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Hospital care utilization of IVF/ICSI twins followed until 2–7 years of age: a controlled Danish national cohort study

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BACKGROUND: IVF/ICSI twins are likely to have a higher risk of prematurity associated with higher morbidity. The aim of this study was to assess the use of hospital care resources in IVF/ICSI twins on data retrieved until 2–7 years of child age. METHODS: National controlled cohort study on hospital admissions and surgical interventions in 3393 IVF twins, 10 239 spontaneously conceived twins and 5130 IVF singletons born between 1995 and 2000 in Denmark. Cross-linkage of data from the Danish IVF Registry and the National Patient Registry enabled us to identify children who were admitted to hospital or underwent an operation. RESULTS: The frequency of hospitalized children was 69.8, 69.6 and 49.8%, and of children who underwent a surgical intervention 10.6, 11.2 and 8.5% in IVF/ICSI twins, control twins and IVF/ICSI singletons respectively. Odds ratios (OR) (95% confidence intervals) of hospitalization in IVF/ICSI twins versus control twins and IVF/ICSI singletons were 1.04 (0.96, 1.14) and 2.44 (2.22, 2.63) and OR adjusted for year of birth, maternal age and parity were 1.00 (0.91, 1.11) and 2.38 (2.17, 2.63) respectively. Also for term birth infants, IVF/ICSI twins were more likely to be hospitalized than IVF/ICSI singletons: adjusted OR 1.37 (1.22, 1.51). Similar risk of a surgical procedure was observed in IVF/ICSI versus control twins. However, IVF/ICSI twins more often underwent a surgical intervention than IVF/ICSI singletons: adjusted OR 1.26 (1.08, 1.47). This risk disappeared when restricted to term infants: adjusted OR 1.00 (0.81, 1.22). Different sex IVF/ICSI and control twins had equal risk of admissions and surgical interventions, and ICSI children had the same risk as children born after conventional IVF. CONCLUSIONS: Though the use of hospital care resources was similar in IVF/ICSI and control twins, the over-use in IVF/ICSI twins versus IVF/ICSI singletons adds to the arguments for implementing elective single embryo transfer as our standard procedure.

Key words: epidemiology/hospital admission/hospital care resources/ICSI twins/IVF/surgical procedures

Introduction

In Europe, 39% of infants born after IVF or ICSI in 2000 were twins (Nyboe Andersen *et al.*, 2004). In Finland and Belgium, pregnancy rates after elective single embryo transfer (eSET) have shown good results and currently eSET is being implemented in many European countries (Land and Evers, 2003; Tiitinen *et al.*, 2003; De Neubourg and Gerris, 2003; Templeton, 2004). The major task is to reduce maternal and neonatal risk related to twin pregnancies and births (Bergh *et al.*, 1999; Dhont *et al.*, 1999).

In a Swedish register study, the risk of hospital admissions was higher in a cohort of IVF children born between 1982 and 1995 than in naturally conceived children born during the same period. This was to a large extent due to the increased incidence of multiple births in IVF children (Ericson *et al.*, 2002). Similar results were provided in a small Australian study on 95 IVF children (Leslie *et al.*, 1998). They found that apart from admissions to neonatal intensive care unit (NICU), IVF infants did not seem to over-utilize health care resources during the remainder of their first year of life.

Our questionnaire survey on ($n = 1740$) 4 year old IVF/ICSI children born in 1997 showed similar frequency and length of hospitalizations in IVF/ICSI twins and singletons after exclusion of NICU admissions (Pinborg *et al.*, 2003). Two register studies on the same Danish cohort of IVF/ICSI twins born between 1995 and 2000 revealed that IVF/ICSI twins were twice as likely to be admitted to NICU than IVF/ICSI singletons and also, to a less but still significant extent, more likely to be admitted to NICU than naturally conceived twins (Pinborg *et al.*, 2004a,b). As data on other assisted reproductive procedures such as ovarian induction or intrauterine insemination until 2002 were not recorded in The Danish IVF Registry, a certain proportion of the control twins was not spontaneously conceived. Our previous national questionnaire survey on the 1997 twin birth cohort

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in Denmark demonstrated that 17.3% of the control twins were born after assisted reproduction treatment other than IVF/ICSI (Pinborg *et al.*, 2003).

To further emphasize on whether to keep our policy of dual embryo transfer or to implement eSET as our daily clinical practice, the aim of this study was to assess the risk of hospital admissions and surgical procedures in the same Danish National cohort of IVF/ICSI twins born between 1995 and 2000 aged 2–7 years compared with all IVF/ICSI singletons and all non-IVF/ICSI twins born during the same period.

Material and methods

Participants

All women giving birth to twins from January 1st, 1995 to December 31st, 2000 in Denmark were identified through the Danish Medical Birth Registry (MBR) (Knudsen and Olsen, 1998). All citizens in Denmark are provided with a unique identification number in the Civil Registration System (CPR number). Recording of women in MBR is based on this number. A cross-reference with the Danish IVF Registry enabled us to dichotomize the participants into women with IVF and naturally conceived twins. Women, who delivered IVF singletons, were enrolled in a similar way. The CPR number on every individual child in the three cohorts was identified through a unique existing linkage between the CPR number of a mother and her children in MBR.

Records on fertilization method and obstetric outcome were drawn from the IVF Registry and MBR, respectively. Since January 1st, 1994 it has been compulsory to register each initiated IVF or ICSI cycle to the Danish IVF Registry in the National Board of Health (Nyboe Andersen *et al.*, 1999). We enrolled all 3393 IVF/ICSI twins, 5130 IVF/ICSI singletons and 10 239 non-IVF/ICSI twins born in Denmark between 1995 and 2000. Data on neonatal outcome including neonatal admissions, the risk of neurological sequelae and mortality rates in the three cohorts have recently been published (Pinborg *et al.*, 2004a,b,c).

Outcome measures

By cross-reference with the National Patient Registry, we identified all children diagnosed or treated in a hospital setting between their delivery and December 31st, 2002. The National Patient Registry contains information on all hospitalizations in Denmark including diagnoses and operations performed, dates of entrance to and discharge from the hospital (Andersen *et al.*, 1999). Diagnosis codes and surgical procedures in the National Patient Registry are classified according to the International Classification of Diseases, 10th edn (ICD-10).

We studied the proportion of infants in the three cohorts, who had been hospitalized at any age (up to a maximum of 7 years) and we calculated the frequency of hospitalizations and the mean number of days spent in hospital. The frequency of children, who underwent a surgical procedure and the average number of interventions were assessed. To ensure an appropriate age at diagnosis, all children were between 2 and 7 years of age at time of retrieval of diagnoses from the National Patient Registry with the average age in the study group being 4.2 years (Table I). Diagnosis codes, recorded between January 1st, 1995 and December 31st, 2002 in the National Patient Registry, were included in the study. International definitions were followed for term birth (delivery ≥ 37 completed weeks) and neonatal admission (children with day of entrance to hospital within the first 28 days of life).

Hospital admission included both data on in- and outpatients. Outpatients were classified as having 1 day of admission. If date of entrance and discharge were the same, duration was called 1 day. Surgical interventions also included diagnostic procedures such as endoscopies and lumbar punctures.

Analysis

Statistical analysis was performed using SPSS for Windows (Statistical Packages for Social Sciences) version 10.0. $P < 0.05$ was considered statistically significant. Differences of means of continuous parametric data were analysed with the use of Student's *t*-test. Pearson χ^2-analyses were used to compare distributions between groups. The study group was compared separately with each of

Table I. Maternal and infants characteristics of women and children in the three cohorts

	IVF/ICSI twins	Control twins	P	IVF/ICSI singletons	P
No. of children	3393	10 239		5130	
Child age at follow-up (years) (mean ± SD)	4.2 ± 1.7	4.4 ± 1.7	<0.001	4.1 ± 1.7	0.12
Child sex (%)					
Boy	52.1	51.3	0.4	52.6	0.6
Girl	47.9	48.7		47.4	
Same sex twin pairs (%)	50.8	65.4	<0.001	–	
Monozygotic twin rate (%)[a]	1.6	31.0	–	–	
Birthweight (g) (mean ± SD)	2508 ± 615	2540 ± 612	0.01	3457 ± 629	<0.001
Gestational age (weeks) (mean ± SD)	35.9 ± 3.0	36.1 ± 2.9	0.02	39.3 ± 2.2	<0.001
Mortality rates, number per 1000					
Stillborn	13	12	0.6	7	0.002
Infants deaths <1 year	10	15	0.04	7	0.1
Total (stillborn + infants deaths)	23	27	0.3	14	0.001
Maternal age at delivery (years) (mean ± SD)	33.1 ± 3.7	30.5 ± 4.5	<0.001	33.8 ± 3.7	<0.001
Age <30 years (%)	20.0	45.4	<0.001	15.4	<0.001
OR (95% CI)	1	3.4 (2.9–3.8)		0.7 (0.6–0.8)	
Nulliparity (%)	76.6	40.9	<0.001	72.5%	0.001
OR (95% CI)	1	3.4 (2.9–3.8)		0.9 (0.8–1.0)	
Treatment method (%)					
IVF	75.4	–		75.0	0.8
ICSI	24.6	–		25.0	

[a]Estimated rate of monozygotic twins according to Weinberg's law (Weinberg, 1902; Pinborg *et al.*, 2004a).
Data in this table have previously been published (Pinborg *et al.*, 2004 a,b).
OR = odds ratio; CI = confidence interval.

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the two control groups. We calculated OR (OR) with 95% confidence intervals (CI) for hospitalization and surgical procedure with Mantel–Haenszel estimate after stratification for year of birth, maternal age (<25, 25–30, 30–35, ≥35 years) and parity (0 or ≥1 previous deliveries). To exclude the monozygotic twins, we performed separate analyses restricted to different sex twin pairs. OR in ICSI children versus conventional IVF children were also calculated with respect to hospital admissions and surgical procedures.

Infant was the unit of analysis, since each child in a twin pair was calculated with a separate record and not as a pair. To evaluate the co-dependency of twin variables, we made two separate analyses comparing IVF/ICSI singletons with only one IVF/ICSI twin of a pair. In each of the two analyses the IVF/ICSI twin of a pair was randomly selected. These analyses were performed for both admissions and operations and further restricted to term birth infants.

Results

Hospital admissions

Maternal and infant characteristics are presented in Table I. These data have previously been published (Pinborg *et al.*, 2004a,b). Control twins were significantly older than IVF twins at time of diagnosis retrieval, implying a longer time span from birth to assessment of hospitalization rates in control twins versus IVF twins. To take account of this, all OR were subsequently adjusted for child year of birth. Figure 1 illustrates the distribution of admissions in IVF/ICSI twins, IVF/ICSI singletons and control twins according to child age at hospitalization: the vast majority of admissions (58.3%) among IVF/ICSI twins occurred during the first 4 weeks of life. A similar pattern was seen in both control groups. Data on hospital admissions are summarized in Table II. Approximately 70% of IVF/ICSI and control twins had been admitted to hospital versus half of the IVF/ICSI singletons ($P < 0.001$). Though of less clinical importance due to the very small differences, the average number of hospital admissions per hospitalized child was significantly lower in IVF/ICSI twins (2.14 days) compared with control twins (2.33 days) ($P = 0.006$), but equal as compared with IVF/ICSI singletons (2.15 days) ($P < 0.9$). The distribution of the number of hospital admissions in the three cohorts is listed in Table II. For all levels of number of admissions, significantly more IVF/ICSI twins were hospitalized than IVF/ICSI singletons. A significant higher proportion of control twins were admitted > 5 times compared with IVF/ICSI mins ($p = 0.04$); however, on all the other levels of number of hospitalizations, we observed no increased frequency in IVF/ICSI versus control twins.

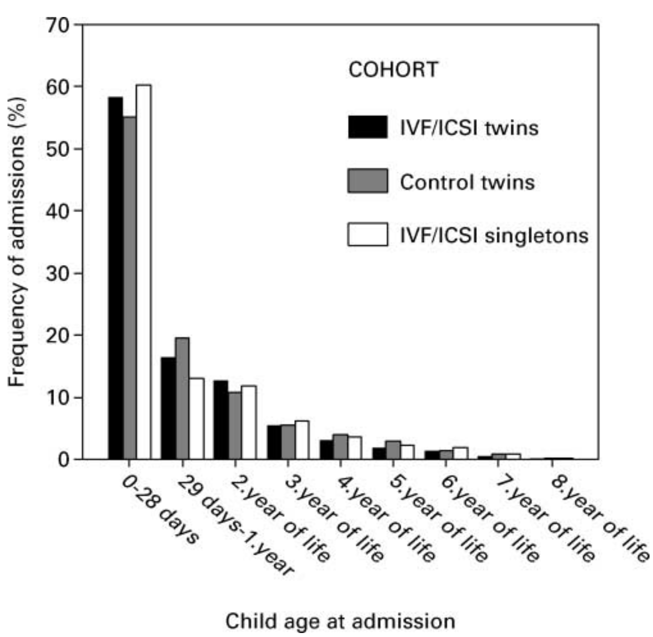

Figure 1. The distribution of hospital admissions in IVF/ICSI twins. IVFI/ICSI singletons and control twins according to child age at hospitalisation.

The average number of days spent in hospital for all children in the three cohorts was 14.5, 13.8 and 5.3 days for IVF/ICSI twins, control twins and IVF/ICSI singletons respectively. IVF/ICSI twins spent on average 9.2 days more in hospital than IVF/ICSI singletons ($P < 0.001$). A similar comparison with non-IVF/ICSI twins showed no excess hospitalization in IVF/ICSI twins.

We calculated OR of being hospitalized with stratification for year of birth, maternal age and parity (Table III). Since the boy:girl ratio was equal in all three cohorts, we did not stratify for child sex. Similar adjusted OR of admissions in IVF/ICSI versus control twins were observed; however, a 2.5-fold increased risk in IVF/ICSI twins was seen, when compared with IVF/ICSI singletons (adjusted OR 0.42, 95% CI 0.38, 0.46). The ten most frequent discharge diagnoses listed in descending order were prematurity, low birthweight, fever convulsions, observation, pneumonia, asthma, virus, diarrhoea, bronchitis, and respiratory distress syndrome. Since most of these diagnoses are related to preterm birth, we calculated adjusted OR for term infants to eliminate the influence of prematurity (Table III). Even after exclusion of premature infants, IVF/ICSI twins had a 1.4-fold increased risk of hospital admission compared with IVF/ICSI singletons (adjusted OR 0.73, 95% CI 0.66, 0.82).

Surgical procedures

The number of children with surgical interventions and the mean number of surgical procedures are shown in Table II. The crude percentage of children who underwent at least one surgical procedure in IVF/ICSI twins, control twins and IVF/ICSI singletons was 10.8%, 11.2% ($P = 0.5$) and 8.5% ($P < 0.001$) respectively. The average number of operations in children who underwent a surgical procedure was ∼2 in all three cohorts. IVF/ICSI twins were more likely to have had an operation as compared with IVF/ICSI singletons, but similar adjusted risks were observed for IVF/ICSI and control twins (Table III). The increased risk of a surgical procedure in IVF/ICSI twins versus singletons disappeared in the analyses restricted to term infants. There were no alterations in OR of hospital admissions and surgical interventions, when restricted to term birth IVF/ICSI twins versus control twins (Table III). Specific operations sorted on different organ systems are listed in Appendix I. Diagnostic procedures and less severe operations constituted more than half of the total number of surgical procedures. Minor surgical interventions such as ear surgery and mouth, nose and throat surgery, including

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Table II. The frequency of hospital admissions and surgical interventions in the three cohorts

	IVF/ICSI twins	Control twins	P	IVF/ICSI singletons	P
No. of children	3393	10 239		5130	
Hospitalized children, *n* (%)	2367 (69.8)	7122 (69.6)	0.3[a]	2557 (49.8%)	<0.001[a]
Average number of hospital admissions per hospitalized child*	2.14	2.33	0.001[b]	2.15	0.9[b]
No. of admissions (%)					
0	29.4	30.3		50.2	
1	34.3	33.8	0.7	27.9	<0.001
2	18.6	17.5	0.4	11.2	<0.001
3–5	14.6	14.6	0.5	8.6	<0.001
>5	3.1	4.0	0.04	2.2	0.01
Total (%)	100	100		100	
No. of children with surgical interventions, *n* (%)	361 (10.6)	1145 (11.2)	0.5[a]	436 (8.5)	<0.001[a]
Average no. of surgical interventions per operated child	1.90	2.15	0.02[b]	2.21	0.05[b]
No. of surgical interventions (%)					
0	89.2	88.8		91.5	
1	6.3	6.2	0.5	4.6	0.001
≥2	4.5	5.0	0.3	3.9	0.2
Total	100	100		100	

[a]χ^2-Test.
[b]Student's *t*-test.
Average number of hospital admissions was calculated as the total number of admissions in the cohort as the numerator and the total number of children in the cohort as the denominator.
Average number of surgical interventions was calculated as the total number of surgical interventions in the cohort as the numerator and the total number of children in the cohort as the denominator.

Table III. Odds ratios of hospital admissions and surgical interventions

	IVF/ICSI twins	Control twins	IVF/ICSI singletons
No. of children	3393	10 239	5130
No. of term birth children	1882	5853	4730
Admissions, all children			
No stratification	1	0.96 (0.88, 1.04)	0.41 (0.38, 0.45)
Year of birth	1	0.95 (0.87, 1.03)	0.41 (0.38, 0.45)
Year of birth, maternal age, parity	1	1.00 (0.90, 1.10)	0.42 (0.38, 0.46)
Admissions, term children			
No stratification	1	0.99 (0.89, 1.10)	0.72 (0.65, 0.80)
Year of birth	1	0.97 (0.88, 1.08)	0.72 (0.65, 0.81)
Year of birth, maternal age, parity	1	0.98 (0.87, 1.11)	0.73 (0.66, 0.82)
Surgical interventions, all children			
No stratification	1	1.05 (0.92, 1.19)	0.77 (0.66, 0.89)
Year of birth	1	1.00 (0.88, 1.13)	0.78 (0.67, 0.90)
Year of birth, maternal age, parity	1	1.00 (0.86, 1.15)	0.79 (0.68, 0.93)
Surgical interventions, term children			
No stratification	1	1.00 (0.83, 1.21)	0.93 (0.77, 1.13)
Year of birth	1	0.95 (0.79, 1.14)	0.95 (0.79, 1.16)
Year of birth, maternal age, parity	1	0.98 (0.79, 1.23)	1.00 (0.82, 1.23)

Data are presented as odds ratio (95% confidence interval) with stratification for year of birth, maternal age and parity.

paracentesis tympani and adeno-tonsillectomy, comprised approximately one-third of the total number of surgical procedures in all three cohorts, whereas diagnostic procedures were attributable to one-fifth.

ICSI

There was no significant difference in the proportion of twins in the IVF VS the ICSI group; 39.4% of the conventional IVF children and 39.8% of the ICSI children were twins. Data on twins and singletons were therefore pooled to estimate OR of being hospitalized and having a surgical intervention in ICSI versus conventional IVF children. Among IVF children (twins + singletons) 58.5% and among ICSI children 56.7% were admitted to hospital ($P = 0.2$). The analyses demonstrated no increased risk of hospital admissions [OR 0.93 (0.84, 1.03)] and surgical procedures [OR 0.89 (0.75, 1.06)] in ICSI as compared with children born after conventional IVF.

Zygosity

To exclude the MZ twin pairs, analyses were restricted to different sex twins. Of the different sex IVF/ICSI and control twins 71.2 and 69.2% had been admitted to hospital respectively. The risk (adjusted OR) of admittance to hospital in different sex IVF/ICSI twins versus control twins was 0.97 (0.83, 1.13) and the adjusted OR calculated for term infants was 1.01 (0.84, 1.21). Risks were adjusted for year of birth, maternal age and parity.

In the different sex twins, 9.6% of the IVF/ICSI and 10.4% of the control twins underwent a surgical procedure.

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The adjusted OR of a surgical procedure in IVF/ICSI versus control twins was 1.02 (0.81, 1.28). The corresponding adjusted OR for term infants was 1.18 (0.84, 1.65).

Co-dependency of variables in twins

To evaluate the co-dependency of twin variables, we made two separate analyses comparing IVF/ICSI singletons with only one IVF/ICSI twin of a pair. In each of the two analyses the IVF/ICSI twin of a pair was randomly selected. These analyses were performed for both admissions and operations and further restricted to only term birth infants with adjustment for year of birth, maternal age and parity. Taken together, as expected, this resulted in a slight broadening of the CI, although the overall OR remained similar and the statistically significant results were not altered. For example, adjusted OR of admission in IVF/ICSI singletons versus one randomly selected IVF/ICSI twin of a pair was 0.41 (0.35, 0.48) and the year of birth, age and parity adjusted OR was 0.42 (0.36, 0.48). The remaining results from these analyses are not shown here.

Discussion

The vast majority of admissions in all three cohorts occurred during the first 4 weeks of life. IVF/ICSI twins were more likely to be admitted to hospital and to undergo a surgical intervention than IVF singletons; however, as compared with control twins the risks were similar. Even though a majority of the diagnoses were related to prematurity, the same pattern was seen after restriction of data to term infants only. The risk of admission and surgical procedure was similar in IVF and control twins also after exclusion of monozygotic twins by restricting data to different sex twins. Moreover no increased risk of admissions and operations was observed in ICSI versus IVF children.

The strength of this study is primarily the nationwide design, which makes it the largest study on the use of hospital care resources in IVF/ICSI twins with a relatively high child age of 4.2 years at retrieval of diagnoses. The unique CPR number system and the compulsory IVF registry enabled us to track the complete cohort of IVF/ICSI twins and IVF/ICSI singletons born during a 6 year period in Denmark. Since the Danish IVF Registry was initiated in 1994, only children born after January 1, 1995 were enrolled. To maintain a sufficient follow-up period, data on admissions and surgical interventions were drawn from the National Patient Registry from infant birth until December 31, 2002. Thus, all children in study and control groups were followed with admissions and surgical procedures until they were aged ≥ 2 years, with the oldest children aged 7 years and a mean age in the study group of 4.2 years at diagnoses retrieval. The sample size allowed us to adjust for relevant confounders (year of birth, maternal age and parity) and to perform sub-analyses on term birth infants, different sex twins and ICSI infants.

Another strength of this study was the essential linkage of a mother and her children. Further, the mandatory recording of all outpatient, discharge and operative diagnoses in the National Patient Registry enabled us to gain information on the use of all health care resources in a hospital setting. Data on non-hospital services such as help to disabled children were not available for any of the three cohorts. Since the main focus was to compare morbidity in IVF/ICSI twins with IVF/ICSI singletons to shed light on the controversy of dual versus single embryo transfer, we did not include a control group of spontaneously conceived singletons.

The Danish IVF Registry records all IVF cycles performed in Denmark; however, assisted reproduction treatments other than IVF cycles are currently not recorded, but will be implemented in the near future. Therefore a limitation of this study was the lack of data on the proportion of women in the control twin group, who conceived after assisted reproduction treatments other than IVF. Our recently published study with data originating from a questionnaire sent to the subpopulation of women in the three cohorts, who delivered in 1997, revealed that 17.3% of women in the control twin group conceived after other kinds of assisted reproduction treatments (Pinborg *et al.*, 2003). However, a recent study has shown that infants conceived after hormonal induction or intrauterine insemination (IUI) have neonatal outcome similar to that of spontaneously conceived children (Basso and Baird, 2003). Thus, it should not bias data on neonatal admissions in the present study. However, follow-up data with sufficient sample size on twins conceived by IUI do not exist.

Moreover, the questionnaire study showed no fundamental differences in terms of socio-economic position between women who conceived after IVF and women who conceived spontaneously. This is probably explained by the fact that the first three IVF/ICSI treatments are reimbursed in Denmark combined with a liberal access to this treatment, which is confirmed by Denmark having the highest number of IVF cycles performed per inhabitant in Europe. In addition, 65% of all cycles are performed in public clinics, making IVF/ICSI treatment available for all citizens.

This study confirms previously published observations that the main increased utilization of health care by IVF twins occurs during the first period of life (Leslie *et al.*, 1998; Ericson *et al.*, 2002). Also in spontaneously conceived pregnancies preterm birth is a major predictor of how much an individual will cost hospital service providers during the first 5 years of life (Petrou *et al.*, 2003). However, after restriction of analyses to term infants, there was still an apparent increased OR of admission in IVF twins versus singletons, albeit considerably reduced from 2.4 to 1.4. The increased odds of surgical interventions disappeared after exclusion of preterm infants. Our previous studies showed that (56.3, 52.4 and 25.0%) of IVF/ICSI twins, control twins and IVF/ICSI singletons respectively were admitted to NICU (Pinborg *et al.*, 2004a,b), whereas frequency of admissions in the present study with follow-up was (69.8, 69.6, 49.8%).

As observations on twins are not fully independent, there is a potential risk of estimating the CI as too narrow. As expected, the analyses performed to evaluate the role of co-dependency of twin data resulted in a slight broadening of the CI, but the overall OR remained similar and the statistically significant results were not altered. This suggests that the co-dependency in twin data was of less importance.

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Almost one out of ten children in each cohort underwent a surgical procedure. However, it is reassuring that more than half of the total number of surgical procedures was attributable to minor operations, e.g. ear surgery and diagnostic procedures such as endoscopies and lumbar punctures. To acknowledge that the majority of surgical procedures recorded in the National Patient Registry are minor and not our primary concern, specific surgical procedures with a prevalence of >5 in 1000 children have been listed in Appendix I.

In population-based studies on naturally conceived children, twins have a 4-fold higher risk of cerebral palsy than singletons (Scher *et al.*, 2002). Among IVF children, only two nationwide studies with sufficient sample size have been published showing contradictory results. Strömberg *et al.* (2002) revealed that IVF twins were more likely to develop cerebral palsy than IVF singletons, whereas in our Danish register study similar risks of neurological sequelae in IVF twins and IVF singletons were observed (Pinborg *et al.*, 2004c).

It is unclear to what extent outcome measures such as number of hospital admissions and average length of hospital stay serve as valid indicators of infant morbidity. The aim of this study was, however, to assess the use of hospital care resources. Data on morbidity and the prevalence of specific diseases in the same cohorts have previously been published (Pinborg *et al.*, 2003, 2004c). Though our previous study showed similar prevalence rates of neurological sequelae in the three cohorts, we observed increased use of hospital care resources in IVF/ICSI twins versus IVF/ICSI singletons in terms of admissions and surgical interventions in the present study. In addition, our questionnaire study revealed that IVF/ICSI twin mothers estimated the physical health and speech development of their children as poorer than IVF/ICSI singleton mothers and that IVF twins were more likely to have special needs than IVF singletons (Pinborg *et al.*, 2003). Taken together these results indicate that even after the neonatal high-risk period mainly related to prematurity, IVF twins at least until 7 years of age in general have an increased use of hospital care resources than IVF singletons, which is in accordance with previous controlled studies (Ericson *et al.*, 2002; Koivurova *et al.*, 2003). However, it must be stated that this over-use of hospital care in these Danish IVF/ICSI twins did not cover severe neurological disabilities, which certainly is reassuring (Pinborg *et al.*, 2004c).

Corresponding with previous studies, we showed no excess morbidity in ICSI children as compared with children conceived after conventional IVF (Sutcliffe *et al.*, 2001). Despite previous studies showing higher morbidity in monozygotic twins (Loos *et al.*, 1998), we did not demonstrate differences between IVF and control twins, when data were restricted to different sex twins.

In conclusion, by implementing eSET, thereby reducing the IVF twin birth rate, a substantial saving of hospital cost could be achieved, most likely counterbalancing one or two extra embryo transfers to obtain pregnancy (Gerris *et al.*, 2004). The increased use of hospital care resources in terms of admissions to hospital and surgical procedures in IVF/ICSI twins versus IVF/ICSI singletons suggested in this study, is another argument for implementing eSET as our standard clinical procedure.

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Appendix I. Total number of surgical interventions in IVF/ICSI twins, IVF/ICSI singletons and control twins sorted according to organ system

Surgical interventions performed with a frequency of >5 per 1000 in all children are specified. One child could be registered more than once.

	IVF/ICSI twins	IVF/ICSI singletons	Control twins
No. of children	3393	5130	10 239
Intracranial and spinal cord			
Ventriculoperitoneal shunt	4	3	22
Revision of ventriculoperitoneal shunt	6	3	28
Other	8	7	41
Sum	18 (26/1000)	13 (13/1000)	91 (37/1000)
Eye surgery			
Operation for:			
Squint	5	3	16
Cataract	0	3	12
Other	14	18	73
Sum	19 (28/1000)	24 (25/1000)	101 (41/1000)
Ear surgery			
Paracentesis tympani	55	63	170
Drainage of the tympanic membrane	36	41	124
Other	12	11	37
Sum	103 (150/1000)	115 (119/1000)	331 (134/1000)
Mouth, nose and throat surgery			
Operation for:			
Cleft palate	5	15	21
Cleft lip	3	11	19
Short frenulum of the tongue	6	8	13
Tonsillectomy	42	45	98
Adeno-tonsillectomy	27	45	84
Adenotomy	48	49	118
Other	14	34	57
Sum	145 (212/1000)	207 (215/1000)	410 (166/1000)
Cardiac and great vessel surgery			
Operation for:			
Persistent arterial duct	2	0	11
Ventricular septal defect	1	3	9
Extracorporal circulation	5	15	17
Other	21	47	73
Sum	29 (42/1000)	65 (67/1000)	110 (45/1000)
Mediastinal surgery			
Sum	8 (12/1000)	6 (6/1000)	20 (8/1000)
Gastro-intestinal surgery			
Hernia repair, inguinal	63	46	217
Hernia repair, other	5	5	36
Operation on:			
Oesophagus	12	20	27
Ventricle	5	11	29
Appendicectomy	4	7	28
Bowel	15	37	75
Anus	1	13	10
Other	7	5	43
Sum	112 (164/1000)	154 (160/1000)	465 (188/1000)
Urogenital surgery			
Operation for:			
Hydrocele testis	6	4	8
Undescended testis	6	12	19
Phimosis	2	7	6
Hypospadia	3	5	12
Penis surgery, other	1	3	16
Male genital surgery, other	5	13	37
Female genital surgery, other	1	1	4

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	IVF/ICSI twins	IVF/ICSI singletons	Control twins
Sum	24 (35/1000)	45 (47/1000)	102 (41/1000)
Orthopaedic surgery			
Operation on:			
Vertebral column	0	4	2
Fracture of upper extremity	19	22	66
Upper extremity, other	9	5	20
Hand/wrist	12	11	38
Pelvis	0	13	10
Hip/femur	4	10	22
Knee/lower leg	5	5	18
Clubfoot	6	7	23
Foot/ankle joint	6	8	34
Sum	61 (89/1000)	85 (88/1000)	242 (98/1000)
Skin surgery			
Sum	22 (32/1000)	48 (50/1000)	126 (51/1000)
Diagnostic procedures			
Lumbar puncture	3	44	19
Catheterization of the heart	11	19	30
Catheterization of central veins	3	11	21
Endoscopy:			
Respiratory tract	35	31	93
Alimentary tract	32	35	68
Endoscopy, other	7	7	19
Diagnostic procedures, other	53	55	216
Sum	144 (210/1000)	202 (210/1000)	466 (189/1000)
Total surgical procedures, *n* (%)	685 (100)	964 (100)	2464 (100)

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