Case–control study of prenatal ultrasonography exposure in children with delayed speech

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Objective: To determine whether there is an association between prenatal ultrasound exposure and delayed speech in children.
Design: Case–control study.
Setting: Network of community physicians affiliated with the Primary Care Research Unit, University of Calgary.
Subjects: Thirty-four practitioners identified 72 children aged 24 to 100 months who had undergone a formal speech-language evaluation and were found to have delayed speech of unknown cause by a speech-language pathologist. For each case subject the practitioners found two control subjects matched for sex, date of birth, sibling birth order and associated health problems.
Main outcome measures: Rates of prenatal ultrasound exposure and delayed speech.
Results: The children with delayed speech had a higher rate of ultrasound exposure than the control subjects. The findings suggest that a child with delayed speech is about twice as likely as a child without delayed speech to have been exposed to prenatal ultrasound waves (odds ratio 2.8, 95% confidence limit 1.5 to 5.3; $p = 0.001$).
Conclusion: An association between prenatal ultrasonography exposure and delayed speech was found. If there is no obvious clinical indication for diagnostic in-utero ultrasonography, physicians might be wise to caution their patients about the vulnerability of the fetus to noxious agents.

Objectif : Déterminer s'il y a un lien entre l'exposition prénatale aux ultrasons et le retard de développement de la parole chez les enfants.
Conception : Étude de contrôle de cas.
Contexte : Réseau de médecins en santé communautaire, affilié à la Primary Care Research Unit de l'Université de Calgary.
Sujets : Trente-quatre praticiens ont identifié 72 enfants âgés de 24 à 100 mois qui ont subi une évaluation de la parole en bonne et due forme et chez lesquels un orthophoniste a découvert un retard de développement de la parole de cause inconnue. Pour chaque sujet, les praticiens ont trouvé deux sujets contrôles du même sexe, nés à la même date, de même rang dans la famille et ayant les mêmes problèmes de santé.
Principales mesures des résultats : Taux d'exposition prénatale aux ultrasons et incidence du retard de développement de la parole.
Résultats : Chez les enfants manifestant un retard de développement de la parole, le taux d'exposition aux ultrasons était plus élevé que chez les sujets contrôles. Les résultats indiquent qu'un enfant manifestant un retard de développement de la parole est environ deux

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fois plus susceptible d'avoir été exposé aux ondes ultrasoniques lors du stade prénatal qu'un enfant n'ayant pas de retard (risque relatif de 2,8, limites de confiance de 95 % de 1,5 à 5,3; $p = 0,001$).

Conclusion : On a découvert un lien entre l'exposition prénatale à l'ultrasonographie et le retard de développement de la parole. S'il n'y a aucune indication clinique évidente sur le plan diagnostic à l'ultrasonographie in utero, il serait sage de la part des médecins d'expliquer à leurs patients la vulnérabilité du foetus aux agents nocifs.

Ultrasonography has been purported to be an effective and safe method of displaying answers to numerous questions that arise during the prenatal period.[1] The goal of prenatal ultrasonography is to reduce the rates of perinatal abnormalities and death from a range of causes. In the 1980s ultrasonography became almost a routine part of prenatal care. It allows for the visual assessment of the developing fetus, and its benefits are widely appreciated. Indeed, there is a demand for the increased precision for dates, size and sex that ultrasonography provides. However, it is not entirely clear whether ultrasound waves are free of risk to the developing fetus. Because of the likelihood that an entire generation of children may be exposed to ultrasound waves, the public health implications of an adverse effect are enormous.

In the 1980s four expert groups concluded that routine ultrasound examination is unwarranted on medical grounds unless there is clinical suspicion of a prenatal problem or abnormality.[1-4] In 1992 the Canadian Task Force on the Periodic Health Examination recommended that there is fair evidence to include a single examination during the second trimester in women without clinical indications.[5]

Recently, one of us (J.D.C.) noted an increased incidence of delayed speech among young children referred for a hearing assessment. In most cases the test results were normal. Speculation about other causes revealed a wide range of possible contributors, such as increased rates of family breakdown, day-care use, inadequate prenatal nutrition and prenatal exposure to noxious agents. One possible exposure, which has only recently become prevalent, is to prenatal ultrasound waves. From provincial health insurance billing data the estimated ratio of ultrasound examinations per delivery has increased from 0.69 (in 1980) to 2.08 (in 1989) (Health Canada: unpublished data, 1990). These examinations are not inexpensive, the cost ranging from $56 to $74. If routine screening provides only marginal diagnostic benefit[6,7] it may be both a waste of resources and a potential source of noxious agent for the fetus.

The purpose of this exploratory study was to determine whether there is an association between prenatal ultrasound exposure and delayed speech.

Literature review

A selected review of the literature concerning the effects of prenatal ultrasound waves on fetal and childhood development revealed that there has been no research into the influence of such waves on speech development. Furthermore, only a few high-quality studies of adverse effects of prenatal ultrasonography on humans were found. To date, there is little evidence to support a noxious relation. However, the following summary of animal and human studies in related areas provided the background logic for us to proceed with our study.

Animal studies tended to focus on two broad effects of ultrasound exposure: musculoskeletal development and aberrant behaviour. In monkeys (cynomolgus macaque) who were exposed to much higher levels of ultrasound than would occur clinically, newborns at 10 minutes were found to have higher Apgar scores, higher muscle tone, lower birth weights and lower leukocyte counts than those who were not exposed. These differences were no longer significant after 6 months.[8] In humans, an increased risk of fetal or newborn abnormality has not been linked to prenatal ultrasound exposure, regardless of the gestational age at the first exposure or the number of exposures.[9] A longitudinal study compared physiologic and anthropometric measurements 5 minutes after birth and at 1 year.[10] A number of differences (in birth weight, reflex tone, convulsions) were thought to be related to why prenatal ultrasound had been ordered (intrauterine growth retardation, abnormal presentation) rather than to the ultrasound exposure. There is a general consensus that ultrasound exposure does not significantly affect growth.[11] Furthermore, prenatal ultrasound exposure at clinical dosages has not been linked to any biologic abnormality in children.[12]

Several human epidemiologic studies have reported an association between medical ultrasound exposure in utero and developmental effects. Two reports have conflicting results about the impact on fetal development.[13,14] One longitudinal study that considered development indicators between 1 month and 2 years of age showed no difference between children who had been exposed to prenatal ultrasonography before 15 weeks' gestation and those exposed later.[15] Furthermore, intelligent-quotient testing after 3 years failed to show any difference between the two groups.

Because delayed speech is viewed not as a pathological or organic syndrome but, rather, as a developmentally defined symptom complex that may have several different or multiple causal factors, it could be difficult to discover a relation to ultrasound exposure. Several cohort studies have examined the effects of exposure. Of some 122 outcome parameters, only an in-

creased incidence of abnormal grasp and tonic neck reflexes was consistently reported.[16] However, a recently published retrospective cohort study of the effects of in-utero ultrasound exposure in humans showed a possible relation between exposure and the occurrence of learning disorders in childhood.[11] Pregnancies in the early 1970s with exposure to ultrasound were identified using records at three Denver hospitals. A comparison group of unexposed children born at the same hospitals and matched for complications of pregnancy was identified. The investigators attempted to locate and examine all of the children, who were at the time of the study aged 7 through 12 years. These examinations included multiple measures of behaviour, learning ability and intellectual function as well as questions about illnesses in childhood. Data were analysed separately for each of the three hospitals. At each centre the proportion of children with dyslexia was higher among the exposed children than among the unexposed ones. Although none of the differences reached conventional levels of statistical significance, when analysed together in a Mantel–Haenzsel χ^2 test the p value was less than 0.001.

The investigators in that study were appropriately cautious in their interpretation of the findings. The number of comparisons between exposed and unexposed children was large, and the association of dyslexia with ultrasound exposure may have been an α error. Moreover, despite the great care taken in matching the exposed and unexposed children for complications of pregnancy, this task is inherently difficult, and matching may not have been perfect. The possibility that the condition prompting the ultrasound examination was the true contributing factor for dyslexia cannot be eliminated as an explanation for the results.

From the studies cited, humans have not been shown to be at biologic risk from ultrasound exposure. However, we found no study in which delayed speech was included as an outcome measure. Because some clinicians have noted an increased incidence of delayed speech in their pediatric patients and because prenatal ultrasonography has only recently become common, we decided to proceed with an exploratory study to determine whether there may be an association and thereby raise the possibility of a developmental noxious effect from prenatal ultrasound exposure.

Methods

Study design

A matched case–control design was used, with two controls per case. Data were collected through a retrospective chart audit. Matching variables were sex, date of birth (within 6 months), sibling order (first v. other) and associated health problems (e.g., family history of speech or hearing problems). The medical literature provides sufficient information about the four matching criteria to expect that each could have a confounding effect. Matching on these criteria was felt to be better than attempting to stratify by these criteria in the data analysis.

Because of the retrospective design, the risk odds ratio was adopted as the basic measure of association. In this study it may not be possible to regard the odds ratio as a good approximation to the risk because of the uncertain prevalence of delayed speech. This limits the practical interpretation of the measure.[17]

The intended sample was 100 case subjects and 200 control subjects; the size was calculated to provide a power of 0.90 to detect a risk odds ratio of 2.6 or greater.[18] The power of a study can potentially be increased by including more control subjects per case, but it has been shown that there are diminishing returns in power for doing so.[19] The choice of two per case was pragmatic, based on the relative availability of control subjects.

Subject recruitment

The community physicians affiliated with the University of Calgary's Primary Care Research Unit were recruited for participation in the study. Each practitioner was assisted through a three-step protocol.

Step 1: Each physician was asked to identify at least two of his or her pediatric patients with delayed speech of unknown cause. The children had to have been clinically assessed by a speech-language pathologist as having "delayed speech of unknown origin." The method used in our study was a clinical case selection process based on a "delay in the use of spoken language," as defined by the speech-language pathologists affiliated with the Alberta Childrens' Hospital program, Calgary, in the mid-1980s. Indeed, even though the case selection was done at the time of our study (1989–90), the case definition was established several months or years previously. All the children had been assessed initially before 3 years of age with the use of standardized instruments for measuring articulation, language comprehension, language production, metalinguistic skills and verbal memory and had been found to have a "delay in the production of spoken language." As a general rule, speech delay was determined on the basis of a compilation of the child's performance compared with developmental norms for the referenced tests as well as the individual speech-language pathologist's judgement.[20] Since prenatal exposure to ultrasound waves had occurred several years previously and was not recorded on the child's chart, for all practical purposes the cases were identified without knowledge of exposure.

Step 2: Practitioners were asked to identify two control subjects for each case from their pediatric patient population. Identical exclusion criteria were used: the presence of a hearing disorder, mental retardation or nonassociated diseases that may influence development

(e.g., congenital abnormality) and the inability to determine the prenatal exposure states from physician, hospital or radiology records.

Step 3: The ultrasound exposure status was determined. To facilitate comparability between the two groups additional factors such as gestational age at delivery and birth weight were collected.

Study implementation

Consenting physicians were asked to provide information for each case subject on "subject demographic sheets" and to forward the sheets to the project team for assessment of the criteria for inclusion or exclusion. During the summer of 1990 a project team member visited the office of each participating physician, identified two suitable control subjects for each case, extracted the exposure status for all the subjects and recorded the information on a data extractor form. Considerable time and effort was needed to find the exposure status on the maternal charts in the physician's office or in the hospital records. The information from the demographic and data extraction forms was then entered into a microcomputer R-base data manager system.

Table 1: Demographic characteristics of 72 children with delayed speech and 142 matched control subjects

Characteristic	Group; % of children	
	Case	Control
Sex		
Male	78	77
Female	22	23
Sibling order		
First	56	55
Second or later	44	45
Family history of a speech disorder	18	16
Socioeconomic status		
Upper class	8	5
Middle class	82	85
Lower class	10	10
Mean age (and standard deviation [SD]), mo (as of January 1990)	60.0 (28.0)	58.4 (28.0)

Data analysis

Conditional logistic regression was used to estimate the odds ratios. The analysis was performed with the statistical programs SAS, S and PECAN.[21]

Results

Thirty-four physicians identified 72 children with delayed speech of unknown origin, 70 of whom were matched to two control subjects each; the remaining two were matched to only one control subject each. The two groups were very similar in terms of demographic characteristics (Table 1), and birth weight and gestational age (Table 2). The children with delayed speech were similar in terms of gestational age and weight at birth to the infants of low-risk births in our local hospital. The case subjects had a higher rate of prenatal ultrasound exposure than those in the control group (Table 3). This pattern was consistent for number of exposures and trimester of pregnancy. Table 4 provides a breakdown by trimester of the exposures for the two groups.

The estimated odds ratio for exposure to ultrasound waves, not accounting for trimester or number of exposures, was 2.8 (95% confidence limit 1.5 to 5.3, $p = 0.001$). Given the prevalence rate observed, this finding suggests that a child with delayed speech is roughly twice as likely as a child without delayed speech to have been exposed to prenatal ultrasound waves. Further analysis revealed no relation to timing of exposure or dose–response effect. However, the power to detect a dose–response relation was low because of the rarity of multiply exposed cases.

Discussion

Health care workers and patients alike are con-

Table 2: Mean birth weights and gestational ages of case and control subjects and children of low-risk births

Variable	Case subjects	Control subjects	Children of low-risk birth*	*p* value†
Mean birth weight (and SD), kg	3.40 (0.59)	3.42 (0.59)	3.39	0.857
% of children with birth weight ≤ 2500 g	8.5	5.0	–	–
Mean gestational age (and SD), wk	39.35 (1.42)	39.70 (1.66)	39.54	0.293
% of children with gestational age ≤ 37 wk	13.0	11.4	7.8	–

*Included were 1445 children born at the Foothills Provincial General Hospital, Calgary, in 1991 with a risk score of 3 or less.
†The *t*-test was used to calculate the *p* values.

cerned about the safety of diagnostic ultrasonography in clinical practice. The embryo is the most sensitive human tissue; however, no harmful biologic effect of diagnostic ultrasonography on the human fetus or child has been reported. Several studies attempting to clarify the long-term developmental effects are equivocal and inconsistent.[22,23]

Our findings are consistent with those in another study,[11] which demonstrated an association between prenatal ultrasound exposure and an adverse developmental outcome in infants. We were unable to detect either a dose–response relation or a timing (trimester) effect. These findings suggest that when there is no obvious need for diagnostic in-utero ultrasonography physicians should caution their patients about the vulnerability of the fetus to noxious agents, one of which might be ultrasound waves. Unfortunately, over the past decade there has been a fivefold increase in the prevalence of prenatal ultrasound exposure; therefore, the replication of this study in Canada is impossible, because there are no longer sufficient numbers of unexposed control subjects.

Case–control studies are susceptible to a number of sampling and measurement biases. Of the nine most frequently observed,[24] only three were felt to be important in our study: misclassification, unmasking and exposure suspicion. Because our case subjects had all undergone a formal evaluation by a speech-language pathologist, there was likely no misclassification. Given the limited number of standardized tests commonly used in English-speaking Canada, the consistency of the diagnostic criteria used by speech-language pathologists between different regions would allow for replication of case finding in other centres. Since the recruitment of case subjects and the determination of exposure to ultrasound were accomplished during two visits to the physician's office, there was little likelihood of preferential selection of cases. For practical purposes the physicians were blinded to the exposure status of their patients, since the case subjects were 5 years old on average and the record of exposure to ultrasonography was on the mother's or hospital chart.

The unmasking bias conceivably could have occurred in our study: the higher incidence of ultrasound exposure among the case subjects than among the control subjects may have reflected a greater clinical concern for a disorder that could cause delayed speech (e.g., intrauterine growth retardation). The two groups were similar in terms of birth weight and gestational age at birth; this confirms that the case subjects had not been premature or of low birth weight and suggests that an unmasking bias was unlikely.

Prenatal ultrasound exposure was determined through a search of the prenatal records. Because Alberta has had a standardized prenatal record since the mid-1970s the exposure status for the subjects in our study was recorded in a uniform manner. In a few instances (no difference between the two groups) we were unable to track down the entire prenatal record, and the subject was considered ineligible for the study. However, because quality socioeconomic information was not readily available on retrospective chart review, we had to postulate that the selection of matched control subjects from within the practice in which the case subject had been identified would minimize the variability of exposure suspicion between the two groups.

When an association between an exposure and an outcome in a case–control study is found, one way to validate it is to search for a biologic explanation. Three mechanisms have been identified that could cause biologic damage and explain the harmful effects of ultrasonography: sonically generated heat, cavitation and radiation force.[25] The neural basis of some well-established developmental milestones (e.g., onset of social smile and the beginnings of speech) are starting to be understood in the context of regional cycles of myelination in particular parts of the developing brain.[26] Dyslexia and delayed speech may represent examples of focal and specific disruptions in the myelination of the neural systems involved in speech and language development.[27,28] Experiments in rats have demonstrated delays in neuromuscular development and in the maturation of neuromotor reflexes following in-utero exposure to 20 mW/cm^2 of ultrasound waves.[26] The possibility of subtle microscopic changes in developing neural tissue exposed to ultrasound waves has to be considered. Investigation of the subtle and delayed effects of in-utero exposure requires careful follow-up for 5 to 8

Table 3: Rates of exposure to ultrasound waves, by group

Exposure	Group; % of children	
	Case	Control
At least once	61	37
More than once	4	2
During trimester		
First	22	14
Second	25	13
Third	25	15

Table 4: Pattern of ultrasonography exposure by trimester

Trimester; group	No. of exposures; no. (and %) of children		
	0	1	2
First			
Case	56 (78)	16 (22)	0
Control	121 (85)	20 (14)	1 (1)
Second			
Case	54 (75)	15 (21)	3 (4)
Control	123 (87)	18 (13)	1 (1)
Third			
Case	54 (75)	18 (25)	0
Control	121 (85)	20 (14)	1 (1)

years or possibly longer. Exactly what combination of factors (e.g., timing of gestation, duration of exposure, position of fetus and variations in technique) is involved cannot be assessed at this time. Any possible deleterious effects resulting from ultrasonography are undoubtedly subtle.

Prenatal ultrasonography should continue to be considered a relatively safe diagnostic tool with many benefits for good obstetric care. Delayed speech is a developmentally defined symptom complex, and it is still premature to suggest a link between it and exposure to ultrasound waves. However, if no obvious clinical indication for ultrasonography exists, physicians might be wise to caution their patients about the vulnerability of the fetus to noxious agents.

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