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 post-natal 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
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).

Figure 1: Study design and the study population. Shaded presentation for the cost study. Full-sample IVF group represents the total cohort of IVF children studied. Singleton control group was derived from the full-sample control group and for IVF twins an additional twin control group was randomly chosen. *Children from multiple pregnancies in the same proportion as in a general population. TThirty-nine IVF children missing second control. *One singleton control missing in plurality matching. *Nineteen IVF children missing second control. *Eighteen twin controls missing in plurality matching.

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,
43% of control singletons were hospitalized by the age of 7 years in comparison to 0.0014) than control singletons. Of the IVF singletons, 61% admitted for significantly longer periods (3.47 vs. 2.56, P = 0.0004) and were due to CP. Of the IVF singletons, 7 out of 11 visits in the DRG regarding brain damage were due to CP, 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.

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.
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 multiply 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).

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 singleton (€79.6 per child). For twins the situation was reversed: the post-neonatal health care costs were 1.3-fold for a control twin (€302.4 per child) compared with that for an IVF twin (€224.1 per child). The costs between IVF singletons and IVF twins were almost equal, but for a control twin the costs were nearly four-fold in comparison to a control singleton. The most common illnesses requiring hospital care among IVF and control children were middle ear infections, upper respiratory tract infections and gastroenteritis. The most costly illnesses among IVF and control singletons were those mentioned above, but for IVF children also the care of seizures affecting the CNS (convulsions, headache) and juvenile rheumatoid arthritis resulted in significant costs. For twins, additional significant costs resulted from the care of preterm birth related conditions, and among IVF twins a, significant proportion of costs were due to diagnoses indicating brain damage.

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 analyses 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 intermediating effect of the alteration in the zygosity and chorionicity 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.

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 respiratory 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; Bondonuelle 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). Bondonuelle 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 diagnoses 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 population has not the power to confirm a statistically significantly 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 hospitalized with disorders affecting the CNS in comparison to 3.9 and 1.9% of control children, respectively. It is notable also that seven CP diagnoses were detected among IVF twins. Furthermore, diseases with immunological backgrounds such as asthma, rheumatoid arthritis and infectious diseases were overrepresented among IVF singletons suggesting that there might be some kind of disturbance in the immunological response after IVF, but this observation needs to be evaluated in further studies.
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 during the end of the study period. Naturally, conditions related to preterm birth caused more, it shows that resulting post-neonatal health care costs 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.

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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.

As our full-sample analysis shows, multiple birth and related factors probably play the major role in determining the post-neonatal outcome of the IVF offspring. Still, the post-neonatal outcome of IVF singletons measured with the level of hospitalization seems more adverse than that of control singletons, indicating that IVF technology and parental factors relating to infertility may also be of importance. Previously it has been shown that infertility as such is a risk factor for adverse perinatal outcome reflecting the differences between fertile and infertile populations as well as the effect of underlying causes of infertility such as Chlamydia infections, prenatal diethylstilbestrol exposure, solvent exposure and psychological stress (Basso and Baird, 2003). Furthermore, the length of involuntary infertility has been shown to be an independent risk factor for child hospitalization (Ericson et al., 2002 even for term children (Källén et al., 2005). Parents of IVF children may seek medical help more easily than other parents, and that may lead to more loose indications of hospital treatments. Unfortunately, we were not able to control for the length of infertility in this study. We believe that the diagnoses set at the hospitals are accurate and non-biased, since the physicians at the hospitals at that time were not necessarily aware of the IVF status of the child. Furthermore, the inpatient hospital care in Finland is almost entirely based on public funding with no private hospitals for children. Only minor procedures such as tympanostomies and adenotomies are partly performed in the private sector as day surgery. The admission policy is homogenous across the country, thus diminishing bias.

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