Parental infertility and cerebral palsy in children

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Submitted on May 31, 2010; resubmitted on July 6, 2010; accepted on July 7, 2010

BACKGROUND: Children born after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) have been reported to have a higher risk of cerebral palsy (CP), perhaps due to the higher frequency of preterm birth, multiple births or vanishing embryo in the pregnancies. However, it has been suggested that the underlying infertility may be part of the pathway. In this study, we examined whether untreated subfecundity (measured by time to pregnancy) or infertility treatment was associated with an increased risk of CP in the offspring.

METHODS: Using the Danish National Birth Cohort (1997–2003), we compared children born after 0–2 months of waiting time to pregnancy (n = 35 848) with those born after a time to pregnancy of 3–5 months (n = 15 361), 6–12 months (n = 11 528) and >12 months (n = 7 387), as well as those born after IVF/ICSI (n = 3617), ovulation induction with or without intrauterine insemination (n = 3000), and unplanned pregnancies (n = 13 462). CP cases were identified through the Danish CP Register.

RESULTS: In total, 165 (0.18%) children were diagnosed with CP in the entire cohort. We found no significant association between time to pregnancy and the risk of CP in children conceived spontaneously. Children born after IVF/ICSI had an increased risk of CP, even after adjustment for preterm birth and multiplicity (hazard ratio 2.30, 95% confidence interval 1.12–4.73).

CONCLUSIONS: Subfecundity per se did not appear to be associated with the risk of CP in children, whereas being born after IVF/ICSI conferred an increased risk.

Key words: cerebral palsy / infertility / infertility treatment / time to pregnancy / Danish National Birth Cohort

Introduction

Cerebral palsy (CP) is a rare but serious disorder, with a prevalence of about 2 per 1000 live births. It can confer lifelong disability with a substantial impact on family life and societal healthcare costs (Rosenbaum et al., 2007; O’Shea, 2008). Children born after in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) have been reported to have a higher risk of CP in a number of studies (Ericson et al., 2002; Stromberg et al., 2002; Kallen et al., 2005; Lidegaard et al., 2005; Hvidtjørn et al., 2006, 2010; Klemetti et al., 2006), perhaps because of the higher frequency of preterm birth, multiple births or vanishing embryo in these pregnancies (Pinborg et al., 2005; Hvidtjørn et al., 2006, 2009b, 2010). One study, however, reported that the association between IVF and CP disappeared after adjustment for the years of unwanted childlessness, suggesting that low fecundity (or its determinants) may be part of the pathway leading to CP (Kallen et al., 2005). A recent study also reported a higher risk of CP among spontaneously conceived children of subfertile couples who had been registered for treatment at an IVF clinic (Reid et al., 2010).

In this study, we examined whether untreated subfecundity (measured by time to pregnancy) or infertility treatment was associated with a higher risk of CP in the offspring.

Materials and Methods

The study population, described in detail elsewhere (Hvidtjørn et al., 2009a), comprises all women who participated in the first interview (administered around 16 weeks of gestation) of the Danish National Birth Cohort (Olsen et al., 2001) and whose pregnancy resulted in a live birth between 1997 and 2003. In the interview, women were asked whether their pregnancy was planned, and if so, how long they had tried to become pregnant before succeeding. Response categories for time to pregnancy were: ‘right away’, 1–2, 3–5, 6–12 and >12 months.
Participants reporting a time to pregnancy of >6 months were further asked whether they or their male partner had received any infertility treatment, including ICSI, IVF, intrauterine insemination (IUI), ovulation induction (OI) and other treatments (e.g. surgery). We used information on IVF (including ICSI) and OI (with or without IUI), validated through the Danish IVF Register and the Danish Drug Prescription Register, respectively. We excluded pregnancies resulting from ‘other’ treatments (n = 99) and treatments that were reported by the women but had no matching information in the IVF Register or the Drug Prescription Register (n = 675). We grouped births into seven mutually exclusive categories, based on time to pregnancy, infertility treatment and planning status: time to pregnancy of 0–2 (reference group), 3–5, 6–12, >12 months, born after IVF or ICSI, born after OI with or without IUI and unplanned. Children born in the first four categories of time to pregnancy were not the result of infertility treatment, and those in the last category also included children whose parents partly planned their pregnancy or did not report a time to pregnancy.

Cases of CP were identified by data linkage to the Danish Cerebral Palsy Register (Uldall et al., 2001). The register includes all children with a diagnosis of CP validated by a neuro-pediatrician in Denmark since 1995, with approximately 170 incident cases each year. Criteria for inclusion in the register are: age of 4 years or older, pre- or perinatal etiology (before 28 days post-partum) and meeting the diagnostic criteria according to Surveillance of Cerebral Palsy in Europe (Surveillance of Cerebral Palsy in Europe [SCPE], 2002b). All data linkages were based on the unique civil registration numbers assigned to all residents at birth. All data related to the birth (including gestational age) came from the Medical Birth Register.

We used Cox regression to assess the association between time to pregnancy and the risk of CP. Follow-up started at the time of birth and ended when the child died, emigrated, received a diagnosis of CP or when follow-up ended (1 July 2009), whichever came first. Information on covariates was obtained from the Medical Birth Register and Statistics Denmark: maternal age (20–34, 35+ years), parity (0, 1+), smoking during pregnancy (yes, quit, no) and education [basic school (9–10 years), high school (11–16 years) and university or higher (17+ years)], as well as sex of child (male and female). Multiplicity and preterm birth (<37 weeks of gestation) are potential intermediate factors, and we ran the models with and without them to check their influence on the studied associations. As there were no mothers younger than 20 years of age included in the IVF register, children born to mothers younger than 20 years were excluded (n = 519).

Restricting analysis to term-born singletons yielded similar estimates (Table II). Excluding triplets from the analysis did not change the estimates, either (data not shown).

There were no differences in type and severity (regarding motor function and mental retardation) of CP between CP cases born after infertility treatment and CP cases born without treatment (data not shown).

### Discussion

In this large cohort of prospectively followed children, we found no significant association between time to pregnancy and the risk of CP in children conceived spontaneously, whereas children born after IVF or ICSI had an increased risk of CP.

The absence of an association between time to pregnancy and the risk of CP is not in agreement with two previous studies (Kallen et al., 2005; Reid et al., 2010). A Swedish study reported that the association between IVF treatment and CP disappeared after adjustment for the years of unwanted childlessness (Kallen et al., 2005). We had, however, only one category to represent all waiting times of more than 1 year, and it is possible that couples undergoing IVF had a substantially longer waiting time. On the other hand, it is possible that time of unwanted childlessness does not accurately reflect the severity of infertility. All the children studied by the Swedish investigators were born after IVF or ICSI, which makes the two studies substantially different.

### Results

Among 90 203 children, 165 were diagnosed with CP (0.18%): 145 (0.17%) in 86 223 singletons, 18 (0.47%) in 3834 twins and 2 (2.11%) in 95 triplets. Median follow-up time was 8.7 years.

There was no significant association between time to pregnancy and the risk of CP in children, regardless of adjustment (Table I). The risk of CP was higher among children born after IVF or ICSI, as these children had more than twice the risk of CP than children born after a waiting time to pregnancy of 0–2 months, even after adjustment for multiplicity and preterm birth (hazard ratio 2.30, 95% confidence interval 1.12–4.73) (Table I).

Restricting analysis to term-born singletons yielded similar estimates (Table II). Excluding triplets from the analysis did not change the estimates, either (data not shown).

### Table I Hazard ratios for CP in children according to time to pregnancy and infertility treatment.

<table>
<thead>
<tr>
<th>Time to pregnancy (months)</th>
<th>No. of children</th>
<th>No. (%) with cerebral palsy</th>
<th>Crude HR</th>
<th>Adjusted HR* (95% CI)</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>35 848</td>
<td>59 (0.16)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3–5</td>
<td>15 361</td>
<td>22 (0.14)</td>
<td>0.87</td>
<td>0.79 (0.47–1.31)</td>
<td>0.77 (0.46–1.29)</td>
</tr>
<tr>
<td>6–12</td>
<td>11 528</td>
<td>19 (0.16)</td>
<td>0.95</td>
<td>0.91 (0.53–1.55)</td>
<td>0.88 (0.52–1.50)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>7387</td>
<td>19 (0.26)</td>
<td>1.40</td>
<td>1.27 (0.73–2.22)</td>
<td>1.20 (0.69–2.09)</td>
</tr>
<tr>
<td>OI or IUI</td>
<td>3617</td>
<td>7 (0.19)</td>
<td>1.18</td>
<td>1.19 (0.54–2.64)</td>
<td>1.00 (0.44–2.28)</td>
</tr>
<tr>
<td>IVF or ICSI</td>
<td>3000</td>
<td>17 (0.57)</td>
<td>3.47</td>
<td>3.23 (1.77–5.88)</td>
<td>2.30 (1.12–4.73)</td>
</tr>
<tr>
<td>Unplanned pregnancies</td>
<td>13 462</td>
<td>22 (0.16)</td>
<td>1.00</td>
<td>0.73 (0.43–1.24)</td>
<td>0.72 (0.43–1.22)</td>
</tr>
</tbody>
</table>

Cox regression; HR, hazard ratio; CI, confidence interval; reference group: children born after time to pregnancy of 0–2 months.
*Adjusted for maternal age, parity, smoking, education and sex of child.
*bAdjusted for maternal age, parity, smoking, education, sex of child, multiplicity and preterm birth.

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different. An Australian study reported a higher risk of CP among children of subfertile couples who had been registered at an IVF clinic but received no treatment for the pregnancy (Reid et al., 2010). As the authors noted, there was no information on the conceptions that resulted in the births of the children, and it was possible that IVF treatment might have taken place outside the study area.

We did find an increased risk of CP in children born after IVF or ICSI, a finding in line with most previous studies (Ericson et al., 2002; Stromberg et al., 2002; Kallen et al., 2005; Lidegaard et al., 2005; Hvidtjorn et al., 2006, 2010; Klemetti et al., 2006). However, we found that the association could not be entirely attributed to multiple births or preterm birth, which have been the given explanations in most studies (Kallen et al., 2005; Klemetti et al., 2006; Hvidtjorn et al., 2006, 2010), although not all (Stromberg et al., 2002; Lidegaard et al., 2005). The number of CP cases in our study was small, but the estimated CP prevalence of 0.33% for term-born IVF/ICSI singletons was within the most frequently reported ranges among IVF/ICSI singletons (Stromberg et al., 2002; Pinborg et al., 2003, 2004; Lidegaard et al., 2005; Hvidtjorn et al., 2006). The vanishing embryo may play a part in the increased risk (Pinborg et al., 2005; Anand et al., 2007). Children born after OI have also been shown to have a higher risk of CP, though on a smaller magnitude than children born after IVF (Hvidtjorn et al., 2010). Our data regarding OI were too limited to allow us to draw any meaningful conclusion.

About one-third of all Danish women who were pregnant during the study period participated in the cohort (~60% of those invited). Selection bias is, however, unlikely, since we recruited mothers before they gave birth, and we had no loss to follow up except for the few children who died or left the country.

The information on time to pregnancy and infertility treatment was collected during the first or second trimester of pregnancy. Although time to pregnancy reported by women is subject to some degree of recall bias (Cooney et al., 2009), it is likely that short-term recall is valid, and women in our study were only required to report time to pregnancy approximately 4 months into their pregnancy. The self-reported information on IVF or ICSI was validated using the national IVF register, which is believed to be complete, and misclassification of IVF or ICSI is not likely to be a problem in this study. The self-reported information on OI with or without IUI was validated using the Danish Drug Prescription Register. Hormones used in OI can be prescribed for the next three cycles, and misclassification may occur, but it is likely to be minor and of a non-differential nature. There was a high agreement between the women’s report and the registers (Hvidtjorn et al., 2009a). In case of disagreement, we classified pregnancies according to the registers.

We identified CP cases through the CP diagnoses recorded in the Danish Cerebral Palsy Register. A validation study reported a completeness of 85% for CP cases born between 1979 and 1982 (Topp et al., 1997), and the National Patient Register has since been used as a supplementary source, resulting in more complete registration of cases. On the other hand, up to 50% of CP diagnoses recorded in the National Patient Register were not CP cases according to the criteria for inclusion in the CP register. A CP prevalence of 1.8 per 1000 children is marginally less than 2.0–2.5 per 1000 children in the populations [Surveillance of Cerebral Palsy in Europe (SCPE, 2002a)], probably because the children in the cohort are slightly healthier than the general population (e.g. they had a lower rate of preterm birth), as shown in a validity study (Nohr et al., 2006). Only two studies used CP cases recorded in the CP register as outcome (Reid et al., 2010; Hvidtjorn et al., 2010), and in one of the studies, not all the children had reached 4 years of age (Reid et al., 2010).

Our results do not suggest an association between the underlying subfertility and CP, at least for periods of up to 12 months, whereas IVF or ICSI treatment confers a risk of CP.

### Authors’ roles

All authors contributed to the conception and design, interpretation of data and revision of the manuscript. D.H. did the data analysis and J.L.Z drafted the manuscript.

### Acknowledgement

We thank Donna D Baird at National Institutes of Health for her comments on an earlier version of this manuscript.

### Conflict of interest

none declared.

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**Table II** Hazard ratios for CP in term-born singletons according to time to pregnancy and infertility treatment.

<table>
<thead>
<tr>
<th>Time to pregnancy</th>
<th>No. of children</th>
<th>No. (%) with cerebral palsy</th>
<th>Crude HR</th>
<th>Adjusted HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 monthsa</td>
<td>33 409</td>
<td>43 (0.13)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3–5 monthsb</td>
<td>14 285</td>
<td>16 (0.11)</td>
<td>0.87</td>
<td>0.84 (0.46–1.51)</td>
</tr>
<tr>
<td>6–12 monthsb</td>
<td>10 746</td>
<td>10 (0.09)</td>
<td>0.72</td>
<td>0.72 (0.36–1.44)</td>
</tr>
<tr>
<td>&gt;12 monthsb</td>
<td>6771</td>
<td>13 (0.19)</td>
<td>1.26</td>
<td>1.17 (0.59–2.32)</td>
</tr>
<tr>
<td>OI or IUI</td>
<td>2895</td>
<td>3 (0.10)</td>
<td>0.80</td>
<td>0.84 (0.26–2.75)</td>
</tr>
<tr>
<td>IVF or ICSId</td>
<td>1496</td>
<td>5 (0.33)</td>
<td>2.60</td>
<td>2.55 (0.95–6.86)</td>
</tr>
<tr>
<td>Unplanned pregnancies</td>
<td>12 470</td>
<td>14 (0.11)</td>
<td>0.88</td>
<td>0.68 (0.36–1.29)</td>
</tr>
</tbody>
</table>

Cox regression; HR, hazard ratio; CI, confidence interval; reference group: children born after time to pregnancy of 0–2 months.

*aAdjusted for maternal age, parity, smoking, education and sex of child.

*bWithout infertility treatment.

'OI, ovulation induction; IUI, intrauterine insemination.

'IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection.
Funding

This work was supported by grants from the Danish Medical Research Council (271-07-0402 and 09-063477) and, in part, by the Intramural program of the NIH, National Institute of Environmental Health Sciences (Z01 ES044003). The work of Carsten Obel was funded by a grant from the Danish Research Council for Health and Disease. The Danish National Research Foundation has established the Danish Epidemiology Science Centre that initiated and created the Danish National Birth Cohort. The cohort is furthermore a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort is obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, the Augustin foundation and the Health Foundation.

References


