Post-neonatal hospitalization and health care costs among IVF children: a 7-year follow-up study

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BACKGROUND: The objective of this study was to evaluate whether the post-neonatal hospitalization and resulting health care costs are increased among in vitro fertilization (IVF) children up to 7 years of age. METHODS: We conducted a population-based cohort study with linkage to a national hospital discharge register including 303 IVF children, born from 1990 to 1995, and 567 control children (1:2) randomly chosen from the Finnish Medical Birth Register and matched for sex, year of birth, area of residence, parity, maternal age and socioeconomic status. The cost calculations were stratified for singleton (n = 152 vs. n = 285) and twin (n = 103 vs. n = 103) status. Main outcome measures were hospitalizations and societal health care costs. RESULTS: The full-sample and singleton analyses showed that IVF children were significantly more frequently admitted to hospital (mean 1.76 vs. 1.07, P < 0.0001; 1.61 vs. 1.07, P = 0.0004, respectively) and spent significantly more days in the hospital (mean 4.31 vs. 2.61, P < 0.0001; 3.47 vs. 2.56, P = 0.0014, respectively) than control children. No differences were detected between IVF and control twins. The costs of post-neonatal hospital care per child were 2.6-fold for IVF singletons, but 0.7-fold for IVF twins when compared with controls. Cost estimation showed 2.6-fold costs for total IVF population in comparison to general population based controls. CONCLUSIONS: The incidence of multiple births increases the utilization of post-neonatal health care services and costs among IVF children in comparison to naturally conceived children. Increased hospitalization and costs were also seen among IVF singletons.

Keywords: IVF; health care costs; post-neonatal hospitalization

Introduction

In vitro fertilization (IVF) has proved to be an effective treatment for infertility and has become widely used around the globe. Although offering relief to many couples suffering from involuntary childlessness, concern has risen over the long-term outcome of children born after this treatment. At this point, it has been shown that IVF predisposes children to adverse events such as preterm birth and low birth weight, these factors are strongly related to the increased incidence of multiple births after IVF (Koivurova et al., 2002). However, IVF singletons are also prone to similar neonatal problems (Helmerhorst et al., 2004; Jackson et al., 2004; McGovern et al., 2004) suggesting that factors related to infertility itself (Basso and Baird, 2003; Basso and Olsen, 2005) and IVF technology in the form of ‘vanishing embryo syndrome’ (Pinborg et al., 2005) may play a role on the outcome.

As a consequence of the poorer neonatal outcome, IVF children have been shown to need hospital care more often during the neonatal period than children born after natural conception (Koivurova et al., 2002; Helmerhorst et al., 2004; Jackson et al., 2004). So far, to our knowledge, only five studies have been published concerning postnatal hospitalization after IVF (Leslie et al., 1998; Ericson et al., 2002; Pinborg et al., 2004; Bonduelle et al., 2005; Källén et al., 2005). A large register study showed that the utilization of hospital care was at an increased level up to 6 years of age after IVF, although the hospital care utilization was most prominent during the neonatal period (Ericson et al., 2002). The same phenomenon was also seen in another publication that additionally showed an excess in discharge diagnoses indicating brain damage after IVF (Källén et al., 2005). Bonduelle et al. (2005) showed that IVF and ICSI (intracytoplasmic sperm injection) children were more likely to be admitted to hospital up to the age of 5 years than children conceived naturally. Danish IVF/ICSI twins did not over-utilize hospital care resources in comparison to control twins followed until 2–7 years of age, but the
over-use in comparison to IVF/ICSI singletons was clear pointing out the strong effect of multiple birth on the post-natal child outcome (Pinborg et al., 2004). A Finnish study following children up to the age of four years showed that the odds ratio for having a hospital visit was increased (OR 1.32) and the mean length of hospitalization was higher (3.8 vs. 2.6 days) among IVF singletons (n = 4559) in comparison to control children (n = 190 398) (Klemetti et al., 2006). On the contrary, a small Australian study showed no post-natal over-utilization of health care resources after IVF (Leslie et al., 1998).

To fill in the gap in the present literature, we established a follow-up study, based on our earlier cohort study that followed children from birth until 3 years of age (Koivurova et al., 2002; 2003). The present study used a linkage to the Finnish Hospital Discharge Register (FHDR) on a cohort of IVF and control children to test the hypothesis that IVF children over-utilize hospital care resources post-neonatally up to the age of 7 years in comparison to naturally conceived children. Furthermore, we calculated the resulting health care costs to study whether the post-neonatal health care costs continue to be higher for the IVF children, as they were during the neonatal period (Koivurova et al., 2004).

Materials and Methods

Study design

This study is a continuation to our previous population-based 3-year follow-up study on a cohort of IVF children born from 1990 to 1995 (Koivurova et al., 2003). The study design, study population and drop-out figures are presented in Fig. 1. The information on IVF children were derived from the register of the IVF outpatient clinic at the University Hospital of Oulu and from the Infertility Clinic of the Family Federation of Finland in Oulu, where all IVF treatments in Northern Finland (provinces of Oulu and Lapland) are performed. The pre-study sample size calculations were based on clinical developmental outcomes and are presented in our previous publications (Hadders-Algra and Touwen, 1990; Koivurova et al., 2002; Koivurova et al., 2003).

The analyses regarding post-neonatal hospitalization were performed for the full-sample group (n = 303, 153 singletons, 121 twins, 25 triplets and 4 quadruplets) where the control group (n = 567, 1:2) represents the general population in the proportion of multiple births, as well as for groups stratified according to singleton and twin status. The cost analyses were performed by plurality: the singleton analysis consisted of 152 IVF singletons and their 285 controls (1:2, derived from the full-sample control group) and the twin analysis consisted of 103 IVF twins and their additional control cohort of 103 (1:1) naturally conceived twins. In the present analyses, these children were group matched for sex, year of birth, area of residence, parity, maternal age and socioeconomic status defined by the occupation of the mother. The IVF children were born after conventional fresh ova IVF pregnancies mostly after transfer of two or three embryos. Control children were identified from the Finnish Medical Birth Register that covers all births in the country since 1987 (Gissler et al., 1995). In practise, all children were of the same ethnic origin, since up to 99% of population in the study area was of Finnish genetic origin in 1990.

Data collection and analysis

The data regarding post-neonatal hospitalization including diagnoses and the length of the hospital stay were collected by a linkage to the Finnish Hospital Discharge Register where all hospitalizations in Finland have been recorded since 1967. FHDR covers all general and mental hospitals and beds in local health care centres in the public sector as well as private hospitals nationwide. Additionally, day surgery at public and private hospitals is included. We obtained full data until the end of 2002 when all children were at least 7 years old. Hospital treatments during the neonatal period (0–27 days from birth) were excluded from this analysis as they have been presented previously (Koivurova et al., 2002; 2004).

We calculated the mean numbers of admissions to hospitals and days in hospital for the IVF and control groups. The mean unit prices (year 2001) of hospital treatment for different diagnoses (Diagnoses-Related Groups, DRGs) were collected from the data of National Research and Development Centre for Welfare and Health (STAKES) (Hujanen, 2003). To calculate the health care costs per child, all diagnoses appearing during the 7-year follow-up were reviewed and categorized into corresponding DRGs. DRGs have been used internationally since 1990s and they classify patients into separate groups with a specific diagnosis and treatment. This classification helps to estimate the costs of the treatment in each group (Hujanen, 2003). The costs were calculated for each DRG, but only a fraction of DRGs are shown in Tables 1 and 2. The cost calculations were performed by using the DRG-based unit prices to calculate the cost of one day, and then multiplying it by the mean number of days in the hospital for the corresponding diagnosis to get the costs for the actual length of the hospitalization in question. This was further multiplied by the proportion of children with the diagnosis in question in IVF and control groups to get the cost for each DRG per child (Koivurova et al., 2004). The unit prices were inflated to correspond to the prices during 2004 using the consumer price index compiled by Statistics Finland. Wilcoxon Two-Sample Test was used for group matched data in the statistical analysis (two-sided t-test approximation applied) and Bonferroni correction was used for multiple testing regarding the median of post-natal hospital days per age period among hospitalized children.

Results

In the full-sample analysis, the mean number of admissions to the hospital was significantly higher for IVF children than for control children during the 7-year follow-up (1.76 vs. 1.07,
the groups with regard to the number of admissions (1.76 vs. 0.0014) than control singletons. Of the IVF singletons, 61% were hospitalized by the age of 7 years in comparison to 46% of control singletons. Of the IVF singletons, 61% were hospitalized for significantly longer periods (3.47 vs. 2.56, P < 0.0001). The mean number of days in the hospital was also significantly higher for IVF children (4.31 vs. 2.61, P < 0.0001). In the full-sample group, 61% of IVF children were hospitalized during the follow-up in comparison to 46% of control children. The descriptive presentation of the median of hospital days per age period among hospitalized children showed that the utilization of hospital care appeared to be higher for IVF children during infancy and in the fifth year of life when compared with controls (Fig. 2), but after Bonferroni correction, no significant results remained.

Singleton analysis showed similar results: IVF singletons were significantly more frequently admitted to the hospital during the follow-up (1.61 vs. 1.07, P = 0.0004) and were admitted for significantly longer periods (3.47 vs. 2.56, P = 0.0014) than control singletons. Of the IVF singletons, 61% were hospitalized by the age of 7 years in comparison to 43% of control singletons.

The twin analyses showed no significant differences between the groups with regard to the number of admissions (1.76 vs. 1.43, P = 0.5304) and mean number of hospital days (3.85 vs. 5.50, P = 0.7658). The percentage of hospitalized twins by age 7 was also similar in both groups (43% vs. 44%).

The DRG-based diagnoses showed that risks of having diagnoses related to diseases affecting the central nervous system (CNS) (7.9% of IVF singletons and 13.6% of IVF twins having one or many CNS related diagnoses vs. 3.9% of control singletons and 1.9% of control twins) were doubled among IVF singletons, and further multiplied among IVF twins, in comparison to control children (Tables 1 and 2). No cerebral palsy (CP) diagnoses occurred among IVF singletons, whereas one occurred among control singletons. Among IVF twins, 7 out of 11 visits in the DRG regarding brain damage were due to CP, whereas among control twins both visits were due to CP.

Tables 1 and 2 show the unit prices for the main DRGs, number of days the unit price accounts for, number (%) of children treated at hospital per DRG, mean number of days spent at hospital per child in each DRG and cost per child in each DRG.

### Table 1: Post-neonatal health care costs of the main DRGs per child appearing among the IVF and control singletons up to 7 years of age

<table>
<thead>
<tr>
<th>DRG</th>
<th>Price (€)/days</th>
<th>IVF singletons (n = 152)</th>
<th>Control singletons (n = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean number of days per child</td>
<td>Cost (€)/per child</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>----------------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Brain damage</td>
<td>1311.4/2.29</td>
<td>1 (0.66)</td>
<td>0.013</td>
</tr>
<tr>
<td>CNS disorder</td>
<td>839.1/2.24</td>
<td>4 (2.63)</td>
<td>0.076</td>
</tr>
<tr>
<td>CNS seizures and headache</td>
<td>1867.6/2.15</td>
<td>7 (4.61)</td>
<td>0.579</td>
</tr>
<tr>
<td>CNS infection</td>
<td>7089.4/11.01</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychiatric/psychological disorder</td>
<td>3888.0/4.43</td>
<td>3 (1.97)</td>
<td>0.03</td>
</tr>
<tr>
<td>Otitis media/upper respiratory infection</td>
<td>966.2/1.89</td>
<td>68 (44.74)</td>
<td>0.434</td>
</tr>
<tr>
<td>Asthma/obstructive bronchitis</td>
<td>1495.5/2.96</td>
<td>6 (3.95)</td>
<td>0.089</td>
</tr>
<tr>
<td>Oesophagitis/gastroenteritis</td>
<td>1055.6/2.08</td>
<td>30 (19.74)</td>
<td>0.477</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>1044.8/2.39</td>
<td>7 (4.61)</td>
<td>0.826</td>
</tr>
<tr>
<td>Prematurity</td>
<td>6613.2/13.39</td>
<td>1 (0.66)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Corresponds to a unit price calculated for a certain length of hospitalization for a certain diagnosis. Prices have been inflated to correspond to the year 2004.

### Table 2: Post-neonatal health care costs of the main DRGs per child appearing among the IVF and control twins up to 7 years of age

<table>
<thead>
<tr>
<th>DRG</th>
<th>Price (€)/days</th>
<th>IVF twins (n = 103)</th>
<th>Control twins (n = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean number of days per child</td>
<td>Cost (€)/per child</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>-------------------------</td>
</tr>
<tr>
<td>Brain damage</td>
<td>1311.4/2.29</td>
<td>11 (10.68)</td>
<td>0.335</td>
</tr>
<tr>
<td>CNS disorder</td>
<td>839.1/2.24</td>
<td>2 (1.94)</td>
<td>0.024</td>
</tr>
<tr>
<td>CNS seizures and headache</td>
<td>1867.6/2.15</td>
<td>1 (0.97)</td>
<td>0.010</td>
</tr>
<tr>
<td>Psychiatric/psychological disorder</td>
<td>3888.0/4.43</td>
<td>3 (2.91)</td>
<td>0.194</td>
</tr>
<tr>
<td>Otitis media/upper respiratory infection</td>
<td>966.2/1.89</td>
<td>41 (39.81)</td>
<td>0.519</td>
</tr>
<tr>
<td>Asthma/obstructive bronchitis</td>
<td>1495.5/2.96</td>
<td>4 (3.88)</td>
<td>0.117</td>
</tr>
<tr>
<td>Oesophagitis/gastroenteritis</td>
<td>1055.6/2.08</td>
<td>15 (14.56)</td>
<td>0.413</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>1044.8/2.39</td>
<td>4 (3.38)</td>
<td>0.170</td>
</tr>
<tr>
<td>Prematurity</td>
<td>6613.2/13.39</td>
<td>10 (9.71)</td>
<td>0.844</td>
</tr>
</tbody>
</table>

*Corresponds to a unit price calculated for a certain length of hospitalization for a certain diagnosis. Prices have been inflated to correspond to the year 2004.

$P < 0.0001$. The mean number of days in the hospital was also significantly higher for IVF children (4.31 vs. 2.61, P < 0.0001). In the full-sample group, 61% of IVF children were hospitalized during the follow-up in comparison to 46% of control children. The descriptive presentation of the median of hospital days per age period among hospitalized children showed that the utilization of hospital care appeared to be higher for IVF children during infancy and in the fifth year of life when compared with controls (Fig. 2), but after Bonferroni correction, no significant results remained.

Singleton analysis showed similar results: IVF singletons were significantly more frequently admitted to the hospital during the follow-up (1.61 vs. 1.07, P = 0.0004) and were admitted for significantly longer periods (3.47 vs. 2.56, P = 0.0014) than control singletons. Of the IVF singletons, 61% were hospitalized by the age of 7 years in comparison to 43% of control singletons.

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Tables 1 and 2 show the unit prices for the main DRGs, number of days the unit price accounts for, number (%) of children treated at hospital per DRG, mean number of days spent at hospital per child in each DRG and cost per child in each DRG.
hospital and spent significantly more days there during the
lyses IVF children were significantly more often admitted to
parity, we found that in the full-sample and singleton ana-
In the present population-based cohort study on carefully
Discussion
2.6-fold post-neonatal health care costs for the IVF population.
In a similar size population with a natural multiple birth rate
conditions, and among IVF twins a significant proportion of
The most common illnesses requiring hospital care among
IVF twins were almost equal, but for a control twin the costs
The most common illnesses requiring hospital care among
IVF and control children were middle ear infections, upper res-
by 2.29 (to obtain the cost of one day treatment), multiply this
by 0.013 (to obtain the cost of 0.013 days treatment) and mul-
by 0.0066 (proportion of IVF singletons, 1/152, with brain damage) to obtain the cost of brain damage hospitalization per child in the IVF group (€0.05).
The total costs of post-neonatal hospital care constituting of
all DRG based discharge diagnoses per IVF singleton were
2.6-fold (€205.8 per child) compared with that per control single-
gen brain damage in Table 1) divide the unit price (€) 1311.4
by 2.29 (to obtain the cost of one day treatment), multiply this
by 0.013 (to obtain the cost of 0.013 days treatment) and multi-
plication has not the power to confirm a statistically signifi-
cantly increased risk for such a rare event as CP among IVF children;
however, 7.9% of IVF singletons and 13.6% of IVF twins were
expenditure followed by assisted reproduction.
In our previous publication based on manual data collection from hospital records, we showed that the cumulative morbidity up to 3 years of age of IVF singletons was higher than that for control singletons pointing out a higher incidence of respira-
tory diseases, especially obstructive bronchitis, and diarrhoea
after IVF (Koivurova et al., 2003). Those results are in line
with the present study with a different data source showing
that IVF children were hospitalized more often and for longer
time periods during the 7-year follow-up. Our results are in
accordance with recent previous literature that has shown an
increased hospitalization of IVF children up to 5–6 years of age in larger series of study subjects (Ericson et al., 2002; BON-
duelle et al., 2005; Källén et al., 2005). The Swedish register studies included all IVF children regardless of plurality in the
study, showing the natural effect of multiple birth and relating
adverse outcomes on the results (Ericson et al., 2002; Källén
et al., 2005). Bonduelle et al. (2005) studied only singletons with similar results, indicating that the long-term health even
of IVF singletons is poorer than that of other children.
Previous studies have raised concern over the neurological
health of IVF children with an excess of CP and other diag-
noses indicating brain damage (Ericson et al., 2002; Strömberg
et al., 2002; Källén et al., 2005; Hvidtjørn et al., 2006). This
finding is to a large extent due to the increased incidence of
multiple and preterm births after IVF. Our present study popula-
tion has not the power to confirm a statistically significantly
increased risk for such a rare event as CP among IVF children;
Discussion
In the present population-based cohort study on carefully
matched IVF and control children of women with similar age
and parity, we found that in the full-sample and singleton ana-
yses IVF children were significantly more often admitted to
hospital and spent significantly more days there during the
7-year follow-up than their naturally conceived controls. Consequently, the post-neonatal costs of hospital care of IVF
singletons were also markedly higher than those for control singletons. Among twins, no differences were found reflecting
the more complex nature of twin comparisons with the inter-
mediating effect of the alteration in the zygosity and chorioni-
city rate after IVF as well as decreased power in this respect. To
our knowledge, this is the first study that compares the hospital
care costs based on DRG-classification between the groups.
Knowledge on long-term outcome and utilization of hospital
care of children born after IVF is limited at the moment. So far,
it has been shown that IVF children need more hospital care
services than other children during the first month of their
lives due to events related to preterm birth and low birth
weight which have a higher incidence among IVF children,
mostly as a result of the increased proportion of multiple births. It is of importance to find out whether the hospital
care resources are also over-utilized by IVF children after the
neonatal period as this reflects the general health of the IVF
offspring as well as allowing an estimation of the societal
expenditure followed by assisted reproduction.
Figure 2: Median of post-natal hospital days per age period during
the 7-year follow-up of hospitalized IVF and control children (full-
sample analysis) P-values from Wilcoxon Two-Sample Test
two-sided t-approximation): first year (P = 0.061), second year
(P = 0.630), third year (P = 0.900), fourth year (P = 0.330), fifth
year (P = 0.024), sixth year (P = 0.370), seventh year (P = 0.110)
An example of the health care cost calculations (IVF singletons
with brain damage in Table 1) divide the unit price (€) 1311.4
by 2.29 (to obtain the cost of one day treatment), multiply this
by 0.013 (to obtain the cost of 0.013 days treatment) and multi-
ply this result by 0.0066 (proportion of IVF singletons, 1/152,
with brain damage) to obtain the cost of brain damage hospitalization per child in the IVF group (€0.05).
Total post-neonatal health care costs of the full-sample IVF
(group (n = 303, multiple birth rate 49.5%) were ~€65 000.
In a similar size population with a natural multiple birth rate
around 1.0%, the costs would be ~€25 000, indicating a
2.6-fold post-neonatal health care costs for the IVF population.

Discussion
In the present population-based cohort study on carefully
matched IVF and control children of women with similar age
and parity, we found that in the full-sample and singleton ana-
yses IVF children were significantly more often admitted to
hospital and spent significantly more days there during the
In general, the main diagnoses leading to hospitalization in IVF and control groups were common middle ear, upper respiratory tract and gastrointestinal infections reflecting the benign nature of the health problems during the follow-up period. Naturally, conditions related to preterm birth caused additional and significant hospitalizations among twin groups. In both twin groups, the rate of preterm birth related conditions was 10%, but among control twins the hospitalizations were markedly longer. In this small sample of twins, this finding is probably due to chance. The overall level of hospitalization was similar between the twin groups in this study indicating that multiple birth and relating factors such as zygosity and chorionicity are stronger determinants of child outcome among twins than IVF technique or infertility. Due to our sample size, we cannot detect more severe and rare conditions that might occur in the IVF offspring as a result of the manipulative nature of IVF technique. As another deficiency of this study, we are not aware of the possible deaths in the IVF and control groups after 3 years of age (hospital records have been manually checked up to 3 years of age), because FHDR only records deaths in hospitals and no information on all deaths is gathered to FHDR. It is probable that some deaths have occurred among both groups during the end of the study period, but we believe that no major bias is caused by this lack of information because children’s deaths are likely to happen at hospitals or confirmed at hospitals, although some, such as accidental deaths, may have happened outside the hospitals. In addition, in a larger Finnish register-based study, IVF singletons and control singletons had similar mortality rates during a 2-year follow-up period (Klemetti et al., 2006).

The costs of post-neonatal hospital care among IVF singletons in this study were greater than two-fold in comparison to singletons born after natural conception. In our previous publication on neonatal health care costs after IVF, we showed that neonatal health care costs of IVF singletons until the age of 28 days were 1.5-fold compared with control singletons (Koivurova et al., 2004). Therefore, it seems that societal health care costs after IVF rise up to the age of 7 years in proportion to that for natural conception as far as singletons are concerned. For twins the situation was reversed: for control twins the post-neonatal costs were higher, than for IVF twins, as were the neonatal costs in our previous publication (Koivurova et al., 2004). The costs of post-neonatal care between IVF singletons and IVF twins were, due to relatively high-IVF singleton costs, almost equal, whereas the costs of control twins were nearly four-fold higher than that for control singletons. Nevertheless, it can be concluded that multiple birth increases the health care costs post-neonatally even without the potential effects of IVF technology and infertility. No previous studies exist on the long-term health care costs among IVF children, in accordance with previous larger studies. Furthermore, it shows that resulting post-neonatal health care costs are higher among IVF children. Societal costs after IVF also consist of the even higher costs resulting from the IVF procedure itself, as well as from prenatal and neonatal care. The elevated incidence of multiple births after IVF markedly increases the post-neonatal health care costs among IVF offspring in comparison to the costs of naturally conceived children. Considering long-term child outcome as well as the finances, elective single embryo transfer is recommended.

In conclusion, the present study shows that there is an increase in the use of post-neonatal hospital care among IVF children, in accordance with previous larger studies. Furthermore, it shows that resulting post-neonatal health care costs are higher among IVF children. Societal costs after IVF also consist of the even higher costs resulting from the IVF procedure itself, as well as from prenatal and neonatal care. The elevated incidence of multiple births after IVF markedly increases the post-neonatal health care costs among IVF offspring in comparison to the costs of naturally conceived children. Considering long-term child outcome as well as the finances, elective single embryo transfer is recommended.

References


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