Weight discordance and perinatal mortality in twins: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort

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KEYWORDS: pregnancy outcome; twins; weight discordance

ABSTRACT

Objectives The degree of actual intertwin birth weight (BW) or ultrasound estimated fetal weight (EFW) discordance that justifies elective delivery is yet to be established. The main aim of this study was to ascertain the performance of BW and ultrasound EFW discordance in the prediction of perinatal loss in twin pregnancies.

Methods This was a retrospective study of all twin pregnancy births from a large regional cohort of nine hospitals over a 10-year period. Intertwin BW and ultrasound EFW discordance were analyzed in relation to the occurrence of stillbirth or neonatal death of one or both twins from 26 weeks’ gestation as obtained from a mandatory national register. Receiver–operating characteristics (ROC), survival and logistic regression analyses were performed to evaluate the contribution of weight discordance in determining perinatal loss.

Results A total of 2161 twin pregnancies were included in the analysis. The area under the ROC curve for the prediction of perinatal loss was similar for BW and ultrasound EFW discordance (P = 0.62). Kaplan–Meier analysis showed that twins with BW or EFW of ≥ 25% discordance had a significantly lower survival trend than did those with lesser degrees of discordance (P < 0.001). The hazard ratios for the risk of total perinatal loss in twins with a BW or EFW discordance of ≥ 25% were 7.29 (95% CI, 4.37–12.00) and 7.28 (95% CI, 4.46–11.92), respectively. Logistic regression analysis demonstrated that BW discordance and gestational age, but not chorionicity or individual fetal size percentile, were independently associated with perinatal mortality.

Conclusions An EFW discordance of ≥ 25% represents the optimal cut-off for the prediction of stillbirth and neonatal mortality irrespective of chorionicity or individual fetal size. A policy of increased fetal surveillance commencing from 26 weeks’ gestation might be reasonable for pregnancies beyond this cut-off, but this would require confirmation in large-scale prospective trials. Copyright © 2013 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Discordant growth is a relatively common finding in multiple gestations1. Although certain degrees of growth discordance may represent a normal physiological or adaptive variation, perinatal mortality and morbidity are known to be increased with higher degrees of growth discordance2. Actual birth weight (BW) discordance has been associated with a multitude of adverse outcomes, including stillbirth, neonatal death, preterm birth, respiratory distress and admission to the neonatal intensive care unit3–13. Despite these strong associations, it is still unclear what the optimal cut-off of BW discordance is for predicting, and potentially preventing, adverse perinatal outcome. Moreover, the role and optimal cut-off of ultrasound estimated fetal weight (EFW) discordance in predicting adverse outcome in growth discordant twins have also not been established.

The main aim of this study was to ascertain the performance of BW discordance and ultrasound EFW discordance in the prediction of perinatal loss in twin pregnancies. The second aim was to investigate other variables potentially associated with perinatal loss.

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 the outcome details were obtained from their 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. Terminations of pregnancy, fetal or chromosomal abnormalities, pregnancies of unknown ethicity, monochorionic–monoamniotic and high-order multiple gestations were not included in the analysis.

Gestational age was calculated from crown–rump length measurement of the larger twin at the 11–14-week scan or by head circumference (HC) if assessed after 14 weeks’ gestation. Chorionicity was determined by ultrasound evaluation according to the number of placenta and the presence of the lambda or T signs and confirmed after birth. A routine fetal structural survey was carried out at 20–22 weeks, and all monochorionic 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, women were referred to the local tertiary center for assessment for fetoscopic laser ablation of the placental interconnecting vessels.

Ultrasound EFW was calculated using the Hadlock formula based on HC, abdominal circumference and femur length. Ultrasound EFW discordance was calculated as 100 × (larger EFW – smaller EFW)/larger EFW, while actual BW discordance was calculated as 100 × (larger BW – smaller BW)/larger BW. Only the 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 matched to a mandatory national register of 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. Statistical analysis was performed per pregnancy, with perinatal loss defined as the stillbirth or neonatal death (up to 28 days of age) of one or both twins. The predictive performance of actual BW and ultrasound EFW discordance from 26 weeks’ gestation for perinatal loss was assessed using receiver–operating characteristics (ROC) analysis. After establishing an optimal cut-off for BW discordance the prospective risk of perinatal loss above and below this cut-off was calculated.

Survival trends from 26 weeks’ gestation until delivery according to different degrees of BW and ultrasound EFW discordance (<15%, 15–20%, 21–24% and ≥25%) were assessed using time-to-event analysis (Kaplan–Meier), in which duration of gestation was used as the time scale and perinatal loss as the event. Survival data were plotted as cumulative percentage without event and compared by the log-rank test. Finally, logistic regression analysis was carried out in order to look for independent contributors to perinatal loss in twin pregnancies from 26 weeks’ gestation. Maternal age, chorionicity, weight discordance, gestational age and the presence of at least a twin with BW <5th percentile were included in this analysis. BW centiles were calculated according to published reference ranges in singleton pregnancies. All calculations were 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). Statistical significance was set at P < 0.05, and all P-values were two-tailed.

RESULTS

A total of 2161 twin pregnancies (302 monochorionic and 1859 dichorionic) were included in the final analysis. Perinatal loss from 26 weeks’ gestation was 1.6% (67/4322 twins), comprising 48 stillbirths and 19 neonatal deaths. There were two double stillbirths, both occurring in monochorionic twins, and one double early neonatal death in a dichorionic pregnancy. Both BW and ultrasound EFW discordance were found to be predictive of perinatal loss, with areas under the ROC curves of 0.72 (95% CI, 0.65–0.80) and 0.69 (95% CI, 0.62–0.77), respectively (Figure 1). There was no significant difference between actual BW and ultrasound EFW for predicting perinatal loss (P = 0.62). For both BW and EFW, an intertwin discordance of ≥25% had the best combination of sensitivity and specificity. According to this analysis, BW discordance of 25% had a detection rate of 47% for a false-positive rate of 10% (Table 1) and EFW discordance of 25% had a detection rate of 42% for a false-positive rate of 11% (Table 2).

![Figure 1 Receiver–operating characteristics analysis of actual birth weight (---) and ultrasound estimated fetal weight (-----) discordance for the prediction of perinatal mortality in twin pregnancies.](image-url)
The total risk of perinatal loss (stillbirth and neonatal death) in twins with a BW discordance of ≥25% (60.9 per 1000 fetuses) was significantly greater than that in twins with a BW discordance of <25% (8.6 per 1000 fetuses), with a hazard ratio of 7.29 (95% CI, 4.46–11.92; \( P < 0.0001 \)). The risk of perinatal loss for an EFW discordance of ≥25% (65.8 per 1000 fetuses) was significantly higher than for twins with a <25% discordance (9.6 per 1000 fetuses), with a hazard ratio of 7.28 (95% CI, 4.46–12.00; \( P < 0.0001 \)). Kaplan–Meier analysis showed that twins with BW or EFW discordance of ≥25% had a significantly lower survival trend than those with lesser degrees of discordance (Figure 2; log-rank test \( P < 0.001 \) for both).

BW discordance of ≥25% (46/302 vs 205/1859) and perinatal loss (19/302 vs 48/1859) were significantly higher in monochorionic than in dichorionic twin pregnancies (\( P = 0.04 \) and 0.002, respectively). The presence of at least one twin having a BW <5th percentile was not significantly different between the monochorionic and dichorionic twins (101/302 vs 528/1859; \( P = 0.085 \)).

On multivariable logistic regression analysis, gestational age at delivery (odds ratio (OR) 0.75 (95% CI, 0.69–0.81); \( P < 0.0001 \)) and BW discordance (OR 1.07 (95% CI, 1.05–1.09); \( P < 0.0001 \)) were independent predictors of perinatal loss, while chorionicity, either twin having a BW <5th percentile and maternal age were not (\( P = 0.193, 0.678 \) and 0.767, respectively).

DISCUSSION

Weight discordance is invariably present in all twin pregnancies and may represent a physiological condition or an adaptive measure to the intrauterine milieu; on the other hand it may be the result of pathological conditions involving the fetus or the placenta\(^2\). Severe growth discordance in twins is associated with an increased risk of perinatal loss and morbidity\(^3–13\). In view of the latter association, it is routine obstetric practice to regularly screen twin pregnancies by ultrasound to evaluate the degree of intertwin fetal growth discordance. Despite this almost universal practice, there is no consensus as to the optimum cut-off of actual BW discordance able to predict an adverse outcome. Furthermore, the effectiveness of ultrasound in predicting discordant fetal growth and subsequent BW has not yet been established\(^19–31\). The major limiting factor has been the very small number of twin pregnancies studied and the subsequent, inevitably small number of perinatal losses observed. Hence, most authors have used EFW to predict actual BW discordance as a proxy for perinatal mortality and morbidity.

The STORK cohort studied here is one of the largest twin pregnancy cohorts of known chorionicity to be validated against both a concomitant delivery database and a mandatory national register of stillbirths and neonatal deaths. Suggested thresholds for significant BW discordance range from 10 to 30%\(^3–9,11–13,32\). The data from this cohort show that an actual BW discordance of ≥25% represents the optimal cut-off for the prediction of stillbirth and neonatal mortality. These results are similar to those from large epidemiological studies reporting an increased risk of perinatal mortality when a 25% cut-off for discordant BW is adopted\(^4,7,10,33\). Although a limitation of the current study is the lack of perinatal morbidity data, very few large studies have systematically assessed this parameter in the context of discordant

95% CIs are given in parentheses.

Table 1  Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and positive (LR •) and negative (LR –) likelihood ratios for prediction of perinatal loss (stillbirth and neonatal death) for different cut-offs of birth weight discordance

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>LR+</th>
<th>LR–</th>
</tr>
</thead>
<tbody>
<tr>
<td>5%</td>
<td>84.4 (73.1–92.2)</td>
<td>30.9 (28.9–32.9)</td>
<td>3.6 (2.7–4.7)</td>
<td>98.5 (97.2–99.3)</td>
<td>1.2 (1.1–1.4)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>10%</td>
<td>71.9 (59.2–82.4)</td>
<td>52.6 (50.4–54.8)</td>
<td>4.4 (3.3–5.9)</td>
<td>98.4 (97.5–99.0)</td>
<td>1.5 (1.3–1.8)</td>
<td>0.5 (0.4–0.8)</td>
</tr>
<tr>
<td>15%</td>
<td>59.4 (46.4–71.5)</td>
<td>73.6 (71.7–75.5)</td>
<td>6.4 (4.6–8.7)</td>
<td>98.3 (97.6–98.9)</td>
<td>1.8 (1.5–2.2)</td>
<td>0.6 (0.4–0.7)</td>
</tr>
<tr>
<td>20%</td>
<td>53.1 (40.2–65.7)</td>
<td>84.6 (82.9–86.1)</td>
<td>9.5 (6.7–13.0)</td>
<td>98.3 (97.6–98.9)</td>
<td>3.4 (2.7–4.4)</td>
<td>0.6 (0.4–0.7)</td>
</tr>
<tr>
<td>25%</td>
<td>46.9 (34.3–59.8)</td>
<td>90.3 (88.9–91.5)</td>
<td>12.8 (8.8–17.8)</td>
<td>98.2 (97.5–98.8)</td>
<td>4.8 (3.6–6.4)</td>
<td>0.6 (0.5–0.7)</td>
</tr>
<tr>
<td>30%</td>
<td>37.5 (25.7–50.5)</td>
<td>95.7 (94.8–96.5)</td>
<td>21.1 (14.0–29.7)</td>
<td>98.0 (97.3–98.6)</td>
<td>8.7 (6.0–12.7)</td>
<td>0.7 (0.5–0.8)</td>
</tr>
<tr>
<td>35%</td>
<td>31.3 (20.2–44.1)</td>
<td>97.7 (96.9–98.3)</td>
<td>29.0 (18.7–41.2)</td>
<td>97.9 (97.2–98.5)</td>
<td>13.4 (8.5–21.1)</td>
<td>0.7 (0.6–0.8)</td>
</tr>
</tbody>
</table>

Table 2  Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values and positive (LR •) and negative (LR –) likelihood ratios for prediction of perinatal loss (stillbirth and neonatal death) for different cut-offs of estimated fetal weight discordance

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<td>5%</td>
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<td>10%</td>
<td>71.9 (59.2–82.4)</td>
<td>55.8 (53.6–57.9)</td>
<td>4.7 (3.5–6.2)</td>
<td>98.5 (97.6–99.1)</td>
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<td>74.1 (72.1–75.9)</td>
<td>6.5 (4.7–8.9)</td>
<td>98.4 (97.6–98.9)</td>
<td>2.3 (1.8–2.8)</td>
<td>0.6 (0.4–0.7)</td>
</tr>
<tr>
<td>20%</td>
<td>48.4 (35.8–61.3)</td>
<td>81.8 (80.1–83.4)</td>
<td>7.5 (5.2–10.5)</td>
<td>98.1 (97.4–98.7)</td>
<td>2.6 (2.0–3.4)</td>
<td>0.7 (0.5–0.8)</td>
</tr>
<tr>
<td>25%</td>
<td>42.2 (29.9–55.2)</td>
<td>89.3 (87.9–90.6)</td>
<td>10.7 (7.2–15.2)</td>
<td>98.1 (97.3–98.6)</td>
<td>3.9 (2.9–5.4)</td>
<td>0.7 (0.5–0.8)</td>
</tr>
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<td>30%</td>
<td>29.7 (18.9–42.4)</td>
<td>93.1 (92.9–94.2)</td>
<td>11.7 (7.2–17.6)</td>
<td>97.7 (97.0–98.4)</td>
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<td>96.3 (95.4–97.0)</td>
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</table>
Figure 2 Kaplan–Meier survival plots according to different degrees of intertwin discordance in actual birth weight (a) and estimated fetal weight (b) (—, ≤ 15%; , 15–20%; ————, 21–24%; ——, ≥ 25%). The time scale was gestational age from 26 weeks and the event considered was perinatal loss. For both analyses there were significant differences in survival between groups as defined by discordance (log-rank test $P < 0.001$ for both).

BW. Importantly, this study excluded cases that would influence the association between growth discordance and adverse outcomes such as chromosomal or structural malformations that are known to exhibit aberrant fetal growth.

Despite the widespread use of ultrasound to assess fetal growth, the optimal cut-off of EFW discordance to predict adverse outcome in twins has not yet been established. Indeed, the largest systematic review of the current literature on this topic concluded that an EFW discordance of ≥ 25% was the optimal cut-off, but on the basis of predicting significant BW discordance rather than adverse perinatal outcome. The data from the present study show that an EFW discordance of ≥ 25% represents the optimal cut-off for the prediction of perinatal loss. This cut-off appears to be robust because of the lack of a significant difference between actual BW and EFW discordance for the prediction of perinatal loss. The total risk of perinatal loss from 26 weeks’ gestation in twins with an EFW of ≥ 25% (65.8 per 1000 fetuses) was significantly higher than in twins with a discordance of < 25% (9.6 per 1000 fetuses), and Kaplan–Meier analysis confirmed that twins with an EFW discordance of ≥ 25% have a significantly lower survival rate than those with lesser degrees of discordance. Given the retrospective nature of the current study, it is possible that clinicians’ knowledge of the scan results may have resulted in intervention, introducing the possibility of ‘treatment biases’. Even though the latter is unlikely to have altered the study findings significantly, confirmation of the findings in a prospective large-scale study would be prudent.

The association of BW discordance with increased perinatal mortality and morbidity is established, but what is not known is the extent to which concurrent comorbidities, such as prematurity, choriocicity or growth restriction, may influence the outcome. Logistic regression analysis of the current data demonstrated that gestational age at delivery and BW discordance, but not choriocicity or being small for gestational age, independently contribute towards twin perinatal loss. The lack of influence of individual fetal weight < 5th centile is not surprising, as the majority of twins are ‘small’ by singleton growth references. The latter also explains why using the cotwin as a reference when calculating weight discordance is an effective measure of growth restriction and subsequent mortality. These findings question the need for twin-specific growth references to diagnose twin growth restriction. The additional finding that chorionicity does not independently contribute to perinatal mortality in weight-discordant twins may initially seem surprising. However, the current analysis included pregnancies delivering at ≥ 26 weeks’ gestation only, when pregnancy loss due to complications of monochorionicity, e.g. TTTS, reaches a nadir.

In conclusion, the findings of this study confirm that BW and/or EFW discordance of ≥ 25% represents the optimal cut-off for the prediction of stillbirth and neonatal mortality, irrespective of chorionicity or individual fetal size. A policy of increased fetal surveillance commencing from 26 weeks’ gestation and elective delivery by 38 weeks might be reasonable for pregnancies above this cut-off, but this would require confirmation in large-scale prospective trials.

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REFERENCES


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