Lower risks of adverse outcome in twins conceived by artificial reproductive techniques compared with spontaneously conceived twins

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The outcomes of twins conceived by 136 women after medical assistance (MA) such as ovulation induction with or without assisted reproductive techniques, and twins conceived spontaneously (SP) by 72 women were compared. All 208 women were monitored from <20 weeks gestation; they all delivered at ≥24 weeks gestation. The chorionicity of the placenta was diagnosed antenatally and confirmed after delivery. There were 10 perinatal deaths; the physical and neurological status of the remaining 406 infants was assessed at 1 year of corrected age. There were no differences in gestational age at birth, the birth weights of the larger and smaller twins, the birth weight discordance, or the incidence of life-threatening major malformations between groups. Adverse infant outcomes, such as death, cerebral palsy and mental retardation occurred in nine (3.3%) of 272 MA twins compared with 12 (8.3%) of 144 SP twins (P < 0.05). The placenta was monochorionic in only three (2.2%) of 136 MA twin pregnancies compared with 41 (57%) of 72 SP twin pregnancies (P < 0.001). Of the 21 infants with adverse outcomes, nine had monochorionic placentas. Thus, the risk of an adverse outcome was 2.8-fold higher (95% confidence interval (CI) 1.2–6.4) in monochorionic twins than in dichorionic twins (10 versus 3.7%; P < 0.05). There was no difference in the incidence of adverse infant outcomes between SP (4.8%) and MA (3.4%) twins with dichorionic placentas. These findings suggest that ovulation induction in itself was not associated with an adverse outcome of twin pregnancies. The lower frequency of monochorionic placentas in MA twins may have been responsible for the lower risk of an adverse outcome in MA twins.

Key words: assisted reproductive techniques/cerebral palsy/mental retardation/twin pregnancy

Introduction

Infants conceived after ovulation induction, in-vitro fertilization (IVF) and gamete intra-Fallopian transfer (GIFT) do not have an increased risk of major malformations (Cohen et al., 1988; Beral and Doyle, 1990; Rizk et al., 1991). However, the risks of obstetric and neonatal complications, such as pre-eclampsia, intrauterine growth retardation, premature birth, placenta previa and Caesarean birth, are increased in IVF pregnancies (Tan et al., 1992; Wang et al., 1994; Tallo et al., 1995; Tanbo et al., 1995), suggesting that infants born to these women have an increased risk of an adverse outcome. Twin pregnancies accounts for about 20% of the pregnancies after IVF (Beral and Doyle, 1990; Rizk et al., 1991). It is possible that the risk of an adverse outcome is higher among twins conceived after ovulation induction with or without GIFT/IVF than in naturally occurring twins. However, data on the outcomes of twins conceived spontaneously (SP) and those conceived after medical assistance (MA) are limited (Bernasko et al., 1997).

The twin-to-twin transfusion syndrome (TTTS) occurs in about 15–30% of twins with monochorionic (MC) placentas (Rausen et al., 1965; Patten et al., 1989) but is rare in twins with dichorionic (DC) placentas (Robertson and Neer, 1983) and TTTS markedly increases the risk of an adverse outcome (Rausen et al., 1965; Patten et al., 1989). Thus, the chorionicity of the placenta is an important determinant of the outcome of twins. Because the frequency of MC placentas is expected to be lower in twins conceived after MA than in twins conceived spontaneously (Derom et al., 1987; Wenstrom et al., 1993), it is possible that twins conceived after MA have a lower risk of an adverse outcome than twins conceived spontaneously.

Data from tertiary institutions on the prognosis of twins may include data on women who were referred because they were ill or had complications such as premature labour, TTTS and pre-eclampsia. Thus, the incidence of complications and adverse infant outcomes may be higher than would be found in the general population.

We investigated the influence of ovulation induction with or without GIFT/IVF on the outcome of twins born to women who had been monitored at our antenatal clinic since <20 weeks gestation and in whom the chorionicity of the placenta was determined.

Materials and methods

Of 242 women with twin pregnancies who delivered at ≥24 weeks gestation at the Jichi Medical School Hospital between January 1990 and May 1996, 208 women (86%) booked their delivery at our hospital before 20 weeks gestation and were followed-up at our antenatal clinic. We reviewed the medical records of these 208 women. Twins were spontaneously conceived in 72 women (SP) and conceived after ovulation induction with or without assisted reproductive techniques in 136 medically assisted (MA) women. Medical assistance consisted of clomiphene only in 15 women (11%), human menopausal/chorionic gonadotrophin alone in 24 (18%), GIFT...
in 61 (45%), IVF in 34 (25%) and intracytoplasmic sperm injection in two (1.5%). In general, ultrasound examinations were performed every 2 weeks from the time of diagnosis of twins until delivery, unless more frequent examinations were indicated. At least one scan was performed in the first trimester in all women. The gestational age was based on the date of conception or the chart of the basal body temperature in MA twins and on the last known menstrual period if it was within 7 days of the first-trimester ultrasound-derived estimate in SP twins. If the discrepancy was >7 days, the gestational age was based on the ultrasound estimate. The chorionicity of placentas was confirmed by histological examination after delivery; the presumptive antenatal diagnosis of chorionicity determined by ultrasonography was correct in 205 (99%) of 208 twin gestations. There were 10 infant deaths before the age of 1 year; all 10 died within 28 days of birth. The physical and neurological status of the remaining 406 infants was assessed by paediatricians on a regular basis until at least 1 year of corrected age. Birth weights were recorded, and the intertwin birth weight discordance was calculated as the percentage of the weight of the larger twin. An adverse infant outcome was defined as death or disability, including cerebral palsy, epilepsy, deafness, blindness and mental retardation.

If TTTS was suspected at ≥30 weeks, the pregnancy was terminated. If TTTS occurred at <30 weeks gestation, serial amnioreductions were performed. The antenatal diagnosis of TTTS was based on the following criteria: (i) a gradual increase in the intertwin weight discordance to ≥20%, as estimated by ultrasonography; (ii) a gradual increase in the intertwin discordance of the amniotic fluid volume, as estimated by ultrasonography; and/or (iii) the appearance of signs of fetal cardiac dysfunction, such as an increased cardiothoracic ratio and/or tricuspid regurgitation, as determined by fetal echocardiography.

Pre-eclampsia was defined as a systolic or diastolic blood pressure ≥140 or ≥90 mmHg, respectively, on two occasions recorded 24 h apart in association with the onset of proteinuria in a patient who had been normotensive during the first 20 weeks of gestation. The data were analysed by Student’s t-test or the chi-square test with Yates’ correction. Results are presented as the mean ± SD. Miettinen’s method (1976) was used to determine the 95% confidence interval (95% CI). A probability level of < 0.05 was accepted as statistically significant.

Results

The maternal age and the percentage of nulliparous women were significantly higher in the 136 women with MA twins than in the 72 women with SP twins (Table I). There were no differences in the incidence of pre-eclampsia, the gestational week at delivery, the birth weights of the larger and smaller twins, or the birth weight discordance between groups.

Adverse outcomes occurred in 12 SP infants (seven larger and five smaller twins) born to eight mothers and included four deaths (two larger and two smaller twins) and eight disabled infants (Table I). Both twins were affected in four (6%) of 72 women. There were two deaths due to major malformations; Ebstein’s cardiac anomaly in one infant and anencephaly in one. In the MA group, adverse outcomes occurred in nine infants (three larger and six smaller twins) born to nine women and included six deaths (one larger and five smaller twins) and three disabled infants. There was no case of both twins being affected in any of the 136 women. One death was due to an interrupted aortic arch. Thus, the incidence of adverse outcomes was significantly higher in SP twins than in MA twins and both twins were compromised in a significantly greater proportion of women with SP twins ($P < 0.05$). There was no difference between groups in the incidence of major malformations.

Pairs in which at least one infant was affected had an earlier gestational age at delivery, lower birth weights of both the larger and smaller twins, and a greater birth weight discordance than unaffected pairs (Table I).

Only three (2.2%) of 136 women with MA twins had an MC placenta compared with 41 (57%) of 72 women with SP twins ($P < 0.001$). Thus, the relative risk of an MC placenta was 0.04 (95% CI, 0.01–0.12) in the MA group compared with the SP group. Of the 21 infants with adverse outcomes, nine were born to women with MC placentas and the remaining 12 to women with DC placentas. Thus, the risk of an adverse outcome was 2.8-fold higher (95% CI, 1.2–6.4) in MC twins (10%) than in DC twins (3.7%) ($P < 0.05$). In addition, both twins were compromised in three (7%) of 44 women with MC placentas compared with one (0.6%) of 164 women with DC placentas ($P < 0.05$).

TTTS was diagnosed antenatally in 14 (32%) of 44 women with MC placentas and in none of the 164 women with DC placentas. Delivery occurred at 32.7 ± 2.8 weeks of gestation in the 14 women whose pregnancies were complicated by TTTS. Of the 21 infants with adverse outcomes, eight (38%) were born to women in whom TTTS was suspected. Thus, TTTS was associated with an 8.5-fold increase in the risk of an adverse outcome (95% CI, 3.9–18.9) [8/28 (29%) versus 13/388 (3.4%), $P < 0.001$].

When data were analysed only for twins with DC placentas, there was no difference in the incidence of adverse infant outcomes between SP and MA twins (Table II). Major malformations occurred in none of the SP twins and in one of the MA twins.

Discussion

In the present cohort study, no women had any complications other than twinning at <20 weeks gestation and all were delivered at ≥24 weeks gestation at our hospital. Although only a small number of subjects was studied, the risk of an adverse outcome was found not to be increased in MA twins as compared with naturally occurring twins, thus supporting the results of earlier studies (Bernasko et al., 1997).

In the present study, the risk of an adverse outcome was 2.8-fold higher in MC twins than in DC twins and there was no difference in the incidence of adverse infant outcomes between SP and MA twins with DC placentas. These results suggested that the chorionicity of the placenta was an important determinant of the outcome of twins, and ovulation induction in itself was not associated with an adverse outcome.

Twins with MC placentas are monzygous, while those with DC placentas can be monzygous or dizygous. According to the results of a study in Belgium (Derom et al., 1987), 445 of 869 (51.2%) naturally occurring twin gestations were monozygotic. Of these 445, some 284 (63.8%) had MC
placentas, suggesting that >30% of the SP twins had MC placentas. The monozygotic twinning rate per 1000 total pregnancies is relatively constant worldwide, varying from about three to five (MacGillivray, 1986), which was consistent with the 0.45% expected frequency of splitting after spontaneous ovulation (Derom et al., 1987). However, the dizygotic twinning rate varies largely by race, from 1.3/1000 in Japan to 7–9/1000 in the USA and Europe and 50/1000 in Nigeria (MacGillivray, 1986). Thus, the relative prevalence of MC placentas among twins differs between countries and may be higher in Japan than elsewhere. The relative prevalence of MC placentas among twins conceived after artificial induction of ovulation has not been fully investigated. Although a higher frequency of monozygotic twins is observed in pregnancies conceived after ovulation induction with or without IVF (10–13 per 1000 pregnancies) (Edwards et al., 1986; Derom et al., 1987) than after spontaneous ovulation (3–5 per 1000 pregnancies), monozygotic twins account for only 13% of all MA twins (Derom et al., 1987). Because some monozygotic twins have DC placentas, the frequency of MC placentas among MA twins may be <13%, consistent with the results of Wenstrom et al. (1993) and the present study. Thus, an increase in the number of MA twins decreases the relative prevalence of MC twins in many countries, although the actual number of MC twins increases.

Same-sex twins have an increased risk of an adverse outcome compared with twins of different sexes (Fowler et al., 1991; Rydhstroem, 1996) and the risk of death is higher in twins with MC placentas than with DC placentas (Fusi and Gordon, 1996) and markedly increases the risk of an adverse outcome (Rausen et al., 1989) and markedly increases the risk of an adverse outcome (Rausen et al., 1989) and markedly increases the risk of an adverse outcome (Rausen et al., 1989) and markedly increases the risk of an adverse outcome (Rausen et al., 1989) and markedly increases the risk of an adverse outcome (Rausen et al., 1989). TTTS occurs in about 15–30% of twins with MC placentas (Rausen et al., 1965; Patten et al., 1989) and markedly increases the risk of an adverse outcome (Rausen et al., 1965; Patten et al., 1989). As expected, twins with MC placentas had an increased risk of adverse outcome compared with those with DC placentas in the present study. Only 2.2% of women in the MA group had MC placentas compared with 57% in the SP twin group. There was no difference in infant outcome between MA and SP twins when women with MC placentas were excluded from the analysis.

In the present study, twin pairs in which at least one infant had an adverse outcome had a significantly greater birth weight discordance than the unaffected pairs in both MA and SP twins. Nearly all twins with MC placentas shared placental circulation (Robertson and Neer, 1983). Intertwin blood transfusion may always occur in MC twins. The greater weight discordance in twins with MC placentas may reflect a greater volume of transfused blood and/or a longer duration of hypoxic stress due to anaemia in the donor twin, in whom growth may be retarded (Snijders et al., 1993; Maier et al., 1995). The birth weight discordance in DC twins may reflect a difference in placental function between twins. A greater weight discordance

### Table I. Clinical characteristics and infant outcome

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<tr>
<th></th>
<th>SP twins</th>
<th>MA twins</th>
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<tr>
<td></td>
<td>Overall</td>
<td>Adverse outcome</td>
</tr>
<tr>
<td></td>
<td>(n = 72)</td>
<td>(n = 8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.4 ± 4.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>31.3 ± 4.5</td>
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<tr>
<td>Nullipara</td>
<td>36(50)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5(63)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>18(25)</td>
<td>2(25)</td>
</tr>
<tr>
<td>Gestational week at delivery</td>
<td>35.3 ± 2.4</td>
<td>33.6 ± 2.9&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>Larger twin</td>
<td>2288 ± 470</td>
</tr>
<tr>
<td></td>
<td>Smaller twin</td>
<td>1998 ± 465</td>
</tr>
<tr>
<td>Birth weight discordance (%)</td>
<td>13 ± 11</td>
<td>17 ± 17&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>No. of infants with adverse outcome</td>
<td>12/144(8.3)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>12/1675&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>P < 0.001 versus MA twins.
<sup>b</sup>P < 0.05 versus MA twins.
<sup>c</sup>P < 0.001 versus subgroup of SP twins with better outcome.
<sup>d</sup>P < 0.05 versus subgroup of SP twins with better outcome.
<sup>e</sup>P < 0.001 versus subgroup of MA twins with better outcome.
<sup>f</sup>Four deaths and eight disabled infants.

### Table II. Characteristics and outcome of spontaneous (SP) and medically assisted (MA) dichorionic twins

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<tr>
<th></th>
<th>SP DC twins</th>
<th>MA DC twins</th>
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<tr>
<td></td>
<td>(n = 31)</td>
<td>(n = 133)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>30.8 ± 4.4</td>
<td>32.1 ± 3.6</td>
</tr>
<tr>
<td>Nullipara</td>
<td>14(45)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>116(87)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>10(32)</td>
<td>28(21)</td>
</tr>
<tr>
<td>Gestational week at delivery</td>
<td>36.2 ± 1.3</td>
<td>35.7 ± 2.4</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>Larger twin</td>
<td>2443 ± 354&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Smaller twin</td>
<td>2184 ± 323&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Birth weight discordance (%)</td>
<td>10 ± 4</td>
<td>12 ± 11</td>
</tr>
<tr>
<td>No. of infants with adverse outcome</td>
<td>3/62(4.8)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>9/266(3.4)&lt;sup&gt;f&lt;/sup&gt;</td>
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<sup>a</sup>P < 0.001 versus MA twins.
<sup>b</sup>P < 0.05 versus MA twins.
<sup>c</sup>Three disabled infants.
<sup>d</sup>Six deaths and three disabled infants.

Values in parentheses are percentages.
may indicate that the duration of placental insufficiency and hypoxic stress are greater in the smaller twin (Snijders et al., 1993; Maier et al., 1995). Thus, in addition to immaturity (infants with adverse outcomes had a younger gestational age at birth than the other twins in both MA and SP twins), the greater weight discordance was associated with adverse infant outcomes in both MA and SP twins.

In conclusion, twins conceived after MA such as ovulation induction with or without GIFT/IVF did not have an increased risk of an adverse outcome compared with naturally occurring twins. The frequency of MC placentas was lower in MA twins than in SP twins, which may have favourably influenced the outcome of MA twins.

References


