Very Preterm Birth, Birth Trauma, and the Risk of Anorexia Nervosa Among Girls

Sven Cnattingius, MD, PhD; Christina M. Hultman, PhD; Margareta Dahl, MD, PhD; Pär Sparer, PhD

Background: Obstetrical complications, based on parental recall, have been reported to be associated with development of anorexia nervosa. We used prospectively collected data about pregnancy and perinatal factors to examine the subsequent development of anorexia nervosa.

Methods: This population-based, case-control study was nested in cohorts defined by all liveborn girls in Sweden from 1973 to 1984. From the Swedish Inpatient Register, 781 girls had been discharged from any hospital in Sweden with a main diagnosis of anorexia nervosa at the age of 10 to 21 years. For each case, 5 controls were randomly selected, individually matched by year and hospital of birth (n = 3905). Conditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for potential risk factors.

Results: Increased risk of anorexia nervosa was found for girls with a cephalhematoma (OR, 2.4; 95% CI, 1.4-4.1) and for very preterm birth (≥32 completed gestational weeks) (OR, 3.2; 95% CI, 1.6-6.2). In very preterm births, girls who were small for gestational age faced higher risks (OR, 5.7; 95% CI, 1.1-28.7) than girls with higher birth weight for gestational age (OR, 2.7; 95% CI, 1.2-5.8).

Conclusions: Our results show that perinatal factors, possibly reflecting brain damage, had independent associations with anorexia nervosa. These risk factors may uncover the mechanisms underlying the development of the disorder, even if only a fraction of cases of anorexia nervosa may be attributable to perinatal factors.

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ALTHOUGH anorexia nervosa is a common and distinctive syndrome in industrial countries, its etiology is poorly understood. Genetic factors are thought to play a role, as for other risk factors, no consistent results, to our knowledge, have been reported in the literature.

A search for early vulnerability markers is a promising avenue for future research on eating disorders. It has been reported that girls who later develop anorexia nervosa have higher birth weights than their female siblings. However, birth complications, such as low birth weight and preterm birth, are reportedly associated with increased risks of behavioral problems in childhood, including eating difficulties, which are thought to be predictive of anorexia nervosa in adolescence. A high incidence of obstetrical complications has often but not consistently been observed among patients who later developed anorexia nervosa. However, these results were derived from relatively small studies that used aggregated measures of obstetrical complications rather than single defined prenatal and postnatal complications.

The population-based birth and inpatient registers provide Sweden with exceptional opportunities for studying perinatal risk factors for future development of anorexia nervosa. In this nested case-control study, we used prospectively collected information about exposures during pregnancy, delivery, and the neonatal period to investigate the possible role of perinatal risk factors in the etiology of anorexia nervosa among girls.

RESULTS

The mean (±SD) age at first admission to inpatient care for anorexia nervosa was 14.8 (±2.2) years. In univariate analyses, maternal age, parity, and pregnancy complications did not differ significantly between cases and controls. Vaginal instrumental delivery (vacuum extraction or forceps) and multiple birth were more common among cases than among controls (Table 1).
SUBJECTS AND METHODS

STUDY POPULATION

The National Board of Health and Welfare, Stockholm, Sweden, provided access to data in 2 population-based registers, the birth register and the inpatient register. Individual record linkage across these registers was possible through the unique personal 10-digit national registration number assigned to each resident of Sweden. The birth register contains prospectively collected information on all hospital births, including maternal demographic data and details about reproductive history, pregnancy, delivery, and the neonatal period. More than 99% of all births in Sweden are included in the birth register. The Swedish Inpatient Register provides data on hospital discharges and diagnoses as classified by the treating physician, and computerized information was available through 1994. The diagnoses in the birth and inpatient registers are coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8), through 1986, and according to the *International Classification of Diseases, Ninth Revision* (ICD-9), from 1987 to the time of this report. The inpatient register provides nationwide coverage from 1986 onward, but as no specific diagnostic code of anorexia nervosa was available before 1987 (ie, using ICD-8 codes), the study was restricted to include subjects with anorexia nervosa from 1987 through 1994.

Subjects born from 1973 through 1984 were registered in the birth register and, at the age of 10 years or older, had been discharged from a hospital with a main diagnosis of anorexia nervosa (ICD-9 code 307.6). Seven hundred eighty-one girls and 64 boys fulfilled the inclusion criteria, but the study was restricted to include girls. For each case, we selected 5 controls, individually matched by year and sex. The controls were alive and without a diagnosis of anorexia nervosa at the time of diagnosis of the case subjects.

RISK FACTORS

We studied the effects of the following potential risk factors for anorexia nervosa: maternal age (age in completed years at the infant’s birth); parity (number of births, including the present birth); hypertensive diseases during pregnancy (ICD-8 codes 401 and 637); diabetes (ICD-8 code 250); pregnancy bleeding (ICD-8 codes 632 and 653); inertia uteri (ICD-8 codes 657.0 and 657.1); preterm rupture of the membranes (ICD-8 codes 635.95 and 661.0); vaginal instrumental delivery (vacuum extraction [97%] and forceps [3%]); cesarean section; twin births; Apgar score at 5 minutes; birth trauma, including cephalhematoma (ICD-8 code 772.31) and other head or neck injuries or traumas with central nervous system symptoms (ICD-8 codes 772.00-772.10, 772.24-772.30, and 772.32-772.99); neonatal jaundice (ICD-8 codes 774 and 775); gestational age (in completed gestational weeks based on the last menstrual period); birth weight (in grams); and birth weight for gestational age (in SDs below or above the mean birth weight for gestational age according to the Swedish birth weight curve). Birth weight for gestational age was stratified into small for gestational age (below −2 SDs), appropriate for gestational age (from −2 to +2 SDs), and large for gestational age (above +2 SDs).

STATISTICAL ANALYSES

The independent variables were treated categorically in univariate analyses to examine the effect of each variable on the risk of anorexia nervosa. Tests for independence between cases and controls over the categories were performed using a generalized Mantel-Haenszel χ² test. In the multivariate analyses, all independent variables were included in a conditional logistic regression model, taking into account the matched design. A final model was worked out, including only variables that significantly contributed to the model. Likelihood ratio tests were used to test for goodness of fit between models. Odds ratios (ORs) with 95% confidence intervals (CIs) were used as measures of relative risk.

Table 1. Maternal and Pregnancy Characteristics of Girls With Anorexia Nervosa and Matched Controls

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th>No. (%) of Subjects</th>
<th>Generalized Mantel-Haenszel χ²</th>
<th>df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at delivery, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>35 (4.5)</td>
<td>252 (6.5)</td>
<td>5.29</td>
<td>3</td>
</tr>
<tr>
<td>20-29</td>
<td>542 (69.4)</td>
<td>2714 (69.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>157 (20.1)</td>
<td>725 (18.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35</td>
<td>47 (6.0)</td>
<td>214 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>353 (45.2)</td>
<td>1719 (44.0)</td>
<td>0.46</td>
<td>2</td>
</tr>
<tr>
<td>2-3</td>
<td>392 (50.2)</td>
<td>1992 (51.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>36 (4.6)</td>
<td>194 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy and delivery complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive diseases</td>
<td>20 (2.6)</td>
<td>130 (3.3)</td>
<td>1.24</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (0.1)</td>
<td>18 (0.5)</td>
<td>1.70</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy bleeding</td>
<td>24 (3.1)</td>
<td>90 (2.3)</td>
<td>1.62</td>
<td>1</td>
</tr>
<tr>
<td>Inertia uteri</td>
<td>44 (5.6)</td>
<td>184 (4.7)</td>
<td>1.20</td>
<td>1</td>
</tr>
<tr>
<td>Preterm rupture of the membranes</td>
<td>14 (1.8)</td>
<td>51 (1.3)</td>
<td>1.13</td>
<td>1</td>
</tr>
<tr>
<td>Vaginal instrumental delivery</td>
<td>50 (6.4)</td>
<td>181 (4.6)</td>
<td>4.34</td>
<td>1</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>65 (8.3)</td>
<td>322 (8.2)</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>Multiple birth</td>
<td>22 (2.8)</td>
<td>65 (1.7)</td>
<td>4.74</td>
<td>1</td>
</tr>
</tbody>
</table>

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Distribution of gestational age and birth weight was significantly different between girls with and without anorexia nervosa, while the distribution of birth weight for gestational age was not (Table 2). Birth trauma, especially cephalhematoma (subperiostal bleeding in the skull bone), was more common among cases than among controls.

The ORs of anorexia nervosa among girls were then calculated, and the model that best fitted the data included 3 variables (Table 3). Compared with girls delivered by mothers aged 20 to 29 years, there was a moderately reduced risk of developing anorexia nervosa among girls born to teenage mothers. Very preterm birth was associated with a 3-fold increase in risk of anorexia nervosa, and cephalhematoma was associated with a more than 2-fold increase in risk.

Cephalhematoma was more common among infants with vaginal instrumental delivery than among other infants (12.1% and 2.0%, respectively; \( P = .001 \)), and cephalhematoma may be considered to be an intermediate step in the causal pathway between vaginal instrumental delivery and risk of anorexia nervosa. In a regression model including maternal age and gestational age (but not birth trauma) as covariates, vaginal instrumental delivery was associated with an increased risk of anorexia nervosa (OR, 1.4; 95% CI, 1.0-2.0).

Small for gestational age was more common among very preterm births than among those with a longer period of gestation (17.1% and 5.3%, respectively; \( P = .002 \)). As infants born very preterm and small for gestational age may be especially vulnerable in the neonatal period, cephalhematoma (subperiostal bleeding in the skull bone), was more common among cases than among controls.

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In the present investigation, a 3-fold increase in risk was observed among girls born very preterm (before the 33rd week of gestation), and a more than 2-fold increase was observed among girls with a cephalhematoma. If these associations were not due to chance, what are the possible underlying biological mechanisms?

Prematurity is associated with a suboptimal neurodevelopmental outcome and cognitive delay, which may influence behavioral problems, including severe eating difficulties.7,28-30 Infants born very preterm face a substantial risk of intracranial hemorrhage; this risk may be further increased if birth weight for gestational age also is affected.20,31 The long-term prognosis of infants born very preterm is reported to be more severe in the presence of intracranial hemorrhage,30 and intracranial hemorrhage is also associated with increased risks of some psychiatric disorders in childhood, such as attention-deficit/hyperactivity disorder and tic disorder.7 The prognosis of cephalhematoma is generally considered favorable,24 but we are unaware of any long-term follow-up studies. The reported incidence of skull fractures among infants with cephalhematoma range from 4.5% to 25%,32 indicating the possibility of brain damage.

Severe eating difficulties in children generally start early and persist during childhood.33 Infants with early feeding problems often show signs of subtle brain damage, such as delayed oral-motor development,34 which may be explained by early neurological dysfunction.7 Eating difficulties may also be associated with parental reactions to the birth of a very premature infant, an infant with a birth trauma, or an infant admitted to a neonatal intensive care unit. Secondary interactional dysfunction between the mother and her child may then contribute to the unfavorable long-term prognosis of the eating disorder.9,11,33,35 Children with early eating disorders run an increased risk of eating disorders through adolescence, and eating difficulties often precede the onset of anorexia nervosa.9,11 Thus, for some patients with anorexia nervosa, a subtle pathological condition in the brain may already exist early in life as a consequence of perinatal factors. With this perspective, adolescent dieting, rather than being a direct cause of transition to eating disorder, may be linked to factors even earlier in life.

The association between very preterm birth and anorexia nervosa may also be caused by early hypothalamic dysfunction. Among girls born very preterm, the withdrawal of placental steroids at birth may cause increased levels of hypophysial hormones, including follicle-stimulating hormone, luteinizing hormone, and growth hormone.36,37 If this dysregulation of the hypothalamic-pituitary-gonadal axis also influences the monoamine systems in the brain, this may affect appetite and feeding behaviors.36,38 Increased levels of growth hormone and reduced levels of serotonin and other monoamines have also been associated with anorexia nervosa, although it is debatable whether these are primary changes caused by hypothalamic dysfunction or secondary changes caused by energy restriction.36,38,39

The term obstetrical complications generally refers to a mixture of prenatal and postnatal exposures, which,
within psychiatry, are generally viewed as factors that increase the vulnerability for future development of a variety of psychiatric disorders. Using the same database as in the present study, we recently reported that multiparity and pregnancy bleedings were important risk factors for subsequent development of schizophrenia, but not for early-onset affective or reactive psychosis. Moreover, as very preterm birth and birth trauma are associated with anorexia nervosa but not with increased risks of schizophrenia or affective or reactive psychosis, these results favor the hypothesis of the existence of specific associations between perinatal factors and subsequent risk of psychiatric disease. Anorexia nervosa is probably multiply determined and factors such as very preterm birth and birth trauma may cause subtle brain damage, which, in conjunction with other individual or environmental factors, may result in inability to correctly identify hunger and satiety sensations. The possible association between perinatal factors and maladaptive eating patterns across infancy, childhood, and adolescence merits further investigation in longitudinal studies.

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REFERENCES