First-trimester growth discordance and adverse pregnancy outcome in dichorionic twins

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KEYWORDS: crown–rump length; dichorionic twins; discordance; first-trimester ultrasound; multiple gestations

ABSTRACT

Objective To evaluate the association between first-trimester growth discordance and adverse pregnancy outcome in dichorionic twin pregnancies.

Methods This was a retrospective cohort study of consecutive women with dichorionic twin pregnancies undergoing an ultrasound scan at our institution between 7 and 14 weeks’ gestation. Study groups were defined by the presence or absence of ≥11% crown–rump length (CRL) discordance. Pregnancies were excluded if one twin was dead on initial ultrasound or if a termination was performed. The primary outcome was loss of one or both fetuses before 20 weeks. Secondary outcomes included fetal anomaly, fetal demise after 20 weeks (stillbirth), small-for-gestational-age (SGA) at birth, admission to the neonatal intensive care unit (NICU) and preterm delivery before 34 weeks.

Results Of 805 dichorionic twin pregnancies undergoing first-trimester ultrasound, 610 met the inclusion criteria. Eighty-six had ≥11% CRL discordance and, of these, nine (10.5%) had a fetal loss at <20 weeks (risk ratio (RR) 7.8 (95% CI, 3.0–20.5)). In the surviving pregnancies, an increased risk of fetal anomalies was seen (27.3 vs 17.4%, RR 1.6 (95% CI, 1.1–2.4)). In surviving pregnancies unaffected by anomalies, no increased risk of stillbirth, SGA, NICU admission or delivery before 34 weeks was noted in the discordant group. A post-hoc power analysis demonstrated 80% power to detect a five-fold increase in the risk of stillbirth and 90% power to detect a two-fold increase in other outcomes.

Conclusion Dichorionic pregnancies in which a CRL discordance of at least 11% is noted are at increased risk for fetal anomalies and fetal loss prior to 20 weeks’ gestation. However, patients can be reassured that, in the absence of structural anomalies, CRL discordance does not appear to be associated with other adverse outcomes in continuing pregnancies, although the power to detect small increases in the risk of stillbirth may have been limited by the sample size. Copyright © 2012 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

With the increasing prevalence of twins over the last two decades and the disproportionate burden of neonatal morbidity and mortality in twins1, a large body of research has been dedicated to identifying predictors of adverse outcomes in this population. Birth-weight discordance has been correlated to perinatal morbidity and mortality, especially when associated with fetal growth restriction and low birth weight2–4. Since data from singletons suggest that first-trimester fetal growth is predictive of neonatal outcome5, the impact of first-trimester size discordance in twins is also of interest, but previous studies have presented conflicting data on this association6–12.

The objective of this study was to determine the association between first-trimester size discordance as measured by crown–rump length (CRL) and dichorionic twin pregnancy outcome.

METHODS

We performed a retrospective cohort study of all patients with dichorionic twin pregnancies who underwent a first-trimester ultrasound scan at between 7 + 0 and 14 + 0 weeks’ gestation at our institution between 1990 and 2008. Institutional Review Board approval was obtained from Washington University School of Medicine. Data were collected prospectively by dedicated nurses. Each patient undergoing an ultrasound scan at our institution receives a standardized form requesting information regarding pregnancy complications, delivery complications and neonatal outcome, to be filled out and returned after delivery. If forms were not returned within 4 weeks
of the delivery date the coordinator called the patient or, in cases in which the patient could not be reached, the physician.

Subjects were included in this study if they underwent a first-trimester ultrasound scan and received a diagnosis of dichorionic twin pregnancy. Documentation of fetal heart motion in both fetuses at the first ultrasound scan was required for inclusion in the study. For subjects undergoing multiple first-trimester ultrasound scans, only the first scan was included. Subjects were excluded if chorionicity was undocumented, the pregnancy ended in elective termination, the subject was lost to follow-up or CRL was undocumented. All ultrasound scans were performed by sonographers specialized in obstetric ultrasound, and were interpreted by an attending physician also specialized in obstetric ultrasound. CRL measurements were determined using the longest straight-line length of the fetus. Transabdominal ultrasound was used, but transvaginal ultrasound was also utilized in cases in which adequate visualization of the pregnancy necessitated it. Pregnancy dating was determined by the date of the last menstrual period if known and if it was within 7 days of that deduced from the ultrasound measurements; if the date of the last menstrual period was unknown or disagreed with the ultrasound estimate by more than 7 days, the pregnancy was related using ultrasound measurements of the larger twin.

Study groups were defined by the presence or absence of ≥11% discordance in CRL measurements, as described in the literature. CRL discordance was calculated as (larger CRL − smaller CRL) × 100/larger CRL. The primary outcome was loss of one or both fetuses before 20 weeks’ gestation. Secondary outcomes included anomalies in one or both fetuses, preterm delivery before 34 weeks’ gestation, stillbirth, small-for-gestational age (SGA) for either infant (defined as birth weight less than the 10th percentile on the Alexander growth standard) and admission of either infant to the neonatal intensive care unit (NICU). Because fetal anomalies were not reliably diagnosed and documented until the mid-trimester anatomy scan and fetopsies were not routinely available, the outcome of fetal anomaly was examined only in pregnancies continuing beyond 20 weeks. The fetal anomalies considered were defects of organogenesis, such as myelomeningocele, ventriculomegaly, cystic hygroma, cardiac malformations, congenital diaphragmatic hernia, gastrochisis, omphalocele, multicystic dysplastic kidneys, hydroureter and arthrogryposis. Preterm delivery before 34 weeks was only evaluated in pregnancies continuing beyond 20 weeks. The outcome of stillbirth was evaluated only in non-anomalous fetuses progressing beyond 20 weeks, as fetal anomalies would confound the relationship between CRL discordance and stillbirth. Similarly, SGA and admission to the NICU were examined only in pregnancies not affected by fetal loss before 20 weeks, fetal anomalies or stillbirth. Diagnosis of chorionicity was based on the number of gestational sacs, amnions and yolk sacs present or the presence of the lambda sign.

Study groups were compared using Student’s t-test for normally distributed continuous variables or the Mann–Whitney U-test for non-normally distributed continuous variables, and the chi-square or Fisher’s exact test (for expected cell size less than five) for dichotomous variables. All tests were two-tailed and P < 0.05 was considered to be statistically significant. The relative risks (RR) and 95% CI for each outcome for the exposed (discordant) group compared to the unexposed (non-discordant) group were calculated. A receiver–operating characteristics (ROC) curve was created to determine the utility of CRL discordance for predicting a composite of adverse outcomes, defined as any of the following affecting one or both fetuses/infants: fetal loss prior to 20 weeks, fetal anomaly, delivery prior to 34 weeks, SGA at birth, stillbirth and NICU admission. Statistical analysis was performed using STATA, version 11, Special Edition (Stata Corporation, College Station, TX, USA).

RESULTS

During the study period we identified 805 dichorionic twin pregnancies on first-trimester ultrasound, of which 610 met the inclusion criteria (Figure 1). The median CRL discordance of the 610 twins was 3.6% (interquartile range, 0–7.1%). The 85th percentile for CRL discordance was 10.4%, similar to that reported in other populations and our pre-determined cut-off of 11% discordance. Of the 610 dichorionic twin pregnancies included, 86 were identified as having CRL discordance of at least 11%. Figure 1 shows the number of subjects considered in the evaluation of each study outcome. Study groups were similar with regard to maternal age, Black ethnicity, gravidity, history of stillbirth, chronic hypertension, pre-eclampsia and diabetes (Table 1). The gestational age at CRL measurement was approximately 1 week lower for pregnancies affected by CRL discordance than for pregnancies without CRL discordance.

Pregnancies affected by CRL discordance were more likely to result in the loss of at least one twin prior to 20 weeks’ gestation (10.5 vs 1.3%; RR 7.8 (95% CI, 3.0–20.5)) (Table 2). Of the pregnancies in which both twins survived, the risk of anomalies in twins affected by CRL discordance was nearly 60% higher than in those where CRL was concordant (27.3 vs 17.4%; RR 1.6 (95% CI, 1.1–2.4)). The risk of delivery before 34 weeks was similar between groups (27.3 vs 24.4%; RR 1.1 (95% CI, 0.8–1.7)). In continuing pregnancies not affected by fetal anomalies, CRL discordance did not confer an increased risk of stillbirth (3.6 vs 2.3%; RR 1.5 (95% CI, 0.3–6.8)). CRL discordance did not place the fetuses at increased risk of SGA at birth (39.1 vs 30.5%; RR 1.3 (95% CI, 0.9–1.9)) or NICU admission (17.4 vs 21.8%; RR 0.8 (95% CI, 0.4–1.5)). The area under the ROC curve that described the ability of CRL discordance to predict the composite adverse outcome (Figure 2) was 0.53. At a cut-off of 11% for CRL discordance, the sensitivity for prediction of adverse outcome was 18.4% and the specificity was 90.7%.
CRL discordance in dichorionic twins

DISCUSSION

In our population of dichorionic twins, CRL discordance of at least 11% on first-trimester scan was associated with an increased risk of fetal loss before 20 weeks’ gestation and with the detection of a fetal anomaly beyond this point. However, in surviving pregnancies without fetal anomalies, CRL discordance was not associated with an increased risk of stillbirth, SGA at birth or delivery prior to 34 weeks’ gestation. These findings can be explained in several ways. First, it is possible that the threshold of discordance chosen was too low. We chose to examine CRL discordance at a threshold value of ≥ 11%, based on both the 85th percentile in our population and that reported in previous studies with similar 85th percentile values. It is possible that a higher threshold would display a stronger association with adverse outcome, although when we used a ROC curve to examine CRL discordance as a continuous variable, the area under the curve was 0.53, suggesting that no appropriate cut-off for CRL discordance exists in our population for overall adverse outcome.

Another explanation is that dichorionic twins, each having a unique genetic composition in most cases, have
Table 1 Baseline characteristics of 610 twin pregnancies according to presence (n = 86) or absence (n = 524) of crown–rump length (CRL) discordance of ≥ 11% on first-trimester ultrasound

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRL concordant (n = 524)</th>
<th>CRL discordant (n = 86)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>33.7 ± 5.6</td>
<td>32.9 ± 5.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Black ethnicity</td>
<td>74 (14.1)</td>
<td>12 (14.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>Gravidy</td>
<td>2.5 ± 1.5</td>
<td>2.4 ± 1.4</td>
<td>0.51</td>
</tr>
<tr>
<td>History of stillbirth</td>
<td>18 (3.4)</td>
<td>3 (3.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (4.2)</td>
<td>4 (4.7)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (1.9)</td>
<td>1 (1.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>123 (23.5)</td>
<td>20 (23.3)</td>
<td>0.93</td>
</tr>
<tr>
<td>GA at CRL measurement</td>
<td>11.1 (9.3 – 12.0)</td>
<td>10.2 (8.1 – 11.7)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Data shown as mean ± SD, n (%) or median (interquartile range). GA, gestational age.

Table 2 Risk of adverse pregnancy outcome in dichorionic twins according to presence (n = 86) or absence (n = 524) of crown–rump length discordance of ≥ 11% on first-trimester ultrasound

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CRL concordant</th>
<th>CRL discordant</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal loss &lt; 20 weeks</td>
<td>1.3</td>
<td>10.5</td>
<td>7.8 (3.0 – 20.5)</td>
</tr>
<tr>
<td>Fetal anomaly*</td>
<td>17.4</td>
<td>27.3</td>
<td>1.6 (1.1 – 2.4)</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>24.4</td>
<td>27.3</td>
<td>1.1 (0.8 – 1.7)</td>
</tr>
<tr>
<td>&lt; 34 weeks</td>
<td>2.3</td>
<td>3.6</td>
<td>1.5 (0.3 – 6.8)</td>
</tr>
<tr>
<td>Stillbirth &gt; 20 weeks*</td>
<td>30.5</td>
<td>39.1</td>
<td>1.3 (0.9 – 1.9)</td>
</tr>
<tr>
<td>SGA at birth*</td>
<td>21.8</td>
<td>17.4</td>
<td>0.8 (0.4 – 1.5)</td>
</tr>
</tbody>
</table>

* Affecting one or both twins. NICU, neonatal intensive care unit; SGA, small-for-gestational age.

Figure 2 Receiver–operating characteristics curve for crown–rump length discordance in predicting a composite adverse outcome including fetal loss prior to 20 weeks, fetal anomaly, delivery prior to 34 weeks, small-for-gestational age at birth, stillbirth and admission to neonatal intensive care unit affecting one or both fetuses/infants in a cohort of 610 twin pregnancies.
Pregnancies affected by fetal loss before 20 weeks were not included in the analysis of fetal anomalies. This is because of the inability to document many fetal anomalies in the first trimester as well as incomplete or undocumented evaluations of first-trimester losses in many cases. As early fetal loss is frequently associated with chromosomal and structural anomalies, the association between CRL discordance and fetal anomalies may be stronger than that reported. Additionally, we did not include subjects who lost only one fetus in further analyses of birth weight owing to the limited number of subjects \((n = 16)\). Therefore, the impact of the presence of a dead, or vanishing, twin was not evaluated here, although previous studies suggest that a vanishing twin may have a detrimental effect on the growth of the remaining fetus. The exclusion of subjects with a vanishing twin may have had a minimal impact on our results.

In conclusion, when CRL discordance of at least 11% is diagnosed in dichorionic twins, these pregnancies are at increased risk for fetal anomalies and fetal loss prior to 20 weeks. A follow-up ultrasound examination to confirm viability and a detailed anatomic survey of both fetuses are indicated in these patients. However, in continuing pregnancies with anatomically normal fetuses, patients can be reassured that CRL discordance does not place the pregnancy at risk for growth disorders and preterm delivery beyond that already experienced by dichorionic twins.

REFERENCES