE 1
Characteristics of the study population of children with ASD and controls, Kaiser Permanente Northern California births, 1995-1999

Characteristics	ASD cases (n = 400), n (%)	Controls (n = 410), n (%)	*P* value[a]
Gender (male)	330 (82.5)	335 (81.7)	.77
Plurality			.07
Singleton	377 (94.3)	397 (96.8)	
Twin or triplet	23 (5.7)	13 (3.2)	
Birth order			.003
First born	176 (44.0)	175 (42.7)	
Second born	159 (39.8)	131 (31.9)	
Third or later born	65 (16.3)	104 (25.4)	
Maternal age, y			.07
Younger than 20	6 (1.5)	11 (2.7)	
20-24	44 (11.0)	58 (14.2)	
25-29	99 (24.8)	126 (30.7)	
30-34	135 (33.8)	124 (30.2)	
35-39	98 (24.5)	79 (19.3)	
40 or older	18 (4.5)	12 (2.9)	
Maternal education			.0001
Less than high school	21 (5.3)	30 (7.3)	
High school	78 (19.5)	126 (30.7)	
College	220 (55.0)	206 (50.2)	
Postgraduate	79 (19.8)	44 (10.7)	
Unknown	2 (0.5)	4 (1.0)	
Maternal race/ethnicity			.24
White, non-Hispanic	206 (51.5)	197 (48.1)	
White, Hispanic	65 (16.3)	92 (22.4)	
Black	35 (8.8)	37 (9.0)	
Asian	41 (10.3)	34 (8.3)	
Other	53 (13.3)	50 (12.2)	
Gestational age, mean (SD)	39.35 (2.0)	39.46 (1.8)	.43
Birthweight, mean (SD)	3422 (662)	3485 (596)	.16

[a] Categorical variables, compared with a χ^2 statistic; means, compared with a 2-sample Student *t* test.

Croen. Maternal Rh D status, anti-D immune globulin, and autism spectrum disorders. Am J Obstet Gynecol 2008.

affected children in the siblingship (Table 2).

Of the 87 Rh-negative women, 78 (89.7%) received Rh immunoglobulin during the pregnancy (36 in the prenatal period only, 41 in the prenatal and immediate postnatal period, and 1 in the immediate postnatal period only). Among the 9 Rh-negative women who did not receive RhIg, 7 had an Rh-negative partner. For the remaining 2, it is possible that RhIg was in fact administered but not documented in the prenatal charts. In addition, 1 Rh-positive woman received RhIg in the prenatal period. Although her status was confirmed as Rh positive, her blood type was recorded as both Rh positive and Rh negative in the prenatal record, resulting in the erroneous administration of RhIg.

Of the 78 women (40 cases, 38 controls) with prenatal RhIg exposure, 72 (36 cases, 36 controls) received only 1 prenatal injection and 6 (4 cases, 2 controls) received 2 injections in the prenatal period. The mean gestational age at the first prenatal injection was 27 weeks (SD 6.0 weeks), in accordance with guidelines from the American College of Obstetricians and Gynecologists. The product used for all RhIg injections was RhoGam, which contained thimerosal (10.5 μg of ethyl mercury, on average).

TABLE 2
Association between maternal Rh status and ASD, Kaiser Permanente Northern California births, 1995-1999

Exposure	ASD cases, n (%)	Controls, n (%)	Odds ratio (95% CI)[a]
Total			
Rh-positive status	354 (88.5)	369 (90.0)	1.0 (referent)
Rh-negative status	46 (11.5)	41 (10.0)	1.1 (0.68 to 1.74)[b]
Subgroups (data shown for Rh-negative only)[c]			
Female	8 (11.4)	7 (9.3)	1.3 (0.4 to 3.66)
Male	38 (11.5)	34 (10.2)	1.2 (0.71 to 1.88)
Singleton	42 (11.1)	41 (10.3)	1.1 (0.69 to 1.72)
Multiple	4 (17.4)	0 (0.0)	6.2 (0.31 to 125.53)
First born	17 (10.0)	16 (8.9)	1.1 (0.56 to 2.33)
Second or later born	29 (12.6)	25 (10.9)	1.2 (0.67 to 2.09)
Simplex	44 (11.6)	41 (10.0)[d]	1.2 (0.76 to 1.86)
Multiplex	2 (9.1)	41 (10.0)[d]	0.9 (0.20 to 3.99)
Autistic disorder	27 (10.7)	41 (10.0)[d]	1.1 (0.64 to 1.80)
Asperger/PDD-NOS	19 (12.9)	41 (10.0)[d]	1.3 (0.75 to 2.38)

[a] Odds ratios and 95% confidence intervals estimated from logistic regression models.

[b] Adjusted for sex, birth order, plurality, maternal age, maternal race/ethnicity, and maternal education.

[c] Subgroup analyses were not adjusted for other covariates in the table.

[d] Case subgroups were compared with all controls because controls could not be stratified by number of ASD-affected children in the siblingship or autism severity.

Croen. Maternal Rh D status, anti-D immune globulin, and autism spectrum disorders. Am J Obstet Gynecol 2008.

A similar proportion of the case and control mothers received any RhIg (prenatal and/or postnatal) for the study pregnancy (10.2% vs 9.3%, $P = .64$; OR, 1.12, 95% CI, 0.70 to 1.78). Furthermore, the distribution of the total number of RhIg injections received was similar for both case and control mothers ($P = .66$).

There were no differences between cases and controls in the proportion of mothers who received prenatal RhIg for the study group as a whole (10.0% vs 9.3%, $P = .72$; OR, 1.10, 95% CI, 0.68 to 1.73) or for any subgroups (Table 3). Finally, risk of autism was not associated with prenatal RhIg receipt after adjusting for covariates (Table 3).

Four mothers (1 case, 3 controls) received an influenza vaccine containing thimerosal during the prenatal period. None were Rh negative and none received RhIg during pregnancy. Prenatal thimerosal exposure from either source (RhIg injection or influenza vaccine) was also not associated with autism risk (OR, 1.0, 95% CI, 0.65 to 1.6).

Comment

Our findings of no association between maternal Rh status, prenatal Rh immunoglobulin exposure, and autism spectrum disorders are consistent with the recent study by Miles and Takahashi,[23] who surveyed 214 families of children with ASD ascertained through a university-based autism clinic in Missouri between 1995 and 2005. In comparison with mothers of children with Down syndrome, they found that mothers of children with ASD were no more likely to be Rh negative or to be treated with thimerosal-containing RhIg during their pregnancy. The proportion of Rh-negative mothers among the children with ASD was also similar to the frequency of Rh-negative status among 2 other contemporaneous control groups: patients typed at the university hospital blood bank and individuals who donated blood at the Missouri-Illinois Red Cross.[23] Additionally, they found no evidence to support an association in any autism phenotypic subgroup.

The proportion of children with prenatal exposure to thimerosal from RhIg in our study sample (9.6%) is similar to that reported by Thompson et al (9.3%),[24] who conducted a large national cohort study to examine early thimerosal exposure and neuropsychological outcomes at 7-10 years of age. In that study, increasing prenatal exposure to mercury from thimerosal-containing vaccines and immune globulins was significantly associated with 2 of 42 outcomes; improved performance on the speeded naming test (NEPSY) and poorer performance on the digit-span test of backward recall (Wechsler Intelligence Scale for Children, 3rd edition). Autism was not included as 1 of the outcomes in that study.

In contrast to our findings, 2 clinic-based studies with relatively small sample sizes suggested a positive association between prenatal thimerosal exposure from RhIg and autism. Holmes et al[25] reported that among children with autism who were referred to the clinical practice of 1 of the authors, 46% of the 94 moth-

TABLE 3
Association between prenatal exposure to anti-D immune globulin and ASD, Kaiser Permanente Northern California births, 1995-1999

Exposure	ASD cases, n (%)	Controls, n (%)	Odds ratio (95% CI)[a]
Total			
No anti-D immune globulin	360 (90.0)	372 (90.7)	1.0 (referent)
Prenatal anti-D immune globulin	40 (10.0)	38 (9.3)	1.0 (0.62 to 1.66)[b]
Subgroups[c] (data shown for subjects with prenatal anti-D immune globulin)			
Female	7 (10.0)	7 (9.3)	1.1 (0.36 to 3.25)
Male	33 (10.0)	31 (9.3)	1.1 (0.65 to 1.82)
Singleton	36 (9.6)	38 (9.6)	1.0 (0.62 to 1.61)
Multiple	4 (17.4)	0 (0.0)	6.2 (0.31 to 125.5)
First born	18 (10.6)	15 (8.3)	1.3 (0.63 to 2.68)
Second or later born	22 (9.6)	23 (10.0)	0.95 (0.51 to 1.76)
Simplex	39 (10.3)	38 (9.3)[d]	1.13 (0.70 to 1.80)
Multiplex	1 (4.6)	38 (9.3)[d]	0.45 (0.06 to 3.56)
Autistic disorder	24 (9.5)	38 (9.3)[d]	1.03 (0.60 to 1.76)
Asperger/PDD-NOS	16 (10.9)	38 (9.3)[d]	1.20 (0.65 to 2.22)

[a] Odds ratios and 95% confidence intervals estimated from logistic regression models.

[b] Adjusted for sex, birth order, plurality, maternal age, maternal race/ethnicity, and maternal education.

[c] Subgroup analyses were not adjusted for other covariates in the table.

[d] Case subgroups were compared with all controls because controls could not be stratified by number of ASD-affected children in the siblingship or autism severity.

Croen. Maternal Rh D status, anti-D immune globulin, and autism spectrum disorders. Am J Obstet Gynecol 2008.

ers completing the study survey reported receiving RhIg injections during pregnancy, compared with 9% of the 45 controls. Of note, the clinic draws families from all over the country who are concerned about mercury exposure and interested in chelation therapy. Thus, the study cases are likely unrepresentative of the general population of children with ASD, and estimates of RhIg exposure may be subject to ascertainment bias. Furthermore, exposure data were based on self-report and not validated by medical record review.

Similarly, Geier and Geier[26] found that the frequency of maternal Rh-negative status among 53 consecutive non-Jewish Caucasian patients with ASD referred to their genetic clinic was significantly higher than the frequency among 926 non-Jewish Caucasian pregnant women who presented at their clinic for prenatal genetic care (28.3% vs 14.4%, $P < .01$), and all ASD patients with Rh-negative mothers received RhIg during pregnancy. Given the authors' belief that thimerosal-containing vaccines cause autism, it is likely that the ASD patients who seek out their clinical services are skewed toward higher perceived mercury exposure. For that reason, these study findings may be biased and should be viewed with caution.

Our findings of no association are strengthened by our large, population-based study sample; the use of prospectively collected and clinically documented information on Rh status and RhIg receipt during pregnancy; physician-documented diagnoses of autism spectrum disorder; the use of an appropriately matched internal comparison group; and the use of multivariate analytic techniques to adjust for several important covariates. Because information on the exposures of interest (Rh status and RhIg treatment) was ascertained directly from medical records, and more than 95% of the study population initially identified was included in the final analysis, our results are unlikely to be subject to recall, ascertainment, or selection biases.

One limitation of this study is the lack of validation of the ASD diagnoses by a standardized clinical assessment for all study subjects. However, a subset of the cases in the current study (12.5%) participated in another study for which they underwent clinical evaluation with the Autism Diagnostic Interview-Revised (ADI-R)[27] and the Autism Diagnostic Observation Schedule-Generic (ADOS-G).[28] Among the 50 children evaluated with the ADI-R and ADOS-G, 94% met criteria for ASD on both instruments, and 100% met criteria on at least one. Furthermore, validation studies conducted by the investigators, which included full review of diagnostic information recorded in KPNC medical records, have demonstrated that at least 90% of children with an ASD diagnosis recorded in the KPNC electronic databases meet *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*[29] criteria for autism.

Other than flu vaccine, we did not investigate other sources of prenatal mercury exposure, such as maternal dietary

consumption of fish, airborne exposures, or dental amalgams. We also did not investigate postnatal mercury exposures. Another study designed specifically to examine autism risk associated with mercury exposure from childhood vaccines is currently underway.

We could not assess the risk of autism associated with Rh incompatibility because Rh status of the study children was not routinely available in maternal medical records or KPNC automated databases. Whereas 2 previous epidemiologic studies provided suggestive evidence that Rh incompatibility may contribute to the risk of autism,[30,31] 2 recent, methodologically more rigorous epidemiologic studies found no evidence for an association.[23,32]

In conclusion, we found no evidence for an association between maternal Rh status and prenatal exposure to RhIg and autism spectrum disorders. These results should provide some assurance to Rh-negative women that the proven benefits of prophylactic RhIg treatment to prevent the devastating consequences of hemolytic disease of the fetus and newborn outweigh the perceived risks. ■

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