Antenatal Ultrasound and Risk of Autism Spectrum Disorders

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Abstract We evaluated antenatal ultrasound (U/S) exposure as a risk factor for autism spectrum disorders (ASD), comparing affected singleton children and control children born 1995–1999 and enrolled in the Kaiser Permanente health care system. Among children with ASD ($n = 362$) and controls ($n = 393$), 13% had no antenatal exposure to U/S examinations; case–control differences in number of exposures during the entire gestation or by trimester were small and not statistically significant. In analyses adjusted for covariates, cases were generally similar to controls with regard to the number of U/S scans throughout gestation and during each trimester. This study indicates that antenatal U/S is unlikely to increase the risk of ASD, although studies examining ASD subgroups remain to be conducted.

Keywords Antenatal ultrasound · Obstetrical ultrasound · Autism

Introduction

Autism and other autism spectrum disorders (ASD) are behaviorally defined conditions, characterized by impairments in communication and social skills accompanied by repetitive and stereotypic behaviors. Available evidence indicates that the initiating process leading to ASD typically begins during fetal development (Bauman and Kemper 2005; Rodier 2004), but, little is currently known about causal factors, despite considerable research in recent years. While twin and family studies support a strong genetic underpinning for ASD (reviewed in Muhle et al. 2004), there is also evidence to support a role for nongenetic or environmental factors, probably operating through interaction with genetic susceptibility (reviewed in Newschaffer et al. 2002, and in Lawler et al. 2004). During the past two decades, as the proportion of the childhood population diagnosed with ASD has increased in the United States and elsewhere, there has been considerable speculation about environmental factors that may be contributing to the increase.

Initially introduced into obstetrical (OB) practice in the 1970s (Huang 1994), antenatal ultrasonography (U/S) has become commonplace as a means to visualize fetal growth and development; multiple U/S examinations during pregnancy are now routine in many settings, increasing the number and duration of fetal exposures. Early human studies that examined potential risk associated with antenatal U/S have focused primarily on neonatal outcomes (Scheidt et al. 1978; Stark et al. 1984; Lyons et al. 1988; Newnham et al. 1993; Bellieni et al. 2005). In general, findings have not indicated adverse neonatal consequences, but, with more widespread and frequent examinations and advances in technology, continuing studies have been called for (Huang 1994; Mole 1986; Barnett 2002; Marinac-Dabic et al. 2002; Hershkovitz et al. 2002; Rados 2004; Bly and Van den Hof 2005).

More recently, studies beyond the neonatal period have suggested that dyslexia (Stark et al. 1984), speech delay (Campbell et al. 1993), and non-right handedness (Salvesen

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et al. 1993; Kieler et al. 1998b, 2001) may be associated with fetal U/S exposure; no differences in other behavioral markers have been reported (Stark et al. 1984; Salvesen et al. 1993; Kieler et al. 1998a; Newnham et al. 2004; reviewed in Salvesen 2007). Impairments in communication are a defining characteristic of ASD and non-right handedness has been reported to be more common in children with autism (Gillberg 1983; Lewin et al. 1993; Dane and Balci 2007).

While antenatal U/S has been suggested as a possible causal factor for autism (Rodgers 2006), no studies designed to test the hypothesis of an association have yet been reported. We here report a case–control study designed to evaluate this hypothesis.

Methods

Subjects for this study were singleton children enrolled in Kaiser Permanente of Northern California (KPNC), a large integrated health care delivery system that serves more than three million members living in a 14-county region in Northern California. All subjects were born January 1, 1995 through December 31, 1999 in a KPNC hospital to mothers who were members of the health plan throughout their entire pregnancy; all subjects remained in the health plan for at least 2 years after birth.

Cases were defined as singleton children with at least one diagnosis of an ASD (i.e., autism, Asperger's Disorder, or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)) based on International Classification of Diseases criteria ((ICD-9-CM 299.0 or 299.8) and recorded in KPNC clinical databases. Cases were identified by electronically scanning KPNC clinical databases containing all diagnoses made at outpatient visits occurring at plan facilities and outside approved facilities and recorded between January 1995 and November 2002. One singleton control per case was randomly selected from the cohort of KPNC births without an ASD diagnosis, frequency matched to cases on gender, birth year, and hospital of birth. Following identification of cases and controls, siblings of case and control children born at a KPNC facility between 1990 and 1999 were identified from KPNC files. Since the focus of this study was on maternal factors during pregnancy, siblings were defined as births to the same mother, without regard to paternity.

Clinical data were obtained from multiple sources within KPNC to identify antenatal U/S examinations, date and time of scan, gestational age at time of scan, type of scan (American Medical Association Current Procedural Terminology, 4th Edition (CPT-4), codes 76805, 76815, 76830, 76856, 76946), and related data. Abstraction of maternal medical records was conducted by trained KPNC medical records abstractors for all subjects. Data for U/S examinations conducted within KPNC were also obtained from the KPNC electronic imaging databases. For each child, maternal hard-copy and electronic records were searched to obtain any indication that an antenatal U/S examination was conducted. Based on CPT-4 codes for type of scan, all obstetrical and non-obstetrical pelvic U/S were included; U/S examinations for which CPT-4 codes were missing were assumed to be obstetrical U/S examinations and included in the analysis if the scan date was between the last menstrual period and the date of delivery. Among children with ASD, 25% of scans during this time period had missing information for type of scan, and among controls, 26%. Children for whom no antenatal U/S examinations were recorded were considered to have no scans. Two scans conducted on the same date at the same time were counted as one scan and two scans conducted on the same date at different times or, if time was unknown, with different procedure codes, were counted as two scans. Inconsistencies and discrepancies in reporting of U/S data from multiple sources were manually reviewed and resolved through re-review of medical records as necessary. The one mother–child pair identified with a pulsed Doppler examination was excluded from all analyses, as different risks may be associated with this type of examination.

Estimated gestational age at birth (EGA_{birth}) was obtained from the Kaiser Infant Cohort File, based on a previously designed algorithm that included consideration of aberrant gestational ages and birth weights. Estimated gestational age at time of antenatal U/S (EGA_{scan}) was obtained using an algorithm that gave priority to the gestational age established at time of U/S based on fetal measurements and, if unavailable, calculated EGA based on the date of last menstrual period recorded at the time of U/S scan. For children with documentation of U/S scans but for whom EGA_{scan} was missing, we calculated EGA_{scan} by subtracting the number of completed weeks between birth date and scan date from the gestational age at birth (EGA_{birth}). Data on EGA_{scan} were then classified by trimester (1st trimester = 0–12 weeks, 2nd trimester = 13–24 weeks, 3rd trimester $\geq$ 25 weeks).

Demographic data were obtained from birth certificates to evaluate possible confounding by parity, birth year, birth weight, and maternal education, age, and race/ethnicity.

Statistical Analysis

For case–control analysis of demographic characteristics, we used chi-square tests of association for categorical variables and t-test for continuous variables, with $p < 0.05$ indicating statistical significance. For unadjusted analysis of the number of U/S scans performed during the

pregnancy and within each trimester, we used the chi-square test for trend, comparing case and control frequencies across number of scans treated as a categorical variable. The chi-square trend test does not require the assumption of normality and tests for increasing risk with increased exposure. Adjusted logistic regression models were used to compute odds ratios (OR) for ASD and 95% confidence intervals (95% CI) associated with the number of antenatal U/S examinations. Adjusted models were run encompassing the entire gestational period and within strata defined by trimester and gender. The total number of any antenatal U/S examinations was treated as a continuous exposure variable and, in separate models, as a categorical variable (reference = 0 vs. 1, 2, or ≥3). Demographic variables significantly associated with case–control status were considered as possible confounders and included in the adjusted logistic regression models, as were the matching variables for control selection. Since our study is the first to directly address the concerns about a possible link between ultrasound and ASD, statistical significance was evaluated without correction for multiple comparisons to enhance the likelihood of finding significant associations that could be tested in future studies. Statistical Analysis Software (SAS) was used for all analyses.

To minimize possible confounding by unmeasured maternal or familial factors, analyses were initially restricted to cases from simplex families (only one child with ASD) and controls from families without another child with ASD. Further analyses were then conducted that included multiplex case families (n = 11). To assure independence of observations, one child was randomly selected from families with two siblings in the case group. Three controls with an affected sibling were excluded from all analyses.

This study was approved by the California State Committee for the Protection of Human Subjects and the Institutional Review Board of KPNC.

Results

Final sample size was N = 362 children with ASD from simplex families (N = 373 simplex + multiplex) and N = 393 control children. Mothers of children with ASD had significantly greater mean maternal age than mothers of children in the control group, but maternal age was not different when evaluated in 5-year age categories (Table 1). Mothers of children with ASD had more years of education than mothers of children in the control group and the mean gestational age at birth of children with ASD was somewhat shorter than for control children, approaching statistical significance. Gender, birth weight, parity, year of

birth, and maternal race/ethnicity were not different for children with ASD compared to controls (Table 1).

Thirteen percent of children with ASD from simplex families and 12.5% of control children had no exposure to U/S examinations during gestation. The majority of U/S examinations were conducted in the second trimester; 77.9% of cases and 79.2% of controls had one or more scans during this time. In the first trimester and the third trimester, approximately 28% of both cases and controls had at least one scan. In unadjusted analyses using a chi-square trend test, the number of U/S examinations was not significantly associated with ASD status during the entire gestational period or for any trimester (Table 2).

Logistic regression models were adjusted for maternal education, maternal age (continuous), gestational age, birth hospital, birth year, and gender (for models that included children of both genders). In models with U/S frequency treated as a continuous variable, no significant or consistent increased risk of ASD was observed with increasing numbers of antenatal U/S examinations for the total gestation or for any trimester (Table 3). Within gender strata, no increased risk of ASD was observed with increasing numbers of U/S examinations for either male or female children, with the exception of females in the 2nd trimester (AOR = 2.49, 95% CI 1.20, 5.15; Table 3). In models that treated frequency as a categorical variable, we found no statistically significant elevation in risk with increasing numbers of antenatal U/S examinations for the total gestation or for any trimester. When boys or girls were evaluated separately in models that treated frequency as a categorical variable, no significant elevations in risk were seen for the total pregnancy or for any trimester (data not shown).

All results were similar for the total sample when the 11 children with autism from multiplex families were added to the case group (data not shown).

Discussion

Since being introduced into obstetrical care in the 1970s, antenatal ultrasound examinations have become widely accepted in obstetrical practice as a routine, non-invasive tool for determining the size, location, number, and age of fetuses, and for detecting fetal malformations and intra-uterine growth retardation. Multiple U/S examinations during pregnancy are now common throughout the industrialized world, with many women having three or more U/S scans during a normal pregnancy (Marinac-Dabic et al. 2002; Hershkovitz et al. 2002). Ultrasound uses high-frequency sound waves converted to electric impulses to form an image. Ultrasound energy absorbed locally has the potential for localized loss of cells and tissues if there is a

Table 1 Characteristics of children with autism spectrum disorders (ASD) and control children, Kaiser Permanente, birth years 1995–1999*

| | Children with ASD | | Control children | | p value** |
| | n = 362 | | n = 393 | | |
	n	%	n	%	
Sex					0.403
Female	58	(16.0)	72	(18.3)	
Male	304	(84.0)	321	(81.7)	
Maternal age					0.294
<20	6	(1.7)	12	(3.1)	
20–24	44	(12.2)	58	(14.8)	
25–29	96	(26.5)	120	(30.5)	
30–34	119	(33.0)	116	(29.5)	
35–39	80	(22.1)	74	(18.8)	
≥40	17	(4.7)	13	(3.3)	
Maternal ethnicity					0.504
White, non-Hispanic	184	(50.8)	191	(48.6)	
White, Hispanic US born	35	(9.7)	46	(11.7)	
White, Hispanic not US born	28	(7.7)	44	(11.2)	
Black	32	(8.8)	33	(8.4)	
Asian	35	(9.7)	30	(7.6)	
Other	48	(13.3)	49	(12.5)	
Maternal education					0.001
<High school	21	(5.8)	31	(7.9)	
HS grad	75	(20.7)	123	(31.3)	
College	194	(53.6)	192	(48.9)	
PostGrad	70	(19.3)	44	(11.2)	
Other	2	(0.6)	3	(0.8)	
Parity					0.831
0	164	(45.3)	175	(44.5)	
≥1	198	(54.7)	218	(55.5)	
Birth year					0.999
1995	107	(29.6)	116	(29.5)	
1996	93	(25.7)	100	(25.5)	
1997	69	(19.1)	75	(19.1)	
1998	70	(19.3)	78	(19.9)	
1999	23	(6.4)	24	(6.1)	
Birth weight					
Mean (SD)	3480.9	(611.9)	3522.3	(547.0)	0.329
Gestational age at birth					
Mean (SD)	38.997	(1.8)	39.2	(1.7)	0.060
Maternal age					
Mean (SD)	30.8	(5.5)	29.7	(5.7)	0.005

* Children with ASD from simplex families

** p-value for chi-square test (categorical data) and t-test (continuous data)

sufficient rise in temperature or sufficient cavitation from U/S-induced pressure changes and gas bubbles (Mole 1986; Barnett 2002; Hershkovitz et al. 2002; Rados 2004). When used according to established safety guidelines, antenatal U/S is considered to pose minimal risk to the fetus or mother, but some uncertainties about safety remain, particularly with changes in technology and frequency or duration of application (Mole 1986;

Table 2 Frequency of antenatal ultrasound (U/S) examinations for children with ASD and control children, Kaiser Permanente, birth years 1995–1999*

| | Children with ASD | | Control children | | p value** |
| | (n = 362) | | (n = 393) | | |
	n	%	n	%	
Total number of scans	667		676		
Number of scans with missing CPT-4 code	164	25%	179	26%	
Total per subject					0.18
0	48	(13.3)	49	(12.5)	
1	130	(35.9)	147	(37.4)	
2	101	(28.0)	120	(30.5)	
3	36	(9.9)	46	(11.7)	
4	24	(6.6)	18	(4.6)	
5	13	(3.6)	8	(2.0)	
≥6	10	(2.8)	5	(1.3)	
1st trimester (0–12 weeks)					0.56
0	258	(71.3)	286	(72.8)	
1	88	(24.3)	94	(23.9)	
2	14	(3.9)	10	(2.5)	
≥3	2	(0.6)	3	(0.8)	
2nd trimester (13–24 weeks)					0.44
0	80	(22.1)	82	(20.9)	
1	207	(57.2)	242	(61.6)	
2	60	(16.6)	58	(14.8)	
3	12	(3.3)	11	(2.8)	
4	3	(0.8)	0	(0.0)	
3rd trimester (25+ weeks)					0.21
0	260	(71.9)	283	(72.0)	
1	61	(16.9)	80	(20.4)	
2	22	(6.1)	20	(5.1)	
3	12	(3.3)	6	(1.5)	
≥4	7	(1.9)	4	(1.0)	

* Children with ASD from simplex families

** p value based on chi-square test for trend

Huang 1994; Barnett 2002; Marinac-Dabic et al. 2002; Hershkovitz et al. 2002; Rados 2004; Bly and Van den Hof 2005; Ang et al. 2006; Rodgers 2006). In addition, only limited studies have addressed neurodevelopmental outcomes that may only become clinically apparent in early childhood or later. A recent review article has raised new questions about a possible link between antenatal U/S and "the alarming increase in autism" (Rodgers 2006).

Prior evaluations of human newborn and pediatric outcomes have, in general, demonstrated no measurable associations between prenatal ultrasound exposure and outcomes measured proximal to the time of birth: Apgar scores, gestational age, head circumference, birth weight, length, congenital abnormalities, neonatal infection, and congenital infection (Scheidt et al. 1978; Stark et al. 1984;

Lyons et al. 1988; Newnham et al. 1993). In contrast to these null studies, Bellieni et al. (2005) reported lower mean birth weight with exposure to nine or more U/S scans compared to three or fewer and Newnham et al. (2004) reported increased low birth weight (below the 10th or 3rd percentiles) in a randomized trial comparing intensive monitoring (five diagnostic U/S and Doppler flow studies during gestation) to a single U/S examination at 18 weeks gestation; these birth weight differences resolved by 1 year of age.

Longer term outcomes have also been assessed. Campbell et al. (1993) reported increased antenatal U/S exposures in a case group with delayed speech compared to matched controls. Stark et al. (1984) evaluated hearing, visual acuity and color vision, cognitive function, behavior,

Table 3 Adjusted odds ratio per each ultrasound exposure for children with autism spectrum disorders (ASD) and control children, Kaiser Permanente, birth years 1995–1999*

Frequency of U/S (continuous)	Odds ratio**	95% CI
All subjects		
Total pregnancy	1.06	(0.95, 1.20)
1st trimester	1.05	(0.80, 1.37)
2nd trimester	1.18	(0.92, 1.53)
3rd trimester	1.08	(0.91, 1.28)
Male children		
Total pregnancy	1.05	(0.92, 1.19)
1st trimester	1.07	(0.80, 1.43)
2nd trimester	1.04	(0.79, 1.39)
3rd trimester	1.07	(0.88, 1.30)
Female children		
Total pregnancy	1.20	(0.88, 1.64)
1st trimester	0.87	(0.37, 2.02)
2nd trimester	2.49	(1.20, 5.15)
3rd trimester	1.20	(0.75, 1.92)

* Models based on children with ASD from simplex families ($n = 362$) and controls ($n = 393$), adjusted for maternal education, maternal age, gestational age, birth hospital, birth year, and child gender

** Odds ratio represents risk associated with each additional U/S examination

and neurologic function in children followed to 7–12 years of age, with exposed and unexposed children born of pregnancies matched for pregnancy complications. More exposed children tested positive for dyslexia, a difference that was consistent across all three hospitals included in the study but that did not reach statistical significance in any; no other differences were found. Newnham et al. (2004) found no differences at 8 years of age using standard tests of childhood speech, language, behavior, and neurological development when randomly selected children with intensive exposure were compared to children with low exposure.

Following an initial report by Salvesen et al. (1993) of a modest but statistically significant increase in non-right handedness in children who had been randomly exposed to U/S during gestation, Kieler et al. (1998a, b) evaluated handedness and other characteristics study of children born to women who had been randomly assigned to U/S screening at 15 weeks gestation. A modest, but significant, increase in non-right handedness was seen among boys but not when children of both genders were analyzed as one group. No other behavioral or neurological differences were found in these studies. A further study by Kieler et al. (2001) among men enrolled for military service in Sweden evaluated handedness among men born in hospitals without antenatal U/S compared to men born in hospitals in which

U/S was the standard of care; left-handedness was found to be higher among men who were presumably exposed. No clear association was seen between antenatal U/S exposure and intellectual performance in these men (Kieler et al. 2005). See Salvesen (2007) for a recent review of these epidemiologic studies.

As non-right handedness has been reported to be more common in children with autism (Gillberg 1983; Lewin et al. 1993; Dane and Balci 2007) and delayed speech is one of the early signs of autism, the studies cited above raise the question of a possible link between autism and antenatal U/S exposure. In addition, a recently reported study of prenatal exposure to U/S in mouse models found an effect on neuronal migration in the cerebral cortex (Ang et al. 2006); neuronal migration may be a cellular mechanism contributing to autism (reviewed in Keller and Persico 2003). These observations have contributed to concerns that increased exposure to U/S in routine obstetrical care may be linked to the rising prevalence of autism that has been observed in children over the past two decades (Rodgers 2006).

Focusing on children enrolled in a large health care delivery system that is largely representative of the general population residing in the same geographic region (Krieger 1992), we compared antenatal U/S exposure in children with ASD to exposure in control children from the same population. We did not find an association between the risk of ASD and the number of antenatal U/S examinations. These null findings were consistent for the gestation as a whole, when evaluated by trimester, and among both boys and girls. There is one exception to this pattern of null results: we find an elevated risk for females in the 2nd trimester when U/S was treated as a continuous variable in adjusted models but not when U/S was treated as a categorical variable. This finding cannot be attributed to one or two outliers but could represent a chance finding among the large number of comparisons we conducted; alternatively, there may be risk associated with multiple U/S for girls in the 2nd trimester or with medical indications for repeated U/S during this window of gestation. As the number of U/S examinations in a pregnancy is, to some extent, guided by medical indications, our largely null results suggest that, in general in this study population, relevant medical indications for U/S as a group may not have been substantially more common in pregnancies that produced children who were later diagnosed with autism. We did not measure nor control for medical indications, per se, but by excluding multiple births from the analysis, we effectively excluded pregnancies with one of the most common indications for repeated U/S examinations. Whether specific medical indications are more common in pregnancies leading to autism was outside the scope of this study.

Data on U/S examinations were obtained from medical records, which prospectively captured obstetric events and thus were not subject to maternal recall. Given that all case and control mothers in the study population received their prenatal care within the KPNC system, it is very unlikely that we under-ascertained antenatal U/S examinations conducted in a clinical setting. This study was not designed to evaluate U/S examinations conducted in commercial settings, which may pose risks beyond those conducted under established guidelines in clinical settings.

A possible limitation of our study is that we were unable to construct a more precise estimate of exposure "dose" based on actual duration of exposure or other parameters of the U/S examination, as necessary data were not documented in available records. Due to missing data for type of scan in approximately 25% of scans, we may have failed to exclude some mother–baby pairs for which Doppler evaluations were conducted. Doppler evaluations are only rarely conducted in this setting; evaluation of available data for scans lacking codes for type of scan identified <1% of scans with missing data that might be Doppler. A further limitation is that we were unable to evaluate phenotypic subgroups of cases, based on severity of ASD or other characteristics, as the data in medical records were not sufficient to accurately and completely make these distinctions. We were also unable to validate ASD diagnoses through clinical examination of all children, although a subset of 50 (13.8%) of the children with autism in our study also participated in another study for which they underwent clinical evaluation with the Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G). (Lord et al. 2000). 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 (Croen et al. 2008). In addition, record-review 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 had documentation in their records consistent with a diagnosis of autism based on DSM-IV criteria (Croen et al. 2008). The prevalence of ASD within this study population (4.76/1,000) is within the range reported among U.S. children for this time period (Autism and Developmental Disabilities Monitoring Network 2007).

The predominately null findings of this investigation of fetal exposure to antenatal U/S and risk of autism spectrum disorders may provide assurance that antenatal ultrasound examinations, when performed in a clinical setting according to established guidelines, do not appear to put fetuses at increased risk for developing ASD. Given the substantial size of our study, it is unlikely that an association between U/S exposure and ASD would be seen if larger numbers of cases and controls had been included, although further studies among girls are indicated. Studies of phenotypic subgroups remain to be conducted and as antenatal U/S technologies and procedures change, further evaluation of potential risks may be warranted. This study did not address other possible risks to fetuses associated with antenatal ultrasound.

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