Crown–rump length discordance and adverse perinatal outcome in twins: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort

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KEYWORDS: adverse perinatal outcome; CRL discordance; twin pregnancies

ABSTRACT

Objective Evidence for the role of first-trimester ultrasound in predicting outcome in twin pregnancies is conflicting. The aim of this study was to determine the association between crown–rump length (CRL) discordance and adverse perinatal outcome in twin pregnancies.

Methods This was a retrospective study of all twin pregnancies of known chorionicity from a large regional cohort over a 10-year period. Terminations of pregnancy, cases with fetal or chromosomal abnormalities and monoamniotic pregnancies were excluded. Receiver–operating characteristics (ROC) curve and logistic regression analyses were performed to evaluate the association between CRL discordance and stillbirth, neonatal mortality, intrauterine growth restriction, preterm birth (PTB) at <34 weeks’ gestation and birth weight (BW) and ultrasound estimated fetal weight (EFW) discordance of ≥25%.

Results A total of 2155 twin pregnancies were analyzed, of which 420 were monochorionic (MC) and 1735 dichorionic (DC). There were 42 fetal losses before 24 weeks’ gestation and 23 perinatal deaths. CRL discordance was poorly predictive for fetal loss at <24 weeks (area under the ROC curve (AUC), 0.54 (95% CI, 0.46–0.62)), perinatal loss (AUC, 0.52 (95% CI, 0.41–0.64)), BW discordance (AUC, 0.61 (95% CI, 0.56–0.65)), BW <5th centile (AUC, 0.56 (95% CI, 0.53–0.59)), EFW discordance (AUC, 0.55 (95% CI, 0.51–0.60)) and PTB at <34 weeks (AUC, 0.50 (95% CI, 0.47–0.54)). Overall mortality was significantly higher in MC (5.0%) than in DC (2.6%) twins (P = 0.016). Logistic regression analysis demonstrated that chorionicity (odds ratio 2.09 (95% CI, 1.06–4.10); P = 0.033) independently contributed to determining mortality, while CRL discordance (P = 0.201) did not. Adjusting for chorionicity did not improve the detection of adverse outcomes using CRL discordance.

Conclusion In the absence of aneuploidy or structural fetal abnormality, CRL discordance is of poor predictive value for adverse perinatal outcome in both MC and DC twin pregnancies. CRL discordance should not be used routinely to identify twin pregnancies at high risk of adverse perinatal outcome. Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Chorionicity, preterm birth (PTB) and abnormal fetal growth represent the major determinants of adverse perinatal outcome in twin pregnancies1–2. Although a degree of discordance in fetal growth is invariably present in all twin pregnancies, intertwin discordance in size has been reported in association with a multitude of adverse outcomes including stillbirth, neonatal death, PTB, respiratory distress and admission to the neonatal intensive care unit3–12. On the assumption that discordant growth in twins begins as early as the first trimester of pregnancy, it has been suggested that discordance in crown–rump length (CRL) may have a role in the prediction of weight discordance. Furthermore, discordance in early fetal growth has been associated with other adverse outcomes such as pregnancy loss, chromosomal abnormalities and structural malformations13–26. Despite these associations, the role of first-trimester ultrasound in predicting an adverse outcome in twin pregnancies is still controversial, with different studies reporting conflicting
results. The aim of this study was to ascertain the performance of first-trimester CRL discordance in the prediction of adverse perinatal outcome in a large cohort of twin pregnancies.

METHODS

This was a retrospective study of all twin pregnancies booked for antenatal care in nine hospitals in the Southwest Thames region of London Obstetric Research Collaborative (STORK) over a period of 10 years since 2000. All women registering for routine antenatal care by 11 weeks’ gestation were considered suitable for the analysis. Scan data were obtained by a computerized search of each hospital’s obstetric ultrasound computer database, while outcome details were obtained from the computerized maternity records. These two databases were cross-checked to ensure full data capture of all twin pregnancies during the study period. All data included in the analysis were collected prospectively but analyzed retrospectively. Ethical approval for this retrospective study was obtained from the local research ethics committee. Exclusion criteria were termination of pregnancy, presence of fetal or chromosomal abnormalities, pregnancies of unknown chorionicity, monochorionic monoamniotic pregnancies and high-order multiple gestations.

Gestational age was determined by the CRL of the larger twin at the 11–14-week scan. Chorionicity was determined by ultrasound evaluation according to the number of placentae and the presence of the lambda or T-sign, and confirmed after birth. A routine fetal structural survey was carried out at 20–22 weeks, and all monochorionic (MC) twins had two additional scans at around 17 and 19 weeks specifically to identify early features of twin-to-twin transfusion syndrome (TTTS). If TTTS was suspected, the woman was referred to the local tertiary center for assessment for fetoscopic laser ablation of the placental interconnecting vessels.

CRL discordance (%) was calculated as 100 × (larger CRL – smaller CRL)/larger CRL. Ultrasound estimated fetal weight (EFW) was calculated using the Hadlock formula based on head circumference, abdominal circumference and femur length, while actual birth weight (BW) discordance (%) was calculated as 100 × (larger BW – smaller BW)/larger BW. Only ultrasound examinations just prior to delivery, or in case of stillbirth, prior to the diagnosis of fetal death, were considered for the analysis. Ultrasound and outcome data were linked to a mandatory national register for stillbirth and neonatal losses provided by the former Centre for Maternal and Child Enquiries (CMACE). In accordance with CMACE regulations, patient identifiers such as name, hospital number and date of birth were not made available to the researchers.

The predictive performance of CRL discordance for fetal loss at < 20 and < 24 weeks’ gestation, perinatal loss (defined as the sum of fetal losses at ≥24 weeks, early and late neonatal deaths up to the age of 28 days), BW discordance of ≥25%, small for gestational age (SGA; defined as the presence of at least one twin with BW < 5th centile according to the singleton published reference ranges), EFW discordance of ≥25% and PTB between 24 and 34 weeks’ gestation was assessed using receiver–operating characteristics (ROC) analysis. In the analysis, prenatal and perinatal deaths were defined per pregnancy as the loss of at least one fetus or neonate. Logistic regression analysis was carried out in order to assess the association of pregnancy characteristics, such as chorionicity, CRL discordance, CRL < 5th centile (Fleming et al.), increased nuchal translucency (NT) and NT discordance, with adverse pregnancy outcomes.


Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.04 for Windows (GraphPad Software, La Jolla, CA, USA, www.graphpad.com). Comparisons of continuous and categorical variables between groups were performed using the Mann–Whitney U-test and chi-square test, respectively. Statistical significance was set at P < 0.05. All P-values were two-tailed.

RESULTS

A total of 2155 twin pregnancies (420 MC and 1735 dichorionic (DC)) were included in the study. The median CRL discordance was 3.51% (interquartile range (IQR), 1.47–6.55%). There was no significant difference in median CRL discordance between MC and DC twin pregnancies (3.82% (IQR, 1.35–6.77%) vs 3.45% (IQR, 1.48–6.50%); P = 0.637). The rates of fetal loss at < 20 weeks, fetal loss at < 24 weeks and perinatal loss per pregnancy were 1.0% (n = 21), 1.9% (n = 42) and 1.1% (n = 23), respectively. Overall mortality was significantly higher in MC than in DC twins (5% vs 2.6%; P = 0.016). The rate of PTB at < 34 weeks was 15.8% (340/2155) and this did not vary significantly between MC and DC pregnancies (P = 0.909). BW and EFW discordance of ≥25% was present in 11.8% and 12.8% of twin pregnancies, respectively (P = 0.352). The proportion of pregnancies with BW and EFW discordance of ≥25% was significantly higher in MC than in DC twins (17.6 vs 10.9%; P < 0.001 and 19.8 vs 11.8%; P = 0.003, respectively). In addition, the mean BW discrepancy was significantly higher in MC than in DC twins (13.7 vs
12.1%; \( P = 0.034 \)). The prevalence of SGA at birth was 28.3%, with no significant difference between MC and DC twins (33.5 vs 27.6%; \( P = 0.073 \)).

The predictive accuracy of CRL discordance was poor for fetal loss at <20 weeks (area under the ROC curve (AUC), 0.61 (95\% CI, 0.52–0.70)), fetal loss at <24 weeks (AUC, 0.54 (95\% CI, 0.46–0.62)), perinatal mortality (AUC, 0.52 (95\% CI, 0.41–0.64)), BW discordance (AUC, 0.61 (95\% CI, 0.56–0.65)), BW < 5\(^{th}\) centile (AUC, 0.56 (95\% CI, 0.53–0.59)), EFW discordance (AUC, 0.55 (95\% CI, 0.51–0.60)) and PTB at < 34 weeks (AUC, 0.49 (95\% CI, 0.43–0.54)) (Figure 1). Restricting the ROC analysis to only MC twins, the predictive accuracy of CRL discordance remained poor for fetal loss at < 20 weeks (AUC, 0.63 (95\% CI, 0.47–0.69)), fetal loss at < 24 weeks (AUC, 0.54 (95\% CI, 0.43–0.64)), perinatal mortality (AUC, 0.55 (95\% CI, 0.35–0.75)), BW discordance (AUC, 0.61 (95\% CI, 0.50–0.71)), BW < 5\(^{th}\) centile (AUC, 0.57 (95\% CI, 0.49–0.66)), EFW discordance (AUC, 0.54 (95\% CI, 0.44–0.64)) and PTB at < 34 weeks (AUC, 0.49 (95\% CI, 0.43–0.54)).

Multivariable logistic regression analysis demonstrated that monochorionicity (odds ratio (OR), 2.09 (95\% CI, 1.06–4.10); \( P = 0.033 \)), but not CRL discordance (\( P = 0.201 \)), CRL < 5\(^{th}\) centile (\( P = 0.810 \)), NT discordance (\( P = 0.792 \)) or NT > 95\(^{th}\) centile (\( P = 0.179 \)) was associated with the risk of perinatal loss. Adjusting for chorionicity did not improve the predictive accuracy of CRL discordance for fetal loss at any gestational age. Monochorionicity (OR, 1.74 (95\% CI, 1.18–2.55)) and CRL discordance (OR, 1.05 (95\% CI, 1.02–1.7)) were independently correlated with the finding of BW discordance of ≥ 25\% while CRL < 5\(^{th}\) centile (\( P = 0.987 \)) and NT > 95\(^{th}\) centile (\( P = 0.520 \)) were not. CRL discordance was independently associated with SGA at birth (OR, 1.04 (95\% CI, 1.02–1.06)) while monochorionicity (\( P = 0.071 \)), CRL < 5\(^{th}\) centile (\( P = 0.592 \)), NT discordance (\( P = 0.322 \)) and NT > 95\(^{th}\) centile (\( P = 0.442 \)) were not. The multivariable logistic
regression analysis for PTB at $<34$ weeks' gestation revealed that monochorionicity (OR, $1.98$ (95% CI, $1.41–2.80$)), BW discordance (OR, $1.06$ (95% CI, $1.05 – 1.08$)) and BW $<5^{th}$ centile (OR, $1.95$ (95% CI, $1.35 – 2.83$)) were independent predictors, while CRL discordance ($P = 0.446$), CRL $<5^{th}$ centile ($P = 0.385$), NT discordance ($P = 0.208$) and NT $>95^{th}$ centile ($P = 0.136$) were not.

The results of the literature search on CRL discordance and the adverse outcomes considered in this study are summarized in Table 1. Seventeen studies were included that either evaluated the association between CRL discordance and the adverse pregnancy outcomes investigated in this study or investigated the predictive value of CRL discordance for these outcomes.

**DISCUSSION**

Our data demonstrate that CRL discordance has a poor predictive value for adverse perinatal outcome in twin pregnancies, irrespective of chorionicity. While monochorionicity was associated with double the risk of perinatal loss in this cohort, CRL discordance, CRL $<5^{th}$ centile, NT discordance and NT $>95^{th}$ centile were not significantly associated with the risk of perinatal loss.

Early ultrasound assessment is essential for the management of twin pregnancies. First-trimester determination of chorionicity allows for stratification of the obstetric risk and establishes the timeline for subsequent examinations. Serial scans early in the second trimester in MC twins allow the detection and treatment of the complications unique to these pregnancies, such as TTTS$^{31,32}$. Weight discordance is one of the major determinants of adverse perinatal outcome in twins$^{1–12}$. It has been hypothesized that weight discordance begins as early as the first trimester of pregnancy, leading to the widely held belief that discordance in size may have a role in the prediction of fetal growth discordance and adverse perinatal outcome$^{13–26}$.

CRL discordance is a common finding in twins; it might be related to the different genetic potential or the physiologically unequal placental share of each fetus, thus representing a normal constitutional variant. However, higher degrees of discordance in early pregnancy might herald impending fetal demise, intrauterine growth restriction (IUGR), chromosomal abnormalities or structural malformations. Discordance in CRL is a factor commonly taken into consideration in counseling parents about the outcome of the pregnancy, and different thresholds have been investigated (Table 1). However, data regarding the role of CRL discordance in predicting the outcome of twin pregnancies are still conflicting. Previous studies have been limited by the small sample sizes of the twin pregnancies studied, while comparison between them has been hindered by variable inclusion criteria, different outcome measures and the referral bias of complicated pregnancies (Table 1). The STORK cohort examined here is the largest series to date assessing the value of first-trimester CRL discordance in predicting adverse outcomes in twin pregnancy. The data from this cohort show that intertwin CRL discordance is a poor predictor of early fetal loss, perinatal loss, BW and EFW discordance, IUGR of at least one twin and PTB. Although their study involved a small, single-center cohort, Salomon et al.$^{15}$ reported similar findings to those of our study.

The rationale behind the use of CRL discordance as a predictor of adverse pregnancy outcome is that discordant growth, which carries an increased risk of pregnancy loss, may occur as early as the first trimester. However, when considering the pathophysiology of fetal growth in twin pregnancies, it is unlikely that most fetal losses are related to a first-trimester growth disorder. The uterine milieu is usually able to supply the metabolic demands of both twins during the second and early third trimesters, until approximately 28–32 weeks' gestation, after which twin growth usually diverges from that of singletons$^{33}$. There is also evidence that even in cases of severely discordant growth, the uteroplacental unit functions at a level that is 50–75% higher than that for an average singleton gestation$^{33}$. These findings suggest that delayed growth in one twin during the first trimester is unlikely to occur as a result of dysfunction of the uteroplacental unit.

Most previous studies have reported a significant association between CRL discordance and various adverse pregnancy outcomes (Table 1). However, the majority of studies reporting such an association failed to test the predictive value of CRL discordance for adverse pregnancy outcome. Furthermore, some studies even included cases of fetal aneuploidy and structural fetal abnormality. In our cohort we could not demonstrate any optimal cut-off to be useful for the prediction of mortality (Figure 1). Even considering the upper centiles of discordance, which are similar to those previously reported in the literature, did not add any additional value to the prediction of fetal or perinatal loss. Multivariable analysis showed that chorionicity was the only independent predictor of pregnancy loss after 14 weeks' gestation, while CRL discordance, CRL $<5^{th}$ centile, increased NT and NT discordance did not show any independent contribution to determining mortality. MC twin pregnancies are at increased risk of adverse perinatal outcome compared with DC twin pregnancies, in particular as a result of placental vascular complications such as TTTS. However, even after correction for chorionicity, the predictive performance of CRL discordance did not improve. This is not surprising, because TTTS reflects a state of hemodynamic imbalance rather than placental insufficiency$^{34}$. Likewise, the presence of an increased NT does not seem to have a major impact on survival once chromosomal abnormalities and structural malformations have been ruled out$^{34}$. It seems that the finding of a CRL $<5^{th}$ centile for gestational age calculated on the basis of the larger twin is likely to represent a physiological variation in the majority of cases, and does not have an independent role in predicting mortality.
Chromosomal and structural malformations are usually associated with aberrant fetal growth. Previous studies have also reported that CRL discordance can predict adverse fetal outcome when chromosomal abnormalities and structural malformations are included in the population studied or considered as primary outcomes of the analysis. This may explain the poor predictive value of CRL discordance observed in our cohort, from which fetuses with chromosomal and structural abnormalities were excluded. It is interesting to note that studies that included chromosomal abnormalities and structural malformations in their analyses tended to show a greater association between CRL discordance and adverse outcomes than those that did not (Table 1).

In conclusion, this is the largest series to date assessing the value of CRL discordance in predicting adverse outcomes in twin pregnancies. Once structural malformations and chromosomal abnormalities have been excluded, CRL discordance is weakly associated with adverse perinatal outcome. However, this association is not clinically useful in the prediction of subsequent adverse outcomes after 14 weeks’ gestation in either MC or DC twin pregnancies. The common practice of counseling parents about an adverse pregnancy outcome based on this finding should be discouraged.

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### Table 1 Published studies that include data on crown–rump length (CRL) discordance and adverse pregnancy outcome

<table>
<thead>
<tr>
<th>Study</th>
<th>Chorion</th>
<th>Cases (n)</th>
<th>CRL discordance cut-off (%)</th>
<th>Pregnancy loss (n %)</th>
<th>Early mortality</th>
<th>Perinatal mortality</th>
<th>BW discordance/sIUGR</th>
<th>Preterm birth</th>
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<td>Fajardo-Expósito 2011</td>
<td>MC, DC</td>
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<td>—</td>
<td>Assoc</td>
<td>—</td>
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<tr>
<td>Harper 2012</td>
<td>DC only</td>
<td>610</td>
<td>11</td>
<td>28 (4.6)</td>
<td>Assoc</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Only the first author of each study is given. *Cumulative rate of miscarriage and intrauterine fetal death of one or both fetuses considered as outcome of analysis; gestational age at death not stated. *Results reported as a comparison between medians, means or proportions. *Fetal anomalies included in analysis of association between CRL discordance and fetal loss or anomalies. *Expressed as 90th and 95th percentiles of discordance for population analyzed. *Expressed as 95th and 99th percentiles of discordance for population analyzed. 1CRL from 7 to 14 weeks. 2Chromosomal or structural abnormalities not included in analysis of this outcome. 3CRL from 14 to 20 weeks < 20 weeks).
REFERENCES


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