Do children born after assisted conception have less risk of developing infantile autism?

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BACKGROUND: A Danish population based matched case–control study of perinatal risk factors in children with infantile autism has provided some interesting and surprising observations regarding infantile autism and children born after assisted conception. METHODS and RESULTS: The cases (461) consisted of all children born between 1990 and 1999 and diagnosed with infantile autism in the Danish Psychiatric Central Register before February 2001. Matched controls were identified in the Danish Civil Registration System. The main exposure measures included obstetric risk factors for infantile autism. We found a 59% decreased risk for developing infantile autism among children conceived after assisted conception (odds ratio [OR] 0.41, 95% [0.19–0.89]) and a 63% decreased risk after adjusting for known risk factors for assisted conception and infantile autism (OR 0.37, 95% [0.14–0.98]). CONCLUSION: We found that children born after assisted conception had a lower risk of developing infantile autism than their matched controls. Our observations could possibly be explained by the mother’s health status before and during early pregnancy. Our findings require further investigation in larger studies.

Keywords: autistic disorders; health behaviour; infertility treatment; pregnancy; assisted conception

Introduction

Infantile autism is a chronic developmental disability with onset in early infancy. The clinical presentation is characterized by impairments in social interactions and communication with others and by a preference for repetitive, stereotyped behaviours (Filipek et al., 1999). The prevalence of autism spectrum disorders is currently estimated to be 30–60 cases per 10 000 (Rutter, 2005). Infantile autism is only one of the disorders in the autism spectrum, which also includes atypical autism and Asperger syndrome. The most homogeneous and also the most validated diagnosis in the autism spectrum is infantile autism. Little is known about the etiology of infantile autism, but like most other behavioural syndromes, it seems to be a disorder with a multifactorial etiology. In the obstetric field, the most consistent findings in children with infantile autism are low birth weight, birth defects, mothers of higher age and mothers who have immigrated (Hultman et al., 2002; Maimburg and Væth, 2006). Assisted conception was available in Denmark in the early 1990s, but the official reporting of IVF and ICSI pregnancies was not mandatory before 1 January 1994. The increasing use of assisted conception and the recent findings of impaired neurological health within children born after IVF (Strömberg et al., 2002; Lidegaard et al., 2005) have made it interesting to study the relationship between assisted conception and infantile autism. Information about all types of of assisted reproduction can be retrieved from the medical records. We therefore used data from a previous matched case–control study of infantile autism (Maimburg and Væth, 2006) on the basis of information from medical records to investigate the association between assisted conception and infantile autism.

Materials and Methods

We obtained data from The Danish Psychiatric Central Register, The Danish Medical Birth Register and from the medical birth records collected from the Danish maternity wards. In total 473 cases were born between 1 January 1990 and 31 December 1999. They were identified, from the Danish Psychiatric Central Register, with a diagnosis of infantile autism (ICD 8, 299.0 or ICD 10 code, F84.0) before February 2001. A total of 473 controls, matched according to gender, birth year and birth county, were identified in the Danish Civil Registration System. This register contains information on all live born children and new residents in Denmark. Information about obstetric risk factors was obtained from the Danish Psychiatric Central Register, with a diagnosis of infantile autism (ICD 8, 299.0 or ICD 10 code, F84.0) before February 2001. A total of 473 controls, matched according to gender, birth year and birth county, were identified in the Danish Civil Registration System. This register contains information on all live born children and new residents in Denmark. Information about obstetric risk factors was obtained from the Danish Medical Birth Register and from the medical birth records collected from the Danish maternity wards. The birth records provided the information about fertility status, so that cases and controls could be divided into either spontaneous conception or assisted conception (including both hormone
therapy and technical treatment). The status of the cases and controls was blinded in the abstraction process.

The data were analysed using conditional logistic regression. The association between assisted conception and infantile autism were described as an odds ratio (OR) with 95% confidence interval (CI). We calculated both crude and adjusted odds ratios. In the adjusted analyses, we controlled for previously identified risk factors for infantile autism (Maimburg and Væth, 2006), for parity and for multiplicity which is more common for women who have assisted conceptions.

The Statistical Package for Social Sciences version 10.0 was used for data management, and the statistical analyses were performed using Stata Statistical Software, version 8.

The study was approved by The Scientific Ethical Committee for Aarhus County and Danish Data Protection Agency.

Results
The study population consisted of 473 cases with infantile autism, with either ICD 8 code 299.0 (2.1%) or with ICD 10 code F84.0 (97.9%) and 473 matched controls. Of the cases, 20% were girls and 80% were boys. Data from 461 cases and 461 controls were obtained from medical records and The Medical Birth Register. A total of 33 (3.8%) children were born after assisted conception, including 10 (2.3%) cases and 23 (5.4%) controls (Table I). To our surprise, we found that children after assisted conception had a 59% decreased risk of developing infantile autism. After adjusting for well-known risk factors for infantile autism and assisted conception, the percentage rose to 63% (Table II).

Discussion
We conducted a population based matched case–control study with cases identified from a national register. The controls were selected among all live born children in the same time period. Collection of exposure data from the birth record was blinded according to case/control status. The prevalence of assisted conception among controls was similar to that of the background population at the same time period (Pinborg, 2004).

Contrary to our expectations, we found that children conceived by assisted conception had a considerably lower risk of developing infantile autism. To our knowledge only one publication has studied the relationship between infertility and infantile autism and that study found no significant association (Stein et al., 2006). An unpublished study found an increased risk for autism when the mother had a history of infertility, but the autism diagnosed was aggregated with several other severe diagnoses, such as cerebral palsy and cancer (M.S. Croughan, University of California, San Francisco, CA). To explain our findings, we focused on the potential advantages related to pregnancies as a result of assisted conception. Women who have assisted conceived pregnancies tend to have more planned pregnancies and are in close contact with the health care system before and during early pregnancy. Therefore, they have the opportunity, and perhaps also a greater motivation, to reduce negative health behaviour. Maternal health in pregnancy has previously been related to intellectual disability in their offspring. (Leonard et al., 2006)

Furthermore the opportunity to follow advice on how to promote good conditions for the child’s development before and during early pregnancy may be more beneficial for women with assisted conceived pregnancies. Folic acid intake before and during early pregnancy has recently been suggested to play an important role in the etiology and severity of autism (Muskiet and Kemperman, 2006) Health behaviour, such as folic acid intake, before and during early pregnancy could perhaps be an interesting topic to study in future research of infantile autism.

Our observations are based on small numbers but raise an interesting hypothesis, which needs to be tested in larger studies.

### Table I: Population characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Mothers age (years)</td>
<td>29.1</td>
<td>4.3</td>
<td>28.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>3450</td>
<td>695</td>
<td>3532</td>
<td>566</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.2</td>
<td>2.3</td>
<td>39.7</td>
<td>1.7</td>
</tr>
<tr>
<td>n</td>
<td>69</td>
<td>13.7</td>
<td>34</td>
<td>7.2</td>
</tr>
<tr>
<td>Mothrs’ country of origin (non-Danish)</td>
<td>198</td>
<td>44.5</td>
<td>225</td>
<td>50.5</td>
</tr>
<tr>
<td>Parity (nullipara)</td>
<td>15</td>
<td>3.4</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>Birth defect (present)</td>
<td>10</td>
<td>2.3</td>
<td>23</td>
<td>5.4</td>
</tr>
</tbody>
</table>

### Table II: Crude and adjusted ORs with 95% CIs for assisted conception and infantile autism

<table>
<thead>
<tr>
<th></th>
<th>Case n (%)</th>
<th>Control n (%)</th>
<th>Crude OR 95% CI</th>
<th>Adjusteda OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assisted conception</td>
<td>10 (2.3)</td>
<td>23 (5.4)</td>
<td>0.41 0.19–0.89</td>
<td>0.37 0.14–0.98</td>
</tr>
</tbody>
</table>

a Adjusted for mothers age, mothers’ country of origin, parity, multiplicity, birth weight, gestational age and birth defect.

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References


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