Obstetric outcome of twin pregnancies after in-vitro fertilization: a matched control study in four Dutch University hospitals

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Introduction

In singleton pregnancies after IVF an increased rate of preterm delivery, low birthweight (birthweight < 2500 g), induction of labour, Caesarean deliveries, and pregnancy-induced hypertension has been reported. Studies that compared IVF twin pregnancies with spontaneously conceived twins have yielded conflicting results. We compared 96 IVF twin pregnancies to 96 controls after elaborate matching. The design of our study precluded matching by zygosity. The yield of conflicting results. We compared 96 IVF twin pregnancies to 96 controls after elaborate matching. The design of our study precluded matching by zygosity. The yield of conflicting results (Tan et al., 1992; Tallo et al., 1995; Olivennes et al., 1996; Ágústsson et al., 1997; Bernasko et al., 1997; Dhont et al., 1997; Fitzsimmons et al., 1998; Moise et al., 1998).

Here we present the results of a study in which four Dutch University IVF centres participated. Twin IVF pregnancies were compared with spontaneous twin pregnancies after matching for maternal age, parity, race, height, weight, smoking habit, obstetric and medical history, the date of delivery as well as for the hospital where the obstetric care was provided.

Materials and methods

The IVF centres and the obstetric units of the University Hospitals of Amsterdam (Vrije Universiteit), Leiden, Nijmegen and Utrecht participated in the study. The ethics committee of each hospital approved the study protocol. Only ongoing twin pregnancies of more than 16 weeks (IVF and controls) were entered into the study.

IVF pregnancies (cases)

IVF patients were included if their pregnancy was established before April 1, 1991 and the obstetric care was provided by the hospital in which the IVF procedure was performed. IVF pregnancies after transfer of frozen embryos and pregnancies in which embryo reduction was performed were excluded.

Control pregnancies (controls)

Spontaneous twin pregnancies were selected as controls from the registry of the same hospital as the cases if the following criteria were met: maternal age at the time of the last menstrual period (LMP) maximal 3 years apart from that of the case, same parity, same ethnic origin (Caucasian, Mediterranean, Asian and black), the date of parturition not more than 3 years apart from that of the case, same height and weight, same smoking habit at the onset of pregnancy (no smoking, 1–5, 5–10, 10–20, and >20 cigarettes a day). The control pregnancies had to be conceived without any kind of infertility treatment and the obstetric care had to be provided by the same hospital that provided the obstetric care for the IVF pregnancy. The gestational length of controls had to be beyond doubt (regular menstrual cycle of normal length (28 ± 2 days), secure date...
of the last menstrual period (LMP) and, when available, ultrasound findings early in pregnancy in accordance with the gestational age.

**Matching procedure**
Potential controls were selected by scanning the obstetric register for women of suitable age, parity and date of delivery. The medical records were retrieved and checked for the other matching criteria. If several patients could serve as control, the best matching patient with regard to maternal height and weight was chosen. The matching criteria of IVF and control women were entered into a form and all the forms were reviewed by one investigator (J.K.) for approval. To avoid selection bias, the results of potential control pregnancies remained unread until the choice was made.

**Definitions**
Gestational age at delivery in IVF pregnancies was defined as the difference between the date of oocyte puncture and the date of delivery with 14 days added. In control pregnancies gestational age at delivery was defined as the number of days between the date of delivery and the date of the first day of the LMP. Preterm delivery was defined as a delivery before 37 completed weeks. Small-for-gestational age (SGA) was defined as birthweight below the 10th percentile of the national reference curve (Kloosterman, 1970). The Dutch reference curve is corrected for parity and sex of the infant. Low birthweight (LBW) was birthweight ≥500 g and <2500 g. Birthweight discordance (discordance) was the weight difference between the smallest and the largest child of a pair of twins expressed as the percentage of the birthweight of the largest child. Stillbirth was the birth of a lifeless child ≥500 g. Neonatal death is the death of a live born child ≥500 g during the first week after birth. Perinatal mortality rate was the sum of stillbirths and neonatal deaths divided by the total number of live and stillbirths. Placenta praevia was a placenta covering the internal os and requiring delivery by Caesarean section. A Caesarean section was called elective if performed before the patient went into labour. For pregnancy-induced hypertension (PIH) as well as for other complications of pregnancy, the classifications of the clinic concerned were used.

All congenital malformations were registered unless mentioned in the list of exclusions of the European Registration of Congenital Anomalies (Eurocat) (Zandwijken et al., 1997). The data of IVF and control pregnancies were entered into a database (SPSS data entry) and analysed by SPSS 7.5 statistical package (SPSS Inc., Chicago, IL, USA).

**Statistics**
For comparison between the two groups we used the McNemar test for dichotomous variables, the Wilcoxon test for ordinal and interval variables and the paired t-test for continuous variables. For comparisons within the same group analysis of variance (ANOVA) or the \( \chi^2 \)-test was used. The significance level was set at 5%, two-tailed.

**Results**
A total of 144 IVF twin pregnancies was eligible for matching. Of these, 96 (66.7%) pregnancies were matched. For 48 (33%) women no match was found due to characteristics such as uncommon ethnic origin \((n = 5)\), accompanying medical disorders \((n = 4)\), uterine abnormalities or previous uterine surgery \((n = 4)\), previous Caesarean \((n = 3)\), diethylstilboestrol history \((n = 3)\), poor obstetric history \((n = 1)\), uncommon weight or smoking habit \((n = 10)\) or for miscellaneous reasons \((n = 18)\).

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**Table I. Maternal characteristics in IVF and control pregnancies at the onset of pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>IVF group ((n = 96))</th>
<th>Control group ((n = 96))</th>
<th>( P ) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31.7 ± 3.6</td>
<td>31.2 ± 3.4</td>
<td>0.01</td>
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<tr>
<td>Weight (kg)</td>
<td>65.2 ± 10.3</td>
<td>63.5 ± 9.8</td>
<td>0.16 (NS)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>167.4 ± 6.8</td>
<td>168.6 ± 6.0</td>
<td>0.17 (NS)</td>
</tr>
<tr>
<td>Cigarettes (no./day)</td>
<td>1.36 ± 3.3</td>
<td>1.42 ± 3.4</td>
<td>0.78 (NS)</td>
</tr>
<tr>
<td>Alcohol (units/week)</td>
<td>0.29 ± 1.7</td>
<td>0.03 ± 0.18</td>
<td>0.16 (NS)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
\(^a\)Paired t-test.
NS = not significant.

**Maternal characteristics**
IVF women were on average 6 months older \((P = 0.007)\); weight and height in IVF and control women were comparable. At the onset of pregnancy in both groups 83% of the women were non-smokers. The mean number of cigarettes smoked and alcohol consumption at the beginning of pregnancy were not different. Maternal characteristics are summarized in Table I.

**Obstetric history**
In both groups, 68 (70.8%) of the women were primiparous. Forty-six women in the IVF and 55 in the control group had not been pregnant before \((P = 0.14)\; not significant\). The rate of previous abortion in the IVF and control group was dissimilar but the difference was not significant \((0.33 \text{ versus } 0.21, P = 0.09)\); a history of an ectopic pregnancy was more often found in IVF women \((0.22 \text{ versus } 0.01, P = 0.001)\). Prior preterm deliveries tended to be more common \((P = 0.06)\) in the IVF group \((6.3 \text{ versus } 1.0%, P = 0.06)\). No differences were found in the rates of stillbirth, PIH, previous Caesarean section and instrumental delivery in the obstetric history of both groups \(\text{data not shown}\).

**Pregnancy**
In the control group, ultrasound examination in early pregnancy was performed in 57.3% of the pregnancies. Invasive prenatal diagnosis was performed in eight IVF and 12 control pregnancies \((P =0.39; \text{not significant})\).

Vaginal bleeding occurred more often in IVF pregnancies than in controls \((32.3 \text{ versus } 18.8%, P = 0.03)\). The majority of vaginal bleeding episodes occurred in the first trimester. The comparison of each trimester separately revealed no significant differences between IVF and control pregnancies \(\text{data not shown}\). No differences were noted in the incidence of PIH, gestational diabetes, placenta praevia, preterm rupture of membranes and preterm uterine contractions \(\text{data not shown}\). The mean number of admission days, including delivery, was 8.8 ± 10.3 days in the IVF group and 6.2 ± 9.1 days in the control group \((P = 0.11; \text{not significant})\).

**Delivery**
The rates for spontaneous onset of labour, elective Caesarean section, and induction of labour were similar in both groups.
Twin pregnancy outcome in IVF

Table II. Onset of labour in IVF and control pregnancies

<table>
<thead>
<tr>
<th></th>
<th>IVF group (n = 96)</th>
<th>Control group (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective Caesarean section</td>
<td>11 (11.5)</td>
<td>11 (11.5)</td>
</tr>
<tr>
<td>Induction of labour</td>
<td>26 (27.1)</td>
<td>29 (30.2)</td>
</tr>
<tr>
<td>Spontaneous onset of labour</td>
<td>59 (61.4)</td>
<td>56 (58.3)</td>
</tr>
</tbody>
</table>

Values are no. (%).

Table III. Gestational age in days at delivery in IVF and control pregnancies

<table>
<thead>
<tr>
<th></th>
<th>IVF group (n = 96)</th>
<th>Control group (n = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>251 ± 27</td>
<td>256 ± 26</td>
</tr>
<tr>
<td>Induction of labour or elective CS\a</td>
<td>263 ± 14b</td>
<td>263 ± 20c</td>
</tr>
<tr>
<td>Spontaneous onset of labour</td>
<td>244 ± 30b</td>
<td>252 ± 29c</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

Table IV. Mode of delivery per child in IVF and control pregnancies

<table>
<thead>
<tr>
<th></th>
<th>IVF group (n = 192)</th>
<th>Control group (n = 192)</th>
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</thead>
<tbody>
<tr>
<td>Normal delivery</td>
<td>86 (44.8)</td>
<td>101 (52.6)</td>
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<tr>
<td>breech delivery--</td>
<td>12 (6.3)</td>
<td>7 (3.7)</td>
</tr>
<tr>
<td>Instrumental delivery</td>
<td>17 (8.8)</td>
<td>25 (13.0)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>77 (40.1)</td>
<td>59 (30.7)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

(Table II). Gestational age in patients with spontaneous onset of labour was in both groups significantly less than in patients who were induced or delivered by elective Caesarean section (244 days versus 263 days, P < 0.001 in the IVF group and 252 days versus 263 days, P = 0.03 in the control group). Spontaneous onset of labour in the IVF group occurred on average 8 days earlier in the IVF group than in the control group, but this difference was not significant (Table III). Forty-nine IVF patients (51.0%) and 40 controls (41.7%) delivered preterm (P = 0.12; not significant). Comparison of gestational length in IVF pregnancies with and without a previous preterm delivery revealed no difference. Gestational age at birth in pregnancies with first trimester bleeding was significantly shorter than that in pregnancies without bleeding in the first trimester, both in the IVF and the control group (238 days versus 255 days, P < 0.001 in the IVF group and 236 days versus 258 days, P = 0.005 in the control group). There was, however, no significant difference in the rate of first trimester bleeding (P = 0.25) between the two groups.

The mode of delivery of the 192 infants in both groups is shown in Table IV. In both groups three Caesareans were performed for the second child after the first child was born vaginally. The rate of Caesarean delivery appeared higher in the IVF group but the difference was not significant (P = 0.17).

Infant outcome

The male/female ratio was 1:1.09 in IVF and 1:0.98 in controls (P = 0.68; not significant). In the IVF group 43.8% and in the control group 71.9% of the children were of the same sex (P < 0.001). The placenta was dichorionic in 97.7% in IVF and 76.8% in control pregnancies (P < 0.001).

Assessment of the neonatal condition at birth revealed no differences [Apgar score ≤7 at 5 min in IVF and control first-born children was 9.8 versus 5.2% (P = 0.55; not significant), and in second-born children 10.1 versus 6.3% (P = 0.58; not significant)]. Perinatal mortality was 32% in the IVF group and 11% in controls (P = 0.29; not significant). In the IVF group three children were stillborn at 23, 38 and 40 weeks respectively. In the two latter pregnancies the second child was born alive while the second child that was born at 23 weeks weighed <500 g. Neonatal mortality in the IVF group comprised three children born before 24 weeks gestational age; each weighed >500 g and each succumbed shortly after birth (in these three cases the second twin weighed <500 g and none of them survived). In the control group, one pregnancy ended at 24 weeks; one child weighed >500 g and was stillborn (the second child weighed <500 g and died shortly after birth). The one neonatal death in the control pregnancies was a child born at 24 weeks who died a few hours after birth (the second child was born at 26 week and survived).

Mean birthweight ± SD in IVF and controls was for the first born child 2279 ± 658 versus 2445 ± 656 g, P = 0.05 and for the second born 2178 ± 713 versus 2370 ± 677 g, not significant, P = 0.08. Mean birthweight of all IVF and control children was 2228 ± 599 and 2407 ± 615 g respectively (P = 0.04). Low birthweight occurred more often in the IVF group than in controls (60.8 versus 44.4%, P = 0.02). The birthweight percentiles are shown in Table V. The proportion of SGA babies was similar in both groups (26.8 versus 25.3%, P = 0.83; not significant). Mean birthweight discordance was 17.6% in IVF and 14.3% in control twins (P = 0.16; not significant). A birthweight discordance of >25% was more often found in the IVF group: 22.9% versus 11.5%, P = 0.04.

Seven (3.7%) congenital malformations were reported in IVF and five (2.6%) in control children (P = 0.83; not significant). In the IVF group one child was born with spina bifida, two children had persistent ductus arteriosus, one child had a defect in the ventricular septum and another a prolapse of the tricuspid valve. One child was born with a clubfoot and one child had an extra digit. In the control group there was also one child with spina bifida, one child had hydronephrosis and one child syndactyly of two digits. Both children of one pair of twins were born with an asymmetric mandible.

The mean number of admission days in a neonatal care unit was 12.4 ± 18.0 days for IVF children and 10.7 ± 21.0 days for control children (P = 0.30; not significant). No significant differences were found in the incidence of neonatal problems such as respiratory distress syndrome, intracranial bleeding, convulsions, hyperbilirubinaemia, gastrointestinal disorders.
and infections (data not shown). Placental weight in IVF (843 ± 223 g) and controls (863 ± 232 g) was not different (P = 0.48).

Discussion
To our knowledge there are eight published studies in which IVF twin pregnancies have been compared with spontaneously conceived twin pregnancies. The number of IVF pregnancies in these studies ranged from 20 to 125 and the number of controls between 21 and 453 (Table VI). In three of the studies matching was not attempted (Olivennes et al., 1996; Ågústsson et al., 1997; Bernasko et al., 1997), whereas in the other five the matching criteria showed considerable variations. In two studies zygosity was taken into account (Dhont et al., 1997; Moise et al., 1998). The studies without matching showed an increased incidence of Caesarean section in the IVF group and, in one study, an increased rate of discordant birthweight (Bernasko et al., 1997). In two matched studies no difference between IVF and control group was found, apart from a lower perinatal mortality in the IVF group in one of them (Fitzsimmons et al., 1998). In a third matched study (Tallo et al., 1994) an increased rate of preterm deliveries and low birthweight in IVF pregnancies was noted, the SGA rate was not different. Finally, in two studies in which zygosity was taken into account, an increased incidence of preterm deliveries in the IVF group was found, whereas in one of these studies a significant lower birthweight, a higher incidence of a birthweight <1500 g and higher perinatal mortality occurred in the IVF group (Moise et al., 1998). These data strongly indicate poorer outcome of IVF pregnancies, since matching without zygosity being taken into account will result in an excess of monozygotic twins in the controls. Monozygotic twins are known to carry increased risks for perinatal mortality, preterm delivery, discordance in birthweight and low birthweight (Kovacs et al., 1989; Fowler et al., 1991; Rydshroen, 1996). If the outcome of IVF and spontaneously conceived twins would be the same, then studies that did not

Table VI. Characteristics and results of studies in which IVF twin pregnancies are compared with spontaneously conceived twin pregnancies

<table>
<thead>
<tr>
<th>IVF (no.)</th>
<th>Controls (no.)</th>
<th>Matched</th>
<th>Preterm deliveries</th>
<th>Birthweight</th>
<th>Birthweight &lt;2500 g</th>
<th>Birthweight &lt;1500 g</th>
<th>Birthweight &lt;10th percentile</th>
<th>Discordant birthweight &gt;20%</th>
<th>Caesarean section (elective)</th>
<th>Caesarean section (emergency)</th>
<th>Caesarean section (all)</th>
<th>Perinatal mortality</th>
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<tr>
<td>72</td>
<td>164</td>
<td>no</td>
<td>n</td>
<td>n</td>
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<td>69</td>
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Values are no. and cumulative percentage.

\[=\text{comparable to controls; } \uparrow \text{increased in comparison to controls; } \downarrow \text{decreased in comparison to controls; } - \text{not stated.}\]

\[a\text{Stratum matched for age, controls primiparous.}\]

\[b\text{Matched for age, race, insurance type, neonatal gender, order of gestation, order in delivery, and date of delivery. Deliveries with live born children only.}\]

\[c\text{Matched for age, parity and medical problems.}\]

\[d\text{Matched for age, parity, date of delivery and zygosity; 61 IVF and 54 ICSI pregnancies.}\]

\[e\text{Matched by age, parity ethnic origin. Only dizygotic twins.}\]
take zygoity into account would have to show a better outcome in the IVF group and this was only found in one of six such studies (Fitzsimmons et al., 1998).

Recently Minakami et al. (1998) found no differences in gestational age at birth and birthweight in twin pregnancies after various forms of medically assisted conception as compared to spontaneously conceived twin pregnancies, despite the fact that the monochorionic placenta rate was significantly higher in the ‘spontaneous’ group (57 versus 2.2%). These data also suggest a negative effect of medically assisted conception on gestational age and weight at birth. Infant outcome at 1 year of age was poorer in the ‘spontaneous’ group and this was completely due to the increased incidence of monozygosity in this group. Also these data underline the necessity to take the zygoity (and thus the chorionicity) into account when medically assisted (IVF) twins are compared with twins after natural conception.

According to the protocol of our study, the outcome of IVF and control pregnancies remained unknown until matching was completed and this precluded matching by zygosity. We gratefully acknowledge C.Arnold Bik, G.J.de Goojer, and control pregnancies remained unknown until matching natural conception. the zygosity (and thus the chorionicity) into account when medically assisted (IVF) twins are compared with twins after natural conception.

According to the protocol of our study, the outcome of IVF and control pregnancies remained unknown until matching was completed and this precluded matching by zygosity. Otherwise our matching criteria were more elaborate than in the other published series. In the control group 28% of the twins were definitely dizygotic (different infant sex) and 23% monogygotic (monochorionic placenta); a quarter of the remaining 49% will be monogygotic (Keith and Machin, 1997), leading to 39% monogygotic twins in the control group. The excess of twin pregnancies in IVF is mainly the result of transfer of more than one embryo. However, it has been found that up to 10% of IVF twin pregnancies are monogygotic (Edwards et al., 1986; Wenstrom et al., 1993), probably due to the ovarian stimulation (Derom et al., 1987). Still the monogygosity rate in our control group must be about 4-fold higher than in the IVF group. Monogygotic twins are either dichorionic or monochorionic and this latter subgroup mainly accounts for the less favourable outcome of monogygotic twin pregnancies (Derom et al., 1995). In our study monochorionic placentae were found in 2.3% of IVF and of 23.2% in control pregnancies. Thus, we had a negative selection towards the control group, but this did not result in a better outcome of the IVF twin pregnancies. On the contrary, in the IVF group gestational age at delivery in pregnancies with spontaneous onset of labour was 8 days lower, although the difference was not statistically significant (possibly a type II error due to small sample size), and the incidence of low birthweight and of discordant birthweight was significantly higher. Lower gestational age in the IVF group in our study was only due to a higher incidence of spontaneous preterm birth since elective delivery occurred in the IVF and the control group in similar numbers and at a similar gestational age. The lower birthweight appears to be due to the lower gestational age since there were no differences in the SGA rate. In IVF singleton pregnancies an increased incidence of SGA has been reported by several authors (Doyle et al., 1992; Tan et al., 1992; Olivennes et al., 1993; Wang et al., 1994; FIVNAT, 1995), but others found no difference (Australian In-Vitro Fertilization Collaborative Group, 1985; Tanbo et al., 1995; Verlaenen et al., 1995; Reubinoff et al., 1997; Maman et al., 1998).

The increased incidence of discordant birthweight that we found is in agreement with one other study (Bernasko et al., 1997). These data, however, are difficult to interpret. Discordant birthweight is generally more common in monogygotic twins and therefore would be expected more commonly in the control group. On the other hand, discordant birthweight is higher for infants of opposite sex (Bernasko et al., 1997) and therefore would be expected, especially in the IVF group.

We noted a higher incidence of vaginal bleeding in our IVF group. In IVF pregnancies an increased rate of first trimester bleeding has been reported to be due to luteal insufficiency, the vanishing fetus syndrome and ovarian stimulation (Goldman et al., 1988); however, we found no difference in the rate of first trimester bleeding between IVF and control pregnancies. In conclusion, this case–control study provides further evidence for a different outcome of IVF twin pregnancies in comparison with naturally conceived twin pregnancies.

Acknowledgements

We gratefully acknowledge C.Arnold Bik, G.J.de Goojer, M.L.C.H.Heiligers, C.J.van de Hoeven, E.A.Huiskamp, P.J.de Jong, S.A.M.Lambrechts, E.van de Lagemaat, A.M.L.Oude Lashof, D.T.W.Salemink, T.Spikjerman, H.A.Wieling and B.Zwart for their help in collecting the data for this study and Ms M.E.Hoeneveld for her skilled secretarial assistance. We also acknowledge Dr P.Westers for his advice in the statistical analysis of the data.

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Received on June 28, 1999; accepted on January 10, 2000