Neonatal outcome in a Danish national cohort of 3438 IVF/ICSI and 10 362 non-IVF/ICSI twins born between 1995 and 2000

Anja Pinborg1,2, Anne Loft1, Steen Rasmussen3, Lone Schmidt4, Jens Langhoff-Roos5, Gorm Greisen6 and Anders Nyboe Andersen1

1The Fertility Clinic, 4Department of Obstetrics and Gynecology, 5Department of Neonatology, University of Copenhagen, Rigshospitalet, 3National Board of Health, Health Statistics, Copenhagen and 1Institute of Public Health, University of Copenhagen, Denmark

To whom correspondence should be addressed at: The Fertility Clinic, University of Copenhagen, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. E-mail: apinborg@rh.dk

BACKGROUND: In Denmark, one-third of twin pregnancies are the result of IVF/ICSI treatment. Limited data on neonatal outcome in IVF/ICSI twins are available in the literature. METHODS: A register study was conducted on neonatal morbidity and mortality in a complete national twin cohort including all 3438 (3393 live-born) IVF/ICSI and 10 362 (10 239 live-born) non-IVF/ICSI twins born between 1995 and 2000. Twins were identified in the National Medical Birth Registry and dichotomized into IVF/ICSI and non-IVF/ICSI by cross-reference with the Danish IVF Registry. Data on neonatal morbidity and mortality were retrieved from the Danish Patient Registry and the Danish Registry of Causes of Deaths. In order to exclude monozygotic twins, sub-analyses on unlike-sex twins were conducted. RESULTS: A birth weight discordance of >20% was observed in 20.6% of IVF/ICSI versus 15.7% of control twin pairs (P < 0.001). The risk of discordant birth weight >20% was OR 1.29 (95% CI 1.04–1.58) in unlike-sex IVF/ICSI twins versus control twins. The risk of delivery at <37 completed weeks and birth weight <2500 g was similar in the two cohorts; however, in unlike-sex IVF/ICSI versus control twins the risk of delivery at <37 weeks and birth weight <2500 g was OR 1.22 (95% CI 1.09–1.38) and OR 1.25 (1.11–1.40) respectively. After stratification for maternal age and parity, these risks disappeared. IVF/ICSI twins carried a higher risk of admission to a neonatal intensive care unit (NICU) than control twins (OR 1.18, 95% CI 1.09–1.27), and this was even more pronounced in unlike-sex twins [OR 1.34 (95% CI 1.19–1.51)]. No differences were observed in malformation or mortality rates between the two cohorts. CONCLUSIONS: Despite higher birth weight discordance and more NICU admissions among IVF/ICSI twins, neonatal outcome in IVF/ICSI twins seems to be comparable with that of non-IVF/ICSI twins, when only dizygotic twins were considered in the comparisons.

Key words: clinical epidemiology/congenital malformations/ICSI twins/IVF/neonatal outcome

Introduction

In some European countries, up to 4% of all infants are born after assisted reproductive technology (ART), implying that overall national perinatal statistics are affected by the contribution of ART (Nygren and Nyboe Andersen, 2002). Although a relatively small proportion of the population uses ART, the introduction of these techniques has imposed worldwide increases in multiple birth rates. Between 1970 and 1996, a 2-fold increase in the twin birth rate was observed in Denmark (Iimaizumi, 1998). The annual ESHRE report from 1999 indicated that 24% of IVF and ICSI deliveries in Europe were twin deliveries, and consequently almost 40% of all IVF and ICSI babies are born as twins (Nygren and Nyboe Andersen, 2002).

Twin pregnancies are the main factor in the overall poorer perinatal outcome in IVF pregnancies, even though surveys on IVF singleton pregnancies have found slightly higher complication rates compared with spontaneously conceived singleton pregnancies (Bergh et al.,1999; Dhont et al., 1999; Westergaard et al., 1999; Schieve et al., 2002). A Danish register study with 854 IVF twins observed significantly higher birth weight in IVF twins than in spontaneously conceived twins (Westergaard et al., 1999), whereas other surveys have reported similar perinatal morbidity and mortality in IVF/ICSI and spontaneously conceived twins (Olivennes et al., 1996; Bernasko et al., 1997; Fitzsimmons et al., 1998; Dhont et al., 1999; Koudstaal et al., 2000). In 1999, one group (Dhont et al., 1999) observed no differences in perinatal outcome between
1241 dizygotic (DZ) IVF and naturally conceived twin pregnancies. However, a later survey on 480 DZ IVF twin pregnancies observed poorer perinatal outcome in IVF compared with naturally conceived twin pregnancies (Lambalk and van Hooff, 2001). The frequency of monozygotic (MZ) babies in IVF twins is 1–2% compared with 30% in spontaneously conceived twins (Schachter et al., 2001; Sperling and Tabor, 2001). Previous studies on spontaneously conceived twins have found perinatal morbidity and mortality to be higher in MZ than in DZ twins (Bryan et al., 1987; Loos et al., 1998). Thus, it could be assumed that IVF twin pregnancies carry less obstetric risks than spontaneously conceived twin pregnancies.

In severe but rare events such as malformations and perinatal death, a large study group is needed to investigate the risk with sufficient power. The aim of the present study was to assess the outcome of a complete Danish IVF/ICSI twin birth cohort from 1995 to 2000 compared with all non-IVF/ICSI twin births in Denmark during the same period. In addition, sub-analyses on unlike-sex twins were performed to exclude all MZ—and thus monochorionic twins—from both cohorts. Data from the Danish IVF registry were cross-linked with existing registries on births, malformations, admissions to the neonatal intensive care unit (NICU) and deaths.

Materials and methods

This population-based cohort study included all twins born in Denmark after IVF or ICSI between January 1, 1995 and December 31, 2000. The control group consisted of all non-IVF/ICSI twins born in Denmark during the same 6-year period.

The National Medical Birth Registry (MBR) recording all live births and stillbirths in Denmark was used to identify all women who gave birth to live-born and stillborn twins between January 1, 1995 and December 31, 2000 (Knudsen et al., 1998). In Denmark, every individual has a unique identification number in the Centralised Civil Registry (CPR number) that is widely used by healthcare and social-service providers. The CPR number in the MBR identified each woman. Subsequently, those women who delivered after IVF or ICSI treatment were identified by cross-reference with data recorded in the Danish IVF Registry. This enabled the twin mothers to be dichotomized into the study population, which included women with IVF/ICSI twins and a control group of women with non-IVF/ICSI twins.

In Denmark, since January 1, 1994 it has been compulsory to register each initiated IVF or ICSI cycle with the Danish IVF Registry in the National Board of Health (Nyboe Andersen et al., 1999). Records on infertility history and fertilization method were retrieved from the Danish IVF Registry. The CPR number of each individual infant in the two cohorts was identified through a unique existing linkage between the CPR number of a mother and her children in the MBR. Information on previous deliveries, duration of pregnancy in completed weeks, birth weight (in grams), rate of Caesarean section and survival of babies was retrieved from the MBR. By using record linkage with the Danish Patient Registry and the Danish Cancer Registry, admissions to the NICU, congenital malformations and cancers were identified (Andersen et al., 1999). Mortality rates were retrieved from the National Registry of Causes of Deaths, while diagnoses of cancer were retrieved from the Danish Cancer Registry and cross-checked in the Danish Cancer Registry. Diagnoses including cancers were classified according to the International Classification of Diseases, 10th Edition (ICD-10) in the Danish Patient Registry. The quality of data on congenital abnormalities from the Danish Patient Registry has been assessed in a recent study and found to be acceptable for general surveillance and epidemiological research (Larsen et al., 2003). In the MBR, the duration of gestation in IVF/ICSI twin pregnancies is determined from 14 days before the date of oocyte aspiration, and in control twin pregnancies from the first day of the last menstrual period.

A total of 3438 IVF/ICSI twins (3393 live-born, 45 stillborn) and 10 362 control twins (10 239 live-born, 123 stillborn) was identified. Stillborn babies were excluded from further statistical analyses regarding neonatal outcome and congenital malformations, as the register recording of the stillborn was inadequate. Only CPR numbers were used in all linkages. The study was approved by the Danish Data Protection Agency and assessed by the Scientific Ethical Committee of Copenhagen and Frederiksberg Municipalities, who recorded no objections.

Definitions

‘Delivery’ was defined as live-born and stillborn babies delivered after 22 completed weeks of gestation, while ‘duration of gestation’ in IVF/ICSI twin pregnancies was defined from 14 days before the date of egg aspiration, and in control twin pregnancies from the first day in the last menstrual period. A pre-term birth was defined as delivery before 37 completed weeks of gestation. Low birth weight was defined as <2500 g and very low birth weight as <1500 g.

‘Neonatal mortality’ was defined as the number of children who died <28 days after delivery per 1000 children born with a gestational age of 22 weeks or more. Intrauterine and intrapartum deaths were not included. ‘Infant mortality’ was defined as live born children who died within the first year.

‘Malformations’ were defined as conditions registered in the International Classification of Diseases and Health Related Problems, 10th Revision (ICD-10; Danish National Board of Health, 1993), as a congenital malformation or chromosome abnormality (ICD-10: Q00-Q99). ‘Major congenital malformations’ were defined as malformations that generally cause functional impairment or required surgical correction. The remaining malformations were considered ‘minor’.

‘Birth weight discordance’ was defined as the weight difference between the smaller and larger child of a pair of twins, expressed as the percentage of the birth weight of the larger child.

Statistical analysis

The results were analysed using SPSS (Statistical Packages for Social Sciences) version 10.0. Statistical significance was defined as P < 0.05. Differences in the means of continuous parametric data were analysed using Student’s t-test. χ² analyses were used to compare distributions between the two groups.

With regard to analyses on gestational age, ‘twin pregnancy’ was the unit of analysis, whereas in terms of birth weight and malformations, ‘infant’ was the unit of analysis. Birth weight was calculated as the mean of two twins in a pair, and malformations were registered for both twins in a pair. Twin data for analysis was either entered as twin individuals, or as a twin delivery. The statistical problem caused by ties between a twin pair (e.g. similar birth weights, similar malformations, etc.) was always present and unavoidable, but was always taken into consideration.

Odds ratios were calculated using the Mantel–Haenszel estimate after stratification. For stratification of data, the following maternal characteristics were used: age (5-year age-groups of <30, 30–34, 35–39 and ≥40 years) and parity (0 or ≥1 previous deliveries). In terms of malformations, data were stratified for treatment method (IVF versus...
Gestational age and birth weight in live-born children with gestational age of 22 completed weeks or more

Parameter | IVF/ICSI twins | Control twins | P
---|---|---|---
No. of children | 3393 | 10 239 |
Birth weight (g) | | |
Mean ± SD | 2508 ± 615 | 2540 ± 612 | 0.009
Range | 450–4682 | 450–5689 |
Proportion of children with birth weight (%): | |
>2500 g | 57.7 | 59.5 |
1500–2499 g | 34.9 | 33.7 |
<1500 g | 7.5 | 6.8 |
Gestational age (weeks)* | 35.9 ± 2.96 | 36.1 ± 2.85 | 0.02
Proportion of deliveries with gestational age: | |
>37 completed weeks | 56.1 | 58.5 |
32–36 completed weeks | 35.4 | 33.7 |
<32 completed weeks | 8.5 | 7.8 |

*Values are mean ± SD.
†Significant, IVF/ICSI versus controls.

### Results

#### Demographic data

The maternal characteristics of the women are listed in Table I. The age and parity distribution of women who delivered IVF/ICSI twins differed strikingly from that of women in the control twin group; as expected, IVF/ICSI twin mothers were ‘elderly’ primiparae. Of the IVF/ICSI twin mothers, 75.4% had received IVF and 24.6% ICSI treatment.

The frequency of boys was similar among IVF/ICSI twins (52.1%) and control twins (52.6%). Of the IVF/ICSI twins, 50.8% were same-sex twin pairs, in contrast to 65.4% same-sex control twin pairs (P < 0.001). The zygosity of twins was determined using Weinberg’s differential method (Weinberg, 1902). Doubling the number of opposite-sex twins gave an estimate of the total number of DZ twins, the remainder being MZ. This calculation assumed that the sex ratio of DZ twins was 50:50. In the present study, 825 opposite-sex IVF/ICSI twin pairs out of 1676 twin pairs were observed for which the sex of both twins was known. This gave an estimate of 26 (1.6%) MZ twin pairs in the IVF/ICSI twin group. The corresponding figures in the control twin group were 1773 opposite-sex twin pairs out of 5103 twin pairs, which gave an estimate of 1557 (31%) MZ twin pairs in the control twin group.

#### Birth weight and gestational age

Gestational age and birth weight for children born after 22 completed weeks are presented in Table II. Mean birth weight and gestational age was significantly lower for IVF/ICSI twins compared with control twins. The unadjusted risk of birth weight <2500 g was similar, but the risk of delivery at <37 weeks was significantly higher in IVF/ICSI twins compared with controls (Table III). After stratification for maternal age, the risk of low birth weight and preterm birth became significantly higher in IVF/ICSI twins compared with controls. In subsequent analyses with stratification for both maternal age and parity, the differences disappeared and IVF/ICSI twins even had a lower risk of birth weight <2500 g compared with control twins [Odds Ratio (OR) 0.88, 95% CI 0.80–0.96] (Table III).

In order to exclude MZ twins, sub-analyses on unlike-sex twin pairs among IVF/ICSI twins (n = 1650) and control twins (n = 3546) were performed, and results indicated that mean birth weight and gestational age were significantly lower in unlike-sex IVF/ICSI twins than in unlike-sex control twins. As observed for the total twin groups, the discrepancies between the unlike-sex twin groups remained after stratification for maternal age only, but disappeared after stratification for both maternal age and parity (Table III).

#### Birth weight discordance

The mean birth weight discordance was 12.5% in IVF/ICSI twins and 11.3% in control twins (P < 0.001). The risk of discordant birth weight in unlike-sex and same-sex IVF/ICSI twins was equal, whereas the risk of discordant birth weight in unlike-sex control twin pairs was higher than in same-sex control twin pairs (OR 1.25, 95% CI 1.07–1.47). A birth weight discordance of more than 20% was observed in 20.6% of the IVF/ICSI twin pairs, and in 15.7% of the control twin pairs (P <0.001). Unlike-sex IVF/ICSI twins were more likely to have discordance >20% than unlike-sex control twins (OR 1.29, 95% CI 1.04–1.58).

#### Congenital malformations

The number of major and minor birth defects in different organ systems is presented in Table IV. A complete list of malformations with exact diagnoses is available from the first author. Data on malformations were collected from date of birth until death.
Table III. Odds ratios (OR, 95% CI) for low birth weight and short duration of gestation in IVF/ICSI twins (n = 3393) versus control twins (n = 10 239) and in opposite-sex IVF/ICSI twins (n = 1650) versus opposite-sex control twins (n = 3546)

<table>
<thead>
<tr>
<th>Stratification criteria</th>
<th>Birth weight</th>
<th>Gestational age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1500 g</td>
<td>&lt;2500 g</td>
</tr>
<tr>
<td>All twins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stratification</td>
<td>1.16 (0.92–1.46)</td>
<td>1.08 (0.99–1.27)</td>
</tr>
<tr>
<td>Maternal age</td>
<td>1.20 (1.03–1.41)</td>
<td>1.13 (1.04–1.23)</td>
</tr>
<tr>
<td>Maternal age and parity</td>
<td>0.94 (0.80–1.12)</td>
<td>0.88 (0.80–0.96)</td>
</tr>
<tr>
<td>Opposite-sex twins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No stratification</td>
<td>1.16 (0.92–1.46)</td>
<td>1.25 (1.11–1.40)</td>
</tr>
<tr>
<td>Maternal age</td>
<td>1.27 (1.00–1.61)</td>
<td>1.28 (1.13–1.45)</td>
</tr>
<tr>
<td>Maternal age and parity</td>
<td>0.98 (0.76–1.26)</td>
<td>1.03 (0.90–1.18)</td>
</tr>
</tbody>
</table>

Maternal age in 5-year intervals (<30, 30–34, 35–39 or ≥40 years). Parity in 0 or ≥1 previous deliveries.
*Significant value.

Table IV. Number of major and minor congenital malformations and rates per 1000 children in live-born children with gestational age ≥22 weeks

<table>
<thead>
<tr>
<th>Major birth defect or malformation</th>
<th>IVF/ICSI twins (n = 3393)</th>
<th>Control twins (n = 10 239)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td>15</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Eye/ear</td>
<td>3</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>41</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>7</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Genital/urinary</td>
<td>23</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Orofacial cleft</td>
<td>8</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>22</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Chromosomal</td>
<td>5</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Gene defects</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sum, major births defects</td>
<td>139 (41.0/1000)</td>
<td>488 (47.7/1000)</td>
<td>0.11</td>
</tr>
<tr>
<td>Minor birth defects + PDA</td>
<td>111 (32.7/1000)</td>
<td>267 (26.1/1000)</td>
<td>0.05</td>
</tr>
<tr>
<td>Minor birth defects without PDA</td>
<td>53 (15.6/1000)</td>
<td>140 (13.7/1000)</td>
<td>0.40</td>
</tr>
<tr>
<td>Total + PDA</td>
<td>250 (73.7/1000)</td>
<td>755 (73.7/1000)</td>
<td>1.00</td>
</tr>
<tr>
<td>Total without PDA</td>
<td>192 (56.6/1000)</td>
<td>628 (61.3/1000)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

PDA = patent ductus arteriosus.
Data on congenital malformations were recorded from delivery until December 31, 2001.

Among the 10 239 live-born control twins, 596 (58.2/1000) children with 755 malformations were identified (Table IV). There was no increased risk of malformations in IVF/ICSI versus control twins, neither between the total cohorts (OR 1.08, 95% CI 0.92–1.28) nor in the sub-analyses on unlike-sex twins (OR 1.24, 95% CI 0.97–1.58).

Mode of delivery
The Caesarean section (CS) rate was 52.9% in IVF/ICSI twin and 42.7% in control twin deliveries; moreover, the risk of CS in IVF/ICSI twin deliveries was 1.5-fold higher than that in control twin deliveries (OR 1.5, 95% CI 1.3–1.7). This risk disappeared after adjustment for maternal age and parity (OR 1.1 95% CI 1.0–1.2).

NICU admissions
Among the IVF/ICSI twins and control twins, 56.3% and 52.4% respectively of the children were admitted to the NICU. IVF/ICSI twins carried a higher risk of admittance to NICU than control twins (OR 1.18, 95% CI 1.09–1.27). Stratification for gestational age yielded the same increased risk for IVF/ICSI versus control twins (OR 1.17, 95% CI 1.06–1.28). By restricting data to only DZ twins, sub-analyses on unlike-sex twins were carried out. The risk of admittance to NICU was even higher for unlike-sex IVF/ICSI compared with unlike-sex control twins (OR 1.34, 95% CI 1.19–1.51), and this higher risk was maintained after adjustment for gestational age (OR 1.30, 95% CI 1.13–1.50).

The average number of days spent in the NICU was 19.8 and 18.4 (P = 0.003) for IVF/ICSI twins and control twins respectively. The frequency of children hospitalized for more than 7 days was 74.6% and 69.9% (P = 0.02), and for more than 28 days was 27.6% and 24.6% (P = 0.02) for IVF/ICSI twins and control twins respectively.

Mortality
Mortality rates in the IVF/ICSI twin group and the two control groups are presented in Table V. No significant difference in stillborn rate (P = 0.6) and neonatal mortality rate (P = 0.3) was seen between the IVF/ICSI and control twins. The total infant
Table V. Mortality rates among IVF/ICSI and control twins

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IVF/ICSI twins</th>
<th>Control twins</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live-born</td>
<td>3393</td>
<td>10 239</td>
<td></td>
</tr>
<tr>
<td>Stillborn</td>
<td>45 (13/1000)</td>
<td>123 (12/1000)</td>
<td>0.6</td>
</tr>
<tr>
<td>Total</td>
<td>3438</td>
<td>10 362</td>
<td></td>
</tr>
<tr>
<td>Dead children (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early neonatal up to day 6</td>
<td>26</td>
<td>119</td>
<td>0.05</td>
</tr>
<tr>
<td>Late neonatal day 7–28</td>
<td>4</td>
<td>22</td>
<td>0.26</td>
</tr>
<tr>
<td>From day 29–1 year</td>
<td>5</td>
<td>13</td>
<td>0.78</td>
</tr>
<tr>
<td>Total infant deaths</td>
<td>35 (10/1000)</td>
<td>154 (15/1000)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stillborn</td>
<td>45</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>Infant deaths</td>
<td>35</td>
<td>154</td>
<td></td>
</tr>
<tr>
<td>Total (stillborn + infant deaths)</td>
<td>80 (23/1000)</td>
<td>277 (27/1000)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Data on stillbirths were retrieved from the Medical Birth Registry; data on deaths later in life were retrieved from The Danish Registry of Causes of Deaths from child date of birth until 1 year of age. χ² analyses were carried out to compare IVF/ICSI twins with control twins.

The limitations of the present study were the lack of information on the use of ovarian stimulation among spontaneously conceived twins, and also on socioeconomic status. In order to compensate for this restriction in the register data, a questionnaire survey was carried out which included all those women in the three cohorts who gave birth in 1997. Data from this study showed no differences in socioeconomic status between the women in the three different groups (Pinborg et al., 2003b). Moreover, the results indicated that 17.3% of women in the control twin group had a history of ovarian stimulation, while among 10 239 control twins 11 children (1.1/1000) = 0.076) developed cancer before December 31, 2001. The minimum period of observation was one year. The cancer diagnoses were acute lymphatic leukaemia, astrocytoma, and non-specific tumours in the heart, cerebrum, suprarenal gland and soft tissues.

Cancer incidence

Among the 3393 twins born after IVF, none developed cancer, while among 10 239 control twins 11 children (1.1/1000 children; P = 0.076) developed cancer before December 31, 2001. The minimum period of observation was one year. The cancer diagnoses were acute lymphatic leukaemia, astrocytoma, and non-specific tumours in the heart, cerebrum, suprarenal gland and soft tissues.

Discussion

To the best of the present authors’ knowledge, this is the largest controlled survey on neonatal outcome in IVF/ICSI twins. It is a population-based cohort study consisting of all twins born after IVF or ICSI treatment in Denmark from 1995 to 2000. Moreover, all spontaneously conceived twins born during the same 6-year period were included as the control group. This national survey has several advantages. First, the compulsory Danish IVF Registry and unique CPR number system enabled all IVF and ICSI twin births from 1995 to 2000 to be traced. Second, the linkage between women and children in the National Medical Birth Registry (MBR) allowed the identification of all individual infants in the three cohorts, and for information to be retrieved from other registries such as the Danish Patient Registry, the National Registry on Causes of Deaths, and the Danish Cancer Registry. Moreover, the confounding effects of maternal age and parity were minimized by stratification, which also made it possible to investigate the role of preterm labour on neonatal morbidity between the two cohorts. As data on zygosity were unavailable in the MBR, separate analyses were performed on unlike-sex twin pairs to exclude MZ twins.

Although a similar obstetric outcome was observed in IVF/ICSI and spontaneously conceived twins, the former were more likely to be admitted to the NICU. Even after stratification for...
gestational age, the unlike-sex IVF/ICSI twins had a 1.3-fold higher risk of NICU admittance. Although this might reflect the fact that healthcare professionals take more precautions when treating twins born after IVF or ICSI treatment, an increased neonatal morbidity cannot be excluded. In accordance with more precautions being taken in women who conceived after ART, or in their children, the results of the previous questionnaire survey indicated that IVF/ICSI twin mothers more often required sick leave and hospitalization during pregnancy than control twin mothers, though their morbidity during pregnancy was not higher (Pinborg et al., 2003c).

In line with the results of previous studies on birth weight discordance, an increased risk of discordance >20% was observed in IVF/ICSI versus control twins (Bernasko et al., 1997; Daniel et al., 2000; Koudstaal et al., 2000). Previously, it has been shown that birth weight discordance is higher in spontaneously conceived MZ compared with DZ twin pregnancies (Rydhstroem, 1996), but this has been explained by a net imbalance in directional blood flow through placental anastomotic vessels (Bernasko et al., 1997). Hence, it is difficult to interpret the present finding of a higher risk of discordance in unlike-sex versus same-sex control twins, but this was also observed by others (Bernasko et al., 1997). One possibility is that same-sex control twin pairs consist of both MZ and DZ twins, and a plausible explanation for the difference in fetal growth in DZ pregnancies is genetic dissimilarity.

Previous reports on neonatal mortality in IVF/ICSI versus spontaneously conceived twins have yielded contradictory results (Bergh et al., 1999; Dhont et al., 1999; Westergaard et al., 1999; Koudstaal et al., 2000; Lambalk and van Hooff, 2001; Koivurova et al., 2002). Similar to the majority of studies, the present results showed no significant differences in stillbirth and total mortality rates between IVF/ICSI and control twins. However, a significantly higher mortality rate was found during the first year after delivery in the total control twin cohort than in IVF/ICSI twins ($P = 0.04$). The majority of control twins died within the first week of life, when the biggest difference in mortality rates between IVF/ICSI and control twins was seen (Table V). This higher mortality rate of control twins within the first year of life was not present in the comparison restricted to unlike-sex IVF/ICSI and control twins, presumably while the MZ control twins were excluded.

No comparative reports exist on increased malformation rates in IVF/ICSI twins and spontaneously conceived twins. In the present study, the malformation rate was similar in both total cohorts and also when the data were restricted to unlike-sex twins.

Patent ductus arteriosus (PDA) is a developmental anomaly which has strong associations with preterm birth. As in a previous Swedish register study, the decision was made here to define PDA as a minor congenital malformation (Ericson and Källén, 2001). Excluding this anomaly from the analyses implied no changes in the differences in malformation rates between IVF/ICSI and control twins in the present study. Separate analyses on the infants in IVF/ICSI twin cohort produced similar total malformation rates in infants conceived after IVF and ICSI treatment, and this finding was in agreement with a previously published report (Bonduelle et al., 2002). The Swedish register study yielded significant differences in the incidence of specific conditions (neural tube defects, hypospadias, alimentary tract atresia, omphalocele) between IVF and ICSI and spontaneously conceived children (Ericson and Källén, 2001). In the light of these findings, these specific conditions were examined in detail and no differences were observed either between IVF/ICSI infants and controls or between IVF- and ICSI-conceived children. It should be taken into account that the low number of children with specific malformations provides the present study with a very low power to detect such differences. Except for congenital malformations, separate analyses were not performed for IVF and ICSI children, as no previous studies have assessed differences in obstetric outcome between IVF and ICSI deliveries (Bergh et al., 1999; Bonduelle et al., 2002).

Consistent with a previous survey on cancer incidence in IVF children, no difference was observed between IVF/ICSI and control twins, though any statistical comparison should be carefully considered as only very few cases were observed (Bruinsma et al., 2000).

In conclusion, the results of the present study suggest that neonatal outcome in twins conceived after IVF or ICSI treatment is generally comparable with that in twins after spontaneous conception. However, IVF/ICSI twins were more likely to be of discordant birth weight and to be admitted to the NICU. Even in unlike-sex twins stratified for maternal age and parity, these were the only differences found. Hence, the present findings indicate that IVF/ICSI twins do not carry the slightly increased risk of adverse outcome seen in IVF/ICSI singletons compared with spontaneously conceived singletons, even after maternal age and parity have been taken into account.

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