Does chorionicity or zygosity predict adverse perinatal outcomes in twins?

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OBJECTIVE: The purpose of this study was to evaluate chorionicity and zygosity as risk factors for adverse perinatal outcomes in twins.

STUDY DESIGN: A population-based, retrospective cohort study was conducted of all twin deliveries in Nova Scotia, Canada, from 1988 to 1997. Chorionicity was established by histologic examination. Zygosity was determined by chorionicity, sex, and infant blood group. Three groups were established: monochorionic/monozygotic twins, dichorionic/dizygotic twins, and dichorionic/majority monozygotic twins.

RESULTS: Outcomes from 1008 twin pregnancies were analyzed. Monochorionic/monozygotic twins had lower mean birth weights compared with dichorionic/dizygotic twins. Rates of perinatal mortality of at least 1 twin were significantly higher among monochorionic/monozygotic twins relative to dichorionic/dizygotic twins (relative risk, 2.5; 95% CI, 1.1-2.5). Dichorionic/majority monozygotic twins had similar perinatal outcomes compared with dichorionic/dizygotic twins.

CONCLUSION: Monochorionicity increases the risk of adverse perinatal outcome, whereas the effect of zygosity is less clear. Because chorionicity can be determined by prenatal ultrasound scanning, this information should be considered in the prenatal care of twin pregnancies. (Am J Obstet Gynecol 2002;186:579-83.)

Key words: Twin, chorionicity, zygosity, perinatal outcomes
Pregnancies with one or both infants weighing <500 g, monoamniotic twins, and conjoined twins were excluded. Pregnancies with 1 or 2 intrauterine fetal deaths were excluded from all analyses, except for the analysis of perinatal deaths.

Chorionicity was established by histologic examination, and zygosity was determined by chorionicity, sex, and infant blood group. The cohort was divided into 3 clinically identifiable groups: monochorionic twins (and therefore monozygotic [MC/MZ]), dichorionic twins with different sex or different blood group at birth (and therefore dizygotic [DC/DZ]), and dichorionic twins of the same sex and same blood group at birth. Assuming population probabilities of 30% and 70% for monozygotic and dizygotic twins, respectively, approximately two thirds of same sex, same blood group dichorionic twin pairs are monozygotic. Therefore, this group of dichorionic twins was classified as dichorionic/majority monozygotic (DC/MMZ). Gestational age was calculated with the last menstrual period. If the last menstrual period was unknown or if there was more than a 2-week discrepancy between the gestational age estimate by last menstrual period and the clinical examination, the clinical estimate was used.

The outcomes that were considered in this study included spontaneous or medically indicated preterm birth, birth weight discordance, intrauterine growth restriction (IUGR), and perinatal death. Preterm birth was defined as a delivery that occurred before 37 completed weeks of gestation; early preterm birth was defined as delivery that occurred before 32 weeks. Preterm births were subdivided into births that resulted from spontaneous onset of labor (including premature rupture of the membranes) and medically indicated preterm births (induction of labor for maternal or fetal indications or elective cesarean delivery without labor). IUGR was defined as birth weight of <3rd percentile for gestational age, with Canadian twin and sex-specific birth weight curves. Perinatal death was defined as the death of a fetus ≥500 g or death of a live-born infant before 28 days of age.

Statistical analyses were performed with SAS software (version 6.12; SAS Institute, Cary, NC). To compare proportions, χ² tests were used. Because preterm delivery is prevalent among twin pregnancies, odds ratios do not provide good estimate of relative risks. Therefore, Poisson regression was used to determine adjusted rate ratios.
and 95% CI, while controlling for confounders. Potential confounders included smoking status of the mother, maternal age, nulliparity, and major fetal anomalies. An additional confounder considered for the analyses of perinatal mortality was IUGR. For the purpose of controlling for the confounding effects of IUGR on perinatal death, the definition of IUGR included babies below the bottom 10th percentile, using twin sex-specific birth weight curves.12 Regression modeling was performed, using a step-wise approach, excluding the variable with the highest probability value and evaluating the effect on the model. Variables were maintained in the model if the probability values from the likelihood ratio test were <.05. For each outcome that was evaluated, the same confounders were included so that results could be compared among the same subsets of women. Rate ratios for each outcome were calculated for MC/MZ twins and for DC/MMZ twins relative to DC/DZ twins.

Results

The total cohort included 1080 twin pregnancies. Fifty-two dichorionic twin pairs were excluded because of missing blood group information. Twenty pregnancies with at least 1 intrauterine fetal death (14 monochorionic and 6 dichorionic) were excluded from all but the perinatal death analyses. Of the remaining 1008 pregnancies, 280 births (27.7%) were MC/MZ; 414 births (41.1%) were DC/DZ, and 314 births (31.2%) were DC/MMZ.

As shown in Table I, there were no significant differences in maternal age, smoking status of the mother, antepartum bleeding, type of labor (spontaneous, induced, or no labor), pregnancy-induced hypertension, chronic hypertension, abruptio placentae, premature rupture of membranes, or major anomalies for MC/MZ twins or DC/MMZ twins compared with DC/DZ twins. As expected, oligohydramnios and polyhydramnios occurred more frequently in the MC/MZ twins group compared with DC/DZ twins. Nulliparity was more frequent in MZ/MC pregnancies and in DC/MMZ pregnancies compared with DC/DZ twins.

Table III. Birth weight and weight discrepancy in live-born twins, according to chorionicity and zygosity

<table>
<thead>
<tr>
<th></th>
<th>Mean birth weight (g)*</th>
<th>Weight discrepancy between twins of &gt;25%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bigger twin</td>
<td>Smaller twin</td>
</tr>
<tr>
<td>DC/DZ</td>
<td>2669 ± 605</td>
<td>2356 ± 558</td>
</tr>
<tr>
<td>DC/MMZ</td>
<td>2586 ± 644</td>
<td>2321 ± 616</td>
</tr>
<tr>
<td>MC/MZ</td>
<td>2530 ± 593†</td>
<td>2237 ± 592†</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, and major anomalies, and maternal smoking.

Table IV. IUGR in live born twins according to chorionicity and zygosity

<table>
<thead>
<tr>
<th></th>
<th>Twin A, &lt;3rd percentile</th>
<th>Twin B, &lt;3rd percentile</th>
<th>Either twin, &lt;3rd percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Adjusted rate ratio*</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>DC/DZ</td>
<td>6 (1.5%)</td>
<td>1.0</td>
<td>15 (3.6%)</td>
</tr>
<tr>
<td>DC/MMZ</td>
<td>8 (2.5%)</td>
<td>1.62 (0.56-4.70)</td>
<td>8 (2.5%)</td>
</tr>
<tr>
<td>MC/MZ</td>
<td>15 (5.4%)</td>
<td>2.60 (0.96-6.99)</td>
<td>19 (6.8%)</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, and major anomalies, and maternal smoking.
twins, although MC/MZ twins had the highest proportion (8.6%) of twin pairs with >25% weight discrepancy.

MC/MZ twins had increased rates of IUGR below the third percentile compared with DC/DZ twins, although the rate ratios did not achieve statistical significance after adjustment for age, major anomalies, and maternal smoking. The IUGR rate among DC/MMZ twins was not significantly different from DC/DZ twins (Table IV).

Perinatal death of at least 1 twin was more likely in MC/MZ twins compared with DC/DZ twins, with an adjusted rate ratio of 2.45 (95% CI, 1.10-5.47; Table V). The rate ratios for perinatal mortality of both twins was increased in both DC/MMZ twins and MC/MZ twins relative to DC/DZ twins, but only significantly so for MC/MZ twins.

**Comment**

Chorionicity was determined by histologic examination for all twins in this cohort, although zygosity was inferred with chorionicity, sex, and blood group. Given the probability of dichorionic twins being the same sex and same blood group, we estimated that approximately 64% of twins in this category would be monozygotic. Therefore, some of the twins in the DC/MMZ group were incorrectly classified as monozygotic. If monozygotic twins are at increased risk for the outcomes that were studied, then the rate ratios we reported for the DC/MMZ group were conservative. The distribution by chorionicity observed in this study is comparable with other reports. Derom et al reported higher rates of perinatal mortality among monozygotic twins than dizygotic twins, although the difference is believed to be mainly a result of the chorionicity difference between the groups. Machin et al also reported a higher perinatal mortality rate in MC/MZ twins compared with DC/MZ twins. Because the perinatal mortality rate among DC/MMZ twins was similar to DC/DZ twins, the increased perinatal mortality rate among MC/MZ twins appears to be related to chorionicity and not zygosity. Whether this finding would hold with a pure DC/MZ group remains to be determined.

The increased risk of perinatal deaths among MC/MZ twins persisted even after adjustment for major fetal anomalies and IUGR. This observation suggests that the higher rates of perinatal mortality among MC/MZ twins may be related to other known complications of mono-chorionicity (such as twin-to-twin transfusion syndrome, which was not specifically accounted for in our analysis). Our findings are consistent with the literature. Derom et al reported higher rates of perinatal mortality among monozygotic twins than dizygotic twins, although the difference is believed to be mainly a result of the chorionicity difference between the groups. Machin et al also reported a higher perinatal mortality rate in MC/MZ twins compared with DC/MZ twins. Because the perinatal mortality rate among DC/MMZ twins was similar to DC/DZ twins, the increased perinatal mortality rate among MC/MZ twins appears to be related to chorionicity and not zygosity. Whether this finding would hold with a pure DC/MZ group remains to be determined.

The distribution of birth weights by percentile for dichorionic twins (regardless of zygosity) in our cohort follows the distribution of the Canadian population of twins, although the monochorionic twins were statistically smaller than the reported curves (only the 3rd percentiles are reported, but the findings were similar for 5th and 10th percentiles). The trend toward an increased rate of IUGR and lower birth weights in monochorionic/dizygotic twins, compared with dichorionic/dizygotic twins, agrees with the previous reports. Inter-twin growth disparity was similar among dichorionic and monochorionic twins in our study, which confirm the findings of Sebire et al. Other investigators have demonstrated greater inter-twin disparities among dizygotic versus monochorionic twins, dizygotic twins with fused placetas versus separate placentas, and monochorionic twins with proven vascular anastomoses versus dichorionic twins. These heterogenous findings suggest that mean birth weight and inter-twin growth disparity among twins is determined by many factors that are not likely limited to chorionicity and zygosity.

**Table V. Perinatal death among twins, according to chorionicity and zygosity**

<table>
<thead>
<tr>
<th></th>
<th>Twin A or B</th>
<th>Twin A and B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (95% CI)</td>
<td>n (95% CI)</td>
</tr>
<tr>
<td>DC/DZ</td>
<td>9 (2.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>DC/MMZ</td>
<td>8 (2.6%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>MC/MZ</td>
<td>19 (6.5%)</td>
<td>8 (2.7%)</td>
</tr>
</tbody>
</table>

*Adjusted for maternal age, small for gestational age, and major anomalies.
In this large population-based study of twin births, we confirmed previous reports of adverse perinatal outcomes that were related to monochorionic twins. Monochorionicity was a risk factor for decreased birth weight and perinatal death, whereas monozygosity did not appear to be associated with adverse outcomes. However, the inability to definitively determine zygosity on all twins limits the conclusions regarding monozygosity. Definitive zygosity testing on a population basis is not practical, so alternative approaches to determine zygosity (such as the approach used in this study) will be necessary. Because chorionicity is a risk factor for several adverse perinatal outcomes and can be determined by prenatal ultrasonographic scanning, these findings support the incorporation of this clinically relevant information into prenatal care strategies for twin pregnancies.

We thank the Reproductive Care Program for providing the data.

REFERENCES