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A Nationwide Study on the Risk of Autism After Prenatal Stress Exposure to Maternal Bereavement

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OBJECTIVE. Prenatal stress has been linked to several adverse neurobehavioral outcomes, which may share a common pathophysiology with autism. We aimed to examine whether prenatal stress exposure after maternal bereavement is associated with an increased risk of autism later in life.

METHODS. We conducted a nationwide population-based cohort study of all 1,492,709 singletons in Denmark born from 1978 to 2003. A total of 37,275 children were born to women who lost a close relative during pregnancy or up to 1 year before pregnancy. These children were included in the exposed group, and the remaining children were in the unexposed group. All children were followed up from birth until their death, migration, onset of autism, or the end of 2006. Information on autism was obtained from the Danish Psychiatric Central Register. We used Cox regression models to estimate hazard ratios in the exposed group compared with those in the unexposed group.

RESULTS. Maternal bereavement during the prenatal period was not associated with an increased risk of autism in the offspring. The hazard ratios did not differ by the nature of the exposure (maternal relationship to the deceased or cause of death). The hazard ratios were comparable between the 5 prenatal exposure periods under study (7–12 months before pregnancy, 0–6 months before pregnancy, first trimester, second trimester, and third trimester).

CONCLUSIONS. This is the first population-based cohort study to examine the effect of prenatal stress on autism in childhood. Our data do not support any strong association between prenatal stress after maternal bereavement and the risk of autism. Pediatrics 2009;123:1102–1107

AUTISM SPECTRUM DISORDERS are among the most common neuropsychiatric disorders in childhood with an estimated prevalence of 6 to 8 per 1000 individuals.1–5 The disease has a high public health impact,1,2 with up to 9 times higher health care expenditures in affected children compared with other children.6,7 The etiology of autism is largely unknown,6 but it is probably a complex developmental brain disorder with multiple genetic and environmental causes.1,2 Several prenatal and perinatal factors have been shown to be associated with autism, suggesting that environmental factors operating in early life may play a causal role.1,2 Evidence from animal studies suggests that maternal stress during pregnancy may significantly affect the neurodevelopment of the fetus.8,9 Fetal programming has often been cited as the underlying mechanism, which occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or insult at a critical time point.9,10 Excessive glucocorticoids after stress in pregnant mothers could lead to dysfunction of the hypothalamo-pituitary-adrenocortical axis and have permanent effects on brain development.11–13 In a number of epidemiologic studies, prenatal stress has been linked to congenital malformations,13 social/emotional problems,14,15 and psychiatric disorders including schizophrenia,1,6,17 which may share a common pathophysiology with autism. However, little is known about the effect of prenatal stress on the risk of autism later in life.16,19

We aimed to examine the association between maternal bereavement during pregnancy and autism risk in...
offspring. Bereavement occurs after a severe life event known to induce both short- and long-term stress. We hypothesized that prenatal stress may affect the susceptibility of autism in a timing-specific and dose-response way.

**METHODS**

We conducted a nationwide cohort study based on data from several national registers, including the Danish Civil Registration System, Danish Medical Birth Register, Danish Psychiatric Central Register, and the Integrated Database for Longitudinal Labor Market Research.

**Study Population, Exposure, and Follow-up**

We used data from the Danish Civil Registration System to identify all singletons born in Denmark between January 1, 1978, and December 31, 2004, and their next of kin (mother, father, siblings, mother’s siblings, and mother’s parents). All live-born children and new residents in Denmark are assigned a unique civil personal registration number, which is stored in the Danish Civil Registration System together with information on vital status, emigration, disappearance, address, and family numbers of family members. The CPR number is used as the key to individual information in all national registries.

We categorized children as exposed to stress in prenatal life if their mother lost a child, a spouse, sibling, or a parent during the pregnancy or up to 1 year before the pregnancy. The remaining children were included in the unexposed cohort. Cohort members were followed from birth until first diagnosis of autism, death, emigration, disappearance from the system, or December 31, 2006, whichever came first.

**Autism**

Information on autism for index children and mothers was obtained from the Danish Psychiatric Central Register, which holds information on all admissions to Danish psychiatric inpatient facilities since 1969 and outpatient visits to psychiatric departments since 1995. Diagnostic information was based on the Danish version of the International Classification of Diseases, Eighth Revision (ICD-8) from 1978 to 1993, and the International Classification of Diseases, 10th Revision (ICD-10) from 1994 onward. Autism cases were diagnosed after the first admission to a psychiatric hospital or in receipt of outpatient care because of autism (ICD-8 codes 299.00 and 299.01; ICD-10 codes F84.0 and F84.1).

**Covariates**

Perinatal factors (gestational age, birth weight, sibling order, Apgar score at 5 minutes) were retrieved from the Medical Birth Register. The Medical Birth Register was established in 1968 and has been computerized since 1973. It holds data on all live births and stillbirths in Denmark, including characteristics of both mothers and newborns, and the variables with regard to pregnancy and delivery. Sociodemographic factors (paternal age, maternal age, residential place, maternal education, maternal income, and maternal cohabitation status) were obtained from the Integrated Database for Longitudinal Labor Market Research, which contains longitudinal information on demographic variables and socioeconomic data from 1980 onward.

Data on maternal psychiatric history (ICD-8 codes 290–299; ICD-10 codes F00–F99) was retrieved from the Central Psychiatric Register.

**Statistical Analysis**

We used the Cox regression model (SAS 9.1 PROC PHREG procedure [SAS Institute, Inc, Cary, NC]) to estimate hazard ratios (HRs). The option of COVSANDWICH (AGGREGATE) was applied by using maternal CPR numbers as identification in the model to treat all siblings from the same mother as a matched set, to take into account common familial factors such as genetic predisposition and family environment. To examine whether the associations depended on type and timing of the death, we first categorized the exposed children from 2 groups of mothers: (1) mothers who lost a child or a spouse and (2) mothers who lost a parent or a sibling. We assumed that loss of a child or a spouse was more severe than loss of a parent or a sibling. We further categorized the causes of death into 2 groups: (1) unexpected death (unexpected causes, ICD-8 codes 7950–7959 and ICD-10 codes R95–R97; motor vehicle accidents, ICD-8 codes 8100–8230 and ICD-10 codes V01–V89; suicide, ICD-8 codes 950–959 and ICD-10 codes: X60–X84; other accidents and violence, ICD-8 codes 800–807, 825–949, and 960–999 and ICD-10 codes V90–V99, W00–X59, and X85–Y89) and (2) death by other causes. The exposure window was divided into 5 periods (7–12 months before pregnancy, 0–6 months before pregnancy, first trimester, second trimester, and third trimester) to examine whether a potential effect of prenatal stress on autism differed across these periods.

We adjusted for the following factors that have been suggested to be potentially associated with both prenatal stress and autism: gender (boys or girls), birth year (1978–1986, 1987–1995, or 1996+), gestational age (<37 or ≥37 weeks), Apgar score at 5 minutes (0–7, 8–9, 10, or unknown), sibling order (1, 2, 3, ≥4, or unknown), paternal age group (<29, 29–33, or ≥34 years), maternal age group (<27, 27–30, or ≥31 years), maternal residential area (capital city of Copenhagen area, cities with >100 000 inhabitants, or other places), maternal education (0–9, 10–11, or ≥12 years), maternal income (lowest quartile, second quartile, third quartile, or highest quartile in the calendar year), maternal cohabitation status (yes or no), maternal history of psychiatric diseases before birth of the child (yes or no). These paternal and maternal variables in the model were baseline characteristics at the birth year for the children.

The above-listed analyses also were performed in boys and girls separately. We also restricted the above-listed analyses in the study subjects with a birth weight of >2500 g, gestational age of >37 weeks, and an Apgar score of 10.
RESULTS
Of the 1 492 709 singleton children, 37 275 children were born to mothers who had experienced bereavement during pregnancy or up to 1 year before pregnancy, including 6 721 children of mothers who lost a child or spouse and 30 683 children of mothers who lost a parent or sibling. There were 86 591 (5%) who emigrated or disappeared at the end of follow-up. We identified 2367 (1.6 per 1000) children with a diagnosis of autism at the end of 2006.

The exposed and the unexposed cohorts were comparable on gender, gestational age, paternal age, and maternal age, education, and marital characteristics (age, maternal psychiatric history, maternal education, maternal income, maternal residence, and maternal cohabitation status). The reference group was defined as children whose mothers did not experience bereavement during pregnancy or up to 1 year before pregnancy.

Table 3 shows that the timing of the death did not modify the association between prenatal stress and autism.

The incidence of autism in boys (2.5 per 1000) was fourfold of that in girls (0.6 per 1000). The HR was 1.02 (95% CI: 0.78–1.34) for boys and 0.85 (95% CI: 0.46–
psychiatric illnesses from the effect of prenatal stress.33–41

graphic and perinatal factors as well as family history of
allowed us to disentangle the effect of both sociodemographic
status), and paternal age. To adjust for these factors
characteristics (sibling order, Apgar score at 5 minutes, gestational age), maternal characteristics (psychiatric his-
torical age, education, residence, income, cohabitation status), and paternal age. To adjust for these factors

allowed us to disentangle the effect of both sociodemographic and perinatal factors as well as family history of
psychiatric illnesses from the effect of prenatal stress.33–41

It could be argued, however, that some of these variables
(Apgar score, gestational age, etc) may be partial intermediate steps on the causal pathway from stress to au-
tism,33–41 and they should not have been included in the

final model. Thus, we performed analyses confined to

study participants with a gestational age of >37 weeks,

birth weight of >2500 g, and an Apgar score of 10. However, results yielded were similar to those from the

whole study sample.

It has been also suggested that the effect of prenatal stress on neurodevelopment varies according to the
timing of exposure. Studies on schizophrenia17 and congenital malformations13 suggest that the first tri-

mester is the most vulnerable period, but other studies on psychiatric admissions and experimental animal

studies indicate that the time window of susceptibility

is late in pregnancy.16,42 Two recent studies related an

increased autism risk to prenatal stress exposure in the

middle or end of gestation,18,19 although the timing in

1 of the studies was based on recall of the events that

happened many years ago.18 We did not observe such

associations in any of the time periods. It has been

shown that bereavement by unexpected causes might

be more stressful than death by other causes,15,21,22 and

the death of a child is considered the most severe

among all types of bereavement.27,30,43 We observed no
differences when we stratified for type of death (un-
expected death versus other death, loss of a child/
spouse versus other loss), which is not in line with the
dose-response pattern in the observations of Kinney et

al.19 Autism is found more often in boys than in girls,1,2

but no previous study has examined the gender dif-
ferences in the effects of prenatal stress on autism.

Evidence from animal studies has suggested that the

sensitivity of developing brain areas to stress hor-
mones is related to gender.44 However, we observed
similar results on the association between prenatal
stress and autism in both genders.

One weakness of the study is that a gold standard
diagnostic instrument for autism wasn’t used. How-

ever, it has been shown that an autism diagnosis in

the Danish Psychiatric Central Register has a high
validity.25,45 The validity of reported diagnoses of child-
hood autism was assessed in a small pilot study of 40
children with infantile autism, and 37 (92%) met the
criteria for a correct diagnosis based on a coding
scheme developed by the Centers for Disease Control
and Prevention.45 Furthermore, we had no data on

maternal lifestyle factors, which may confound the
association.1,2 However, harmful lifestyles achieved af-

ter bereavement may be on the causal pathway and
should not be adjusted for. In addition, we do not
have data on other prenatal or postnatal risk factors,
such as maternal infection and intrapartum hypoxia,1,2
but we do not expect these factors to be associated
with prenatal bereavement.

CONCLUSIONS

Our study does not provide support a strong association
between prenatal stress and the risk of autism in later

life.
ACKNOWLEDGMENT
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NEONATAL CEREBRAL INVESTIGATION

Editors: Rennie, Janet M; Hagmann, Cornelia F.; Robertson, Nicola J.
Publisher: Cambridge University Press
List Price: $190.00
Reviewer: Jay Goldsmith, MD (Tulane University School of Medicine)

Description: This is a comprehensive review of all types of cerebral imaging and electroencephalography set in the clinical context of evaluation of the newborn with neurologic abnormalities. Although other aspects of the neurologic evaluation are included, the book is principally concerned with aspects of brain imaging. This is an update of a book published in 1997 by Dr Rennie that was devoted entirely to neonatal ultrasound (Neonatal Cerebral Ultrasound (Cambridge University Press, 1997)).

Purpose: The purpose is to summarize the current knowledge and the authors’ approach to the evaluation of neonatal neurologic abnormalities with an emphasis on the use and interpretation of brain imaging. These are certainly worthy objectives in this rapidly evolving field. Moreover, this British book is unique in that it is written from the perspective of the 3 neonatologist editors, rather than neurologists or neuroradiologists.

Audience: The intended audience includes any healthcare providers caring for high risk and sick newborn infants. It will be especially useful for neonatologists and neonatal fellows, pediatric neurologists, and neuroradiologists since the clinical-pathologic-radiologic correlations are so well done.

Features: A review of the principles of ultrasound, EEG, and magnetic resonance imaging begins the book, which then goes on to discuss the normal findings in these modalities. The rest of the book is devoted to neonatal clinical presentations, including the baby with seizures, depressed at birth, enlarging or large head, central nervous system malformations, and infection. An interesting final chapter covers postmortem imaging which may have medical-legal implications in this country. The imaging quality is superb and the figures are of the highest caliber. The diagnostic review of various problems often includes helpful tables and algorithms for the authors’ academic approach to these issues. The absence of a neurologic or neuroradiologic editor does not appear to lessen the erudite quality of this excellent book.

Assessment: This is a wonderful book, done in the British style, reflecting the academic experience of senior neonatologists. This book fills a very important void in the field of neonatology and does so with a superb presentation.

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