Birthweight discordance and neonatal morbidity in twin pregnancies: Analysis of the STORK multiple pregnancy cohort

Francesco D'Antonio, Basky Thilaganathan, Arianna Laoreti, Asma Khalil
On behalf of the Southwest Thames Obstetric Research Collaborative (STORK).

Fetal Medicine Unit, St George's, University of London & St George's University Hospitals NHS Foundation Trust, Molecular and Clinical Sciences Research Institute
London, SW17 0RE

Running Head: Birthweight discordance and morbidity in twins

Keywords: twin pregnancies, weight discordance, morbidity, outcome

Correspondence: Dr Asma Khalil
Fetal Maternal Medicine Unit
St George's University of London
London SW17 0RE
Telephone: 020 8725 0071
Facsimile: 020 8725 0079
E-mail: akhalil@sgul.ac.uk; asmakhalil79@googlemail.com

*All STORK authors' details are given in appendix

ABSTRACT

Objectives: The main aim of this study was to investigate the relationship between weight discordance and neonatal morbidity in twin pregnancies progressing beyond 34 weeks of gestation. The secondary aim was to determine the predictive accuracy of different weight discordant cut-offs in predicting neonatal morbidity in twin pregnancies.

Methods: This was a retrospective multicentre cohort study of all twin pregnancies booked for antenatal care in four hospitals in the Southwest Thames region of London Obstetric Research Collaborative (STORK) over a period of ten years. The ultrasound data were obtained by a computerized search of each hospital's obstetric ultrasound computer database, while the outcome details were obtained from the computerized maternity and neonatal records. The primary outcome was the incidence of composite neonatal morbidity in twin pregnancies with birthweight discordance.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.18916

Logistic regression was used to identify and adjust for potential confounders, while the receiver operating characteristic curve was used to determine the predictive accuracy.

Results: Nine hundred and thirty-nine twin pregnancies (760 Dichorionic, 179 Monochorionic) were included. The gestation at birth and birthweight decile were significantly lower in the pregnancies complicated by neonatal morbidity compared to those which were not ($p<0.001$ for both). At multivariable logistic regression, gestation at birth ($p<0.001$), birthweight decile ($p=0.029$), birthweight discordance ($p=0.019$) but not chorionicity ($p=0.477$) or the presence of at least one small for gestational age twin ($p=0.245$), were independently associated with the risk of neonatal morbidity. There was a progressive increase in the risk of neonatal morbidity with increasing birthweight discordance. Despite this association, birthweight discordance showed an overall poor predictive accuracy in detecting neonatal morbidity, with an AUC of 0.58 (95% CI 0.53-0.63) with an optimal cut-off of 17.6%, showing a sensitivity and a specificity of 35.2% (95% CI 27.8-43.2) and 83.2% (95% CI 80.0-85.8), respectively.

Conclusion: Inter-twin birthweight discordance is independently associated with the risk of neonatal morbidity in twins born after 34 weeks' gestation, irrespective of the chorionicity or the diagnosis of SGA in either twin. However, its predictive accuracy for neonatal morbidity is poor.

INTRODUCTION

Birthweight discordance is one of the major determinants of the perinatal mortality in twin pregnancies, irrespective of the chorionicity[1,2]. Although a certain degree of discordance in fetal growth is invariably present in all twin pregnancies, inter-twin size discordance has been associated with a multitude of adverse outcomes including stillbirth, neonatal death, preterm birth, respiratory distress and admission to neonatal intensive care unit (NICU)[2-20].

Despite the fact that the association between weight discordance and fetal loss is well established, there are still controversies on the actual role of discordant fetal growth in determining the perinatal morbidity. The pathophysiology of fetal growth disorders in twin pregnancies has not been completely elucidated yet. The uterine milieu can supply the metabolic demands of both twins during the second and early third trimester, until approximately 28-32 weeks; after which twin growth usually diverges from that of singletons[21-22]. A multitude of weight discordance cut-offs have been suggested to be associated with adverse pregnancy outcome, but it is yet to be established which one provides the best combination of sensitivity and specificity.

The primary aim of this study was to investigate the association between weight discordance and neonatal morbidity in twin pregnancies progressing beyond 34 weeks of gestation. The secondary aim was to determine the predictive accuracy of inter-twin weight discordance for the risk of neonatal morbidity.

METHODS

This was a retrospective cohort study of all twin pregnancies booked for antenatal care in four hospitals (St George's, Kingston, Epsom and St Helier Hospitals) in the Southwest Thames region of London Obstetric Research Collaborative (STORK) over a period of ten years since 2000. The scan data were obtained by a computerized search of each hospital's obstetric ultrasound computer database, while the outcome details were obtained from the maternity and neonatal records. These 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. Terminations of pregnancy, fetal or chromosomal abnormalities, cases affected by twin to twin transfusion syndrome (TTTS), pregnancies of unknown chorionicity, monochorionic monoamniotic, higher order multiple gestations, pregnancies complicated by stillbirth and those delivering before 34 weeks were not included in the analysis.

Gestational age was determined according to the crown-rump length of the larger twin at the 11-14 week scan[23]. Chorionicity was determined by ultrasound evaluation according to the number of placentas and the presence of the lambda or T-signs and confirmed after birth[24]. A routine fetal structural survey was carried out at 18-22 weeks, and all monochorionic (MC) twins had two additional scans at around 17 and 19 weeks specifically to identify early features of TTTS. If TTTS was suspected, women were referred to the local tertiary centre for assessment for fetoscopic laser ablation of the placental interconnecting vessels. Decisions regarding mode of delivery were made according to the individual patient's wishes and the attending obstetrician's own clinical practice. Delivery, whether induction of labour or elective Cesarean section, was planned from 37 weeks' gestation in dichorionic diamniotic (DCDA) twin pregnancies and 36 weeks in monochorionic diamniotic (MCDA) twin pregnancies.

The primary outcome was the incidence of composite neonatal morbidity, defined as the occurrence of at least one of the following outcomes in either twin[25]:

- Respiratory morbidity (including respiratory distress syndrome, transient tachypnea of the newborn, continuous positive airway pressure for at least 24 hours, mechanical ventilation, need for supplemental oxygen, pulmonary hypertension or bronchopulmonary dysplasia).
- Infectious morbidity (including pneumonia, meningitis, culture-proven sepsis)
- Neurological morbidity (including seizures, intra-ventricular hemorrhage grade III and IV and periventricular leukomalacia grades II and III detected on ultrasound scan).
- Hypoglycemia (blood glucose less than 2.2mmol/L)
- Hypothermia (core body temperature less than 36.0°C)
- Jaundice and need for phototherapy
- Necrotizing enterocolitis (any grade)
- Retinopathy of prematurity (any grade)

Birthweight discordance was calculated as 100 x (larger birthweight - smaller birthweight)/larger birthweight[1]. Pregnancies affected by single fetal loss or neonatal death were excluded from the analysis.

Statistical analysis

Continuous variables were presented as medians with interquartile ranges, while categorical variables were presented as numbers and percentages. The distribution assumptions were tested with Shapiro-Wilk test. The group comparison of the variables was performed using t-test, Mann Whitney U test or Chi-square test where appropriate. We first examined potential difference in the incidence of neonatal morbidity according to the inter-twin birthweight discordance. We also examined potential confounders, such as chorionicity, gestational age at birth, birthweight decile of each twin (calculated according to published reference ranges in twin pregnancies), presence of one or more small for gestational age (SGA) (defined as a birthweight less than the 10 centile) twin[26]. The potential associations between these parameters and the risk of neonatal morbidity were initially evaluated with the univariable regression analysis.

The potential independent predictors of the risk of neonatal morbidity (monochorionicity, gestational age at birth, BW, BW discordance and SGA status) were then evaluated using binary logistic regression. All covariates were included a priori in the final model. The goodness-of-fit was checked using Hosmer-Lemeshow test, and the predictive accuracy assessed through C-statistics (area under the Receiving Operator Curve). Standard post-estimation tests were used to check the final model validity, performing multicollinearity and influential observation analyses (using standardized residuals, change in Pearson and deviance chi-square). There were no missing values, thus no missing imputation technique was adopted.

Finally, we assessed the predictive accuracy of birthweight discordance for the risk of neonatal morbidity using the summary estimates of sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR–) and diagnostic odd ratio (DOR) for the various cut-offs of birthweight discordance[27].

The statistical significance was defined as a two-sided p-value <0.05, and all analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013) and SPSS version 24 (SPSS Inc., Chicago, IL, USA).

RESULTS

The study included 950 twin pregnancies (768 DC, 182 MC) from 34 weeks of gestation. After exclusion of 7 fetuses who experienced IUD (4 DC and 3 MC) and 4 NND (1 early and 3 late, all occurring in DC pregnancies 939 twin pregnancies (760 DC, 179 MC) were available for the analysis. There was no case of co-twin demise after the death of a fetus if occurred from 34 weeks of gestation. The characteristics of the population analyzed in the present study are shown in Table 1. The incidence of the composite neonatal morbidity in this cohort of twin pregnancies was 16.9% (95% CI 14.6-19.5) (Supplementary Table 1).

The gestational age at birth and median birthweight decile were significantly lower in the pregnancies complicated by neonatal morbidity compared to those which were not ($p<0.001$ for both). When compared to the pregnancies unaffected by neonatal morbidity, the median birthweight, either of the larger and the smaller twin, were significantly lower in the pregnancies complicated by neonatal morbidity ($p<0.001$ for both) (Table 1). The birthweight discordance was significantly higher in the affected (10.9, IQR 4.7- 20.7) compared to unaffected (8.7, IQR 4.0-14.6) twins ($p=0.002$). There was no significant difference in the proportion of pregnancies with birthweight discordance ≥5% ($p=0.692$) or ≥10% ($p=0.128$) between those complicated by neonatal morbidity and those which were not), while birthweight discordance ≥15%, ≥20%, ≥25% and ≥30% were significantly more common in the pregnancies affected by neonatal morbidity compared to those which were not ($p<0.001$ for all) (Table 1). The prevalence of at least one twin affected by SGA was significantly higher in the group affected by neonatal morbidity ($p<0.001$) (Table 1).

At multivariable logistic regression, gestational age at birth (OR 0.43, 95% CI 0.37-0.50; $p<0.001$), birthweight decile (OR 0.90, 95% CI 0.81-0.99; $p=0.029$), birthweight discordance (OR 11.03, 95% CI 1.01-1.05; $p=0.019$), but not chorionicity ($p=0.477$) or the presence of at least one SGA twin ($p=0.245$), were independently associated with the risk of neonatal morbidity. Likewise, the gestational age at birth (OR 0.42, 95% CI 0.36-0.49; $p<0.001$), birthweight decile (OR 0.86, 95% CI 0.79-0.95; $p=0.003$), birthweight discordance (OR 1.03, 95% CI 1.01-1.05; $p=0.018$) but not chorionicity ($p=0.314$) or the presence of at least one SGA twin ($p=0.107$), were independently associated with the risk of admission to the NICU (Table 2).

We then assessed the risk of neonatal morbidity according to the most commonly reported inter-twin birthweight discordance cut-offs (Table 3). When considering a threshold of 20%, the neonatal morbidity (30.7% vs 14.5%, $p<0.001$), gestational age a birth (36.4±1.3 vs 36.4±1.3, $p=0.011$) and the admission to the NICU (35.7% vs 17.1%, $p<0.001$) were significantly higher in the group affected by inter-twin birthweight discordance. Likewise, the neonatal morbidity (39.4% vs 15.1%, $p<0.001$) and the admission to NICU (43.7% vs 18.0%, $p<0.001$) but not gestational age at birth ($p=0.062$) were significantly higher in the twins affected by inter-twin birthweight discordance of 25%, compared

to those which were not. The pregnancy was complicated by neonatal morbidity of both twins in 44.7% (95% CI 36.8-52.7; 71/159) and was significantly higher in the smaller compared to the larger twin, both in the overall population and in the DC pregnancies ($p<0.001$), while there was no difference in MC gestations ($p= 0.772$)

There was a progressive increase in the risk of the neonatal morbidity with increasing birthweight discordance cut-offs (Table 4). Despite this association, the inter-twin birthweight discordance showed an overall poor predictive accuracy in detecting neonatal morbidity, with an AUC of 0.58 (95% CI 0.53-0.63) with an optimal cut-off of 17.6%, showing a sensitivity and a specificity of 35.2% (95% CI 27.8-43.2) and 83.2% (95% CI 80.0-85.8), respectively (Figure 1, Table 4). When looking at the diagnostic accuracy, either inter-twin birthweight 20% or 25% discordance showed a low sensitivity (27.0%, 95% CI 20.3-34.7 and 17.6%, 95% CI 12.0-24.4) in identifying the twins at risk of neonatal morbidity, while their specificity was 87.6 (95% CI 85.0-89.8) and 94.5% (95% CI 92.7-96.0), respectively (Table 5).

DISCUSSION

Summary of study findings

The findings of this study showed that the twin pregnancies affected by neonatal morbidity after 34 weeks have larger inter-twin birthweight discordance compared to those not affected. As expected, they were also delivered at an earlier gestational age. The risk of neonatal morbidity increased with increasing the degree of birthweight discordance. The gestational age at birth and birthweight discordance, but not chorionicity or diagnosis of SGA in either twin, were independently associated with the risk of neonatal morbidity. However, when used as a screening tool, an inter-twin birthweight discordance ≥25% had a high specificity but a low sensitivity in identifying those twin pregnancies complicated by neonatal morbidity.

Interpretation of study findings and comparison with existing literature

Despite the fact that the association between inter-twin weight discordance and adverse pregnancy outcome is well-established, there are no guidelines on how often ultrasound surveillance should be performed in MC and DC twin pregnancies which are affected by growth discordance, and therefore, the management is usually based on local practice. Several weight discordance cut-offs have been reported to be associated with an adverse pregnancy outcome in the published literature[2-20]. The National Institute for Health and Care excellence (NICE) guidance suggests that a fetal weight discordance ≥25% should prompt referral to a tertiary fetal medicine center, while the American College of Obstetricians and Gynecologist (ACOG) guidelines uses a cut-off of 20% to define significant weight discordance[28]. The inclusion of cases affected by anomalies or complications such as TTTS, which are more likely to experience an adverse perinatal outcome, differences in the definitions of adverse pregnancy outcome, lack of stratification of the analysis according to the chorionicity and the gestational age at assessment and at birth could explain such differences in the definitions of significant weight discordance.

We have previously reported that weight discordance was independently associated with the risk of perinatal mortality in twin pregnancies, irrespective of the chorionicity[2]. The findings from this study confirm that the weight discordance was associated with increased risk of neonatal morbidity, irrespective of the chorionicity. This finding may initially seem surprising in view of the reported association between monochorionicity and perinatal morbidity[1]. However, the current analysis included pregnancies delivering ≥34 weeks' gestation only, when the pregnancy loss or preterm birth due to the complications of monochorionicity, such as TTTS, are unlikely to occur. Regardless, the management of growth discordant twins cannot preclude from the chorionicity in view of the higher risk of mortality and adverse neurological outcome observed in case of co-twin demise in MC pregnancies[29].

Clinical and research implications

The inter-twin weight discordance is among the major determinants of perinatal outcome in twin pregnancies. If the assessment of the chorionicity during the first trimester of pregnancy is fundamental to stratify the obstetric risk and tailor the antenatal management of these pregnancies, assessment of the degree of weight discordance during the third trimester is warranted to anticipate the risk of fetal loss and adverse pregnancy outcome and to ensure that an appropriate follow-up and delivery plans are in place.

Furthermore, the degree of weight discordance associated with an adverse pregnancy outcome has been shown to be related to the gestational age at ultrasound, thus suggesting the need for gestational age-specific cut-offs or the use of reference ranges of weight discrepancy according to the gestational age at assessment.

Finally, although independently associated with pregnancy outcome, weight discordance per se should not be used as a primary indication for delivery, as shown by its poor predictive accuracy for perinatal mortality and morbidity[30,31]. In this scenario, an early iatrogenic delivery will reduce the mortality but will increase the morbidity since the gestational age at birth remains the main determinant of perinatal outcome in twin pregnancies[2].

The pathophysiology of discordant growth is different in MC and DC twin pregnancies. While the fact that discordant growth in DC twin pregnancy is mainly caused by discordant placental size and function, in MC twin pregnancy the magnitude of discordant growth is influenced not only by abnormal placental sharing but also by the direction of blood flow interchange through the placental anastomoses[32]. Therefore, the prenatal detection of discordant growth in a MC twin pregnancy should prompt a careful Doppler evaluation of the umbilical artery Doppler flow pattern in order to stratify the risk of adverse pregnancy outcome[33]. Conversely, the management of weight discordance in a DC twin pregnancy should be tailored according to the gestational age primarily. In this scenario, early iatrogenic delivery is likely to increase the risk of perinatal morbidity, given the overall small risk of mortality in twins affected by discordant growth.

In the present study, weight discordance was independently associated with perinatal morbidity while SGA, defined using twin specific growth charts, was not. This finding has been also reported by other studies on weight discordance in twin pregnancies and may seem initially surprising because low BW is universally recognized as an independent contributor to perinatal mortality and morbidity in singletons[34]. The pathophysiology of this association has not been clearly elucidated yet but it is plausible that weight discordance may represents a status of abnormal placental development and sharing between the two twins, leading to aberrant growth pattern and increased risk of adverse perinatal outcome irrespective of weight centile. Further studies exploring the growth trend in twins

affected by weight discordance are needed in order to provide a pathophysiological rationale for this finding.

Strengths and Limitations

The strengths of this study included firstly the large sample size, secondly the exclusion of cases affected by anomalies and TTTS, thirdly the assessment of the strength of the association and the predictive accuracy of weight discordance for neonatal morbidity and fourthly the stratification of the analysis including only twins born after 34 weeks of gestation in order to reduce the contribution of the gestational age at birth in determining the perinatal outcome. The retrospective design of the study and assessment of a composite score for neonatal morbidity in order to acquire statistical power represent its main limitations. Furthermore, although the inclusion of twins born after 34 weeks has theoretically reduced the actual independent contribution of gestational age on the observed outcomes, the gestational age at birth remained independently associated with the risk of neonatal morbidity. Therefore, the differences observed in the study groups might have been the result of late preterm birth rather than weight discordance per se. Another limitation of the study was the lack of stratification according to the severity of the different outcomes explored in view of the small number of events per each outcome, which would have been lowered the power of the analysis. Unfortunately, we could not stratify the analysis according to different gestational ages at birth in order to not reduce the power of the analysis which might have led to misleading results. Finally, the fetal Doppler data were not available for all the cases in the current analysis. However, twin pregnancies complicated by marked selective fetal growth restriction and abnormal Doppler findings are generally delivered before 34 weeks of gestation. Therefore, it is unlikely that our study cohort would have contained twin pregnancies with abnormal umbilical artery Doppler findings.

Conclusions

Weight discordance is independently associated with the risk of neonatal morbidity in twins born after 34 weeks' gestation, irrespective of chorionicity. However, its predictive accuracy for neonatal morbidity is poor. Large prospective multicentre studies sharing the same protocol of antenatal management are needed to ascertain the actual contribution of inter-twin weight discordance towards the risk of neonatal morbidity and to determine whether different weight discordance threshold should be used at different gestational ages.

REFERENCES

1. Miller J, Chauhan SP, Abuhamad AZ. Discordant twins: diagnosis, evaluation and management. *Am J Obstet Gynecol* 2012; **206**: 10-20.
2. D'Antonio F, Khalil A, Dias T, Thilaganathan B; Southwest Thames Obstetric Research Collaborative (STORK). Weight discordance and perinatal mortality in twins: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2013; **41**: 643-648.
3. Erkkola R, Ala-Mello S, Piiroinen O, Kero P, Sillanpää M. Growth discordancy in twin pregnancies: a risk factor not detected by measurements of biparietal diameter. *Obstet Gynecol* 1985; **66**: 203-206.
4. Sonntag J, Waltz S, Schollmeyer T, Schuppler U, Schroder H, Weisner D. Morbidity and mortality of discordant twins up to 34 weeks of gestational age. *Eur J Pediatr* 1996; **155**: 224-229.
5. Hollier LM, McIntire DD, Leveno KJ. Outcome of twin pregnancies according to intrapair birth weight differences. *Obstet Gynecol* 1999; **94**: 1006-1010.
6. Victoria A, Mora G, Arias F. Perinatal outcome, placental pathology, and severity of discordance in monochorionic and dichorionic twins. *Obstet Gynecol* 2001; **97**: 310-315.
7. Hartley RS, Hitti J, Emanuel I. Size-discordant twin pairs have higher perinatal mortality rates than nondiscordant pairs. *Am J Obstet Gynecol* 2002; **187**: 1173-1178.
8. Demissie K, Ananth CV, Martin J, Hanley ML, MacDorman MF, Rhoads GG. Fetal and neonatal mortality among twin gestations in the United States: the role of intrapair birth weight discordance. *Obstet Gynecol* 2002; **100**: 474-480.
9. Redman ME, Blackwell SC, Refuerzo JS, Kruger M, Naccasha N, Hassan SS, Berry SM. The ninety-fifth percentile for growth discordance predicts complications of twin pregnancy. Am *J Obstet Gynecol* 2002; **187**: 667-671.
10. Branum AM, Schoendorf KC. The effect of birth weight discordance on twin neonatal mortality. *Obstet Gynecol* 2003; **101**: 570-574.
11. Amaru RC, Bush MC, Berkowitz RL, Lapinski RH, Gaddipati S. Is discordant growth in twins an independent risk factor for adverse neonatal outcome? *Obstet Gynecol* 2004; **103**: 71-76.
12. Blickstein I, Keith LG. Neonatal mortality rates among growth-discordant twins, classified according to the birth weight of the smaller twin. *Am J Obstet Gynecol* 2004; 190: 170-174.
13. Vergani P, Locatelli A, Ratti M, Scian A, Pozzi E, Pezzullo JC, Ghidini A.Preterm twins: what threshold of birth weight discordance heralds major adverse neonatal outcome? *Am J Obstet Gynecol* 2004; **191**: 1441-1445.
14. Breathnach FM, McAuliffe FM, Geary M, Daly S, Higgins JR, Dornan J, Morrison JJ, Burke G. Definition of intertwin birth weight discordance. *Obstet Gynecol* 2011;118: 94-103.

15. Lanni R, Fusco D, Marinacci C, Grimaldi V, Corchia C, Mastroiacovo P. Birth weight discordancy in twins: new definition and standard. *Eur J Obstet Gynecol Reprod Biol* 1998; **76**: 37-40.
16. Hoopmann M, Kagan KO, Yazdi B, Grischke EM, Abele H. Prediction of birth weight discordance in twin pregnancies by second- and third- trimester ultrasound. *Fetal Diagn Ther* 2011; **30**: 29-34.
17. Diaz-Garcia C, Bernard JP, Ville Y, Salomon LJ. Validity of sonographic prediction of fetal weight and weight discordance in twin pregnancies. *Prenat Diagn* 2010; **30**: 361-367.
18. Gernt PR, Mauldin JG, Newman RB, Durkalski VL. Sonographic prediction of twin birth weight discordance. *Obstet Gynecol* 2001; **97**: 53-56.
19. Caravello JW, Chauhan SP, Morrison JC, Magann EF, Martin JN Jr, Devoe LD.Sonographic examination does not predict twin growth discordance accurately. *Obstet Gynecol* 1997; **89**: 529-533.
20. Chauhan SP, Shields D, Parker D, Sanderson M, Scardo JA, Magann EF. Detecting fetal growth restriction or discordant growth in twin gestations stratified by placental chorionicity. *J Reprod Med* 2004; **49**: 279-284.
21. Blickstein I, Kalish RB. Birthweight discordance in multiple pregnancy. *Twin Res* 2003; 6: 526-531.
22. Blickstein I, Mincha S, D Goldman R, A Machin G, G Keith L. The Northwestern twin chorionicity study: testing the 'placental crowding' hypothesis. *J Perinat Med* 2006; **34**: 158-61.
23. Dias T, Mahsud-Dornan S, Thilaganathan B, Papageorghiou A, Bhide A. First-trimester ultrasound dating of twin pregnancy: are singleton charts reliable? *BJOG* 2010; **117**: 979-984.
24. Dias T, Arcangeli T, Bhide A, Mahsud-Dornan S, Papageorghiou A, Thilaganathan B. Second-trimester assessment of gestational age in twins: validation of singleton biometry charts. *Ultrasound Obstet Gynecol* 2011; **37**: 34-37.
25. Lopriore E, Sluimers C, Pasman SA, Middeldorp JM, Oepkes D, Walther FJ. Neonatal morbidity in growth-discordant monochorionic twins: comparison between the larger and the smaller twin. *Twin Res Hum Genet* 2012; **15**: 541-546.
26. Stirrup OT, Khalil A, D'Antonio F, Thilaganathan B; Southwest Thames Obstetric Research Collaborative (STORK). Fetal growth reference ranges in twin pregnancy: analysis of the Southwest Thames Obstetric Research Collaborative (STORK) multiple pregnancy cohort. *Ultrasound Obstet Gynecol* 2015; **45**: 301-307.
27. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 2003; **56**: 1129-1135.

28. Multiple pregnancy. The management of twin and triplet pregnancies in the antenatal period. National Collaborating Centre for Women's and Children's Health. Commissioned by the National Institute for Clinical Excellence. September 2011.
29. Hillman SC, Morris RK, Kilby MD. Co-twin prognosis after single fetal death: a systematic review and meta-analysis. *Obstet Gynecol* 2011; **118**: 928-940.
30. D'Antonio F, Khalil A, Morlando M, Thilaganathan B. Accuracy of Predicting Fetal Loss in Twin Pregnancies Using Gestational Age-Dependent Weight Discordance Cut-Offs: Analysis of the STORK Multiple Pregnancy Cohort. *Fetal Diagn Ther* 2015; **38**: 22-28.
31. Leombroni M, Liberati M, Fanfani F, Pagani G, Familiari A, Buca D, Manzoli L, Scambia G, Rizzo G, D'Antonio F. Diagnostic accuracy of ultrasound in detecting birthweight discordance in twin pregnancies: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2016. doi: 10.1002/uog.17348. [Epub ahead of print].
32. Gratacós E, Lewi L, Muñoz B, Acosta-Rojas R, Hernandez-Andrade E, Martinez JM, Carreras E, Deprest J. A classification system for selective intrauterine growth restriction in monochorionic pregnancies according to umbilical artery Doppler flow in the smaller twin. *Ultrasound Obstet Gynecol* 2007; **30**: 28-34.
33. Buca D, Pagani G, Rizzo G, Familiari A, Flacco ME, Manzoli L, Liberati M, Fanfani F, Scambia G, D'Antonio F. Outcome in monochorionic twin pregnancies with selective intrauterine growth restriction according to the umbilical artery Doppler pattern of the smaller twin: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol* 2016. doi: 10.1002/uog.17362. [Epub ahead of print].

Table 1. Characteristics of the study cohort.

	Overall (n=939)	**Neonatal Morbidity* (n=159)**	**No Neonatal Morbidity (n=780)**	**P value***
Monochorionic twin pregnancies, n (%)[a]	179 (19.1)	31 (19.5)	148 (19.0)	0.876
Mean gestational age at birth in weeks (SD)[b]	36.7 (1.3)	35.5 (1.3)	36.9 (1.2)	<0.001
Median birthweight in grams (overall) (IQR)[c] • *Larger twin* • *Smaller twin*	2572.5 (2323.8-2824.5) 2700.0 (2460.0-2980.0) 2440.0 (2175.5-2679.0)	2267.5 (2005.8-2550.5) 2440.0 (2197.5-2705.0) 2120.0 (1777.5-2402.5)	2625.5 (2397.5-2860.0) 2750.0 (2520.0-3021.5) 2482.5 (2332.0-2711.5)	<0.001 <0.001 <0.001
Median birthweight decile (overall) (IQR)[c] • *Larger twin* • *Smaller twin*	4.53 (2.5-6.5) 5.07 (3.2-7.2) 3.88 (1.8-6.0)	3.05 (1.4-6.1) 3.99 (2.3-6.8) 2.25 (0.5-4.9)	4.81 (2.78- 6.6) 5.36 (3.4-7.3) 4.07 (2.2-6.1)	<0.001 <0.001 <0.001
Intertwin birthweight discordance:				
Median discordance in % (IQR)c	9.0 (4.2-15.4)	10.9 (4.7- 20.7)	8.7 (4.0-14.6)	0.002
Birthweight discordance ≥5%, n (%)[a]	644 (68.6)	114 (71.7)	530 (67.9)	0.692
Birthweight discordance ≥10%, n (%)[a]	424(45.1)	81 (50.9)	343 (43.9)	0.128
Birthweight discordance ≥15%, n (%)[a]	246 (26.1)	60 (37.7)	186 (23.8)	<0.001
Birthweight discordance ≥20%, n (%)[a]	140 (14.9)	43 (27.0)	97 (12.4)	<0.001
Birthweight discordance ≥25%, n (%)[a]	71 (7.6)	28 (17.6)	43 (5.5)	<0.001
Birthweight discordance ≥30%, n (%)[a]	31 (3.3)	15 (9.4)	16 (2.1)	<0.001
Small for gestational age affecting one or both twins, n (%)[a]	421 (44.8)	95 (59.7)	326 (41.3)	<0.001
Admission to the neonatal intensive care unit, n (%)[a]	187 (19.9)	156 (98.1)	31 (3.9)	<0.001

a Chi-squared test. B: T-test. c: Mann-Whitney U Test

*Combined outcome of: respiratory morbidity, infectious morbidity, neurological morbidity, hypoglycemia, hypothermia, jaundice, need for phototherapy, necrotizing enterocolitis, retinopathy.

Table 2. The results of the logistic regression model evaluating the potential predictors of neonatal morbidity and admission to the neonatal intensive care unit (NICU) in the twin pregnancies which delivered beyond 34 weeks' gestation*.

	Adjusted OR (95% CI)	P value		Adjusted OR (95% CI)	P value
	Neonatal morbidity			***Admission to NICU***	
Monochorionicity	1.20 (0.73-1.96)	0.477		1.48 (0.91-2.42)	0.314
Gestational age at birth in weeks	0.43 (0.37-0.50)	<0.001		0.42 (0.36-0.49)	<0.001
Birthweight decile	0.90 (0.81-0.99)	0.029		0.86 (0.79-0.95)	0.003
Small for gestational age affecting one or both	0.70 (0.38-1.28)	0.245		0.62 (0.35-1.11)	0.107
Birthweight discordance	1.03 (1.01-1.05)	0.019		1.03 (1.01-1.05)	0.018

* Combined outcome of: respiratory morbidity, infectious morbidity, neurological morbidity, hypoglycemia, hypothermia, jaundice, need for phototherapy, necrotizing enterocolitis, retinopathy.
OR = Odds Ratio; CI = Confidence interval.

Table 3. Characteristics of the study cohort in discordant versus concordant twins, stratified by the degree of birthweight discordance.

	BW discordance ≥20% (n=140)	**BW discordance <20% (n=799)**	**P value**		**BW discordance ≥25% (n=71)**	**BW discordance <25% (n=868)**	**P value ***
Monochorionic twin pregnancies, n (%)[a]	18 (12.9)	161 (20.0)	0.094		11 (15.4)	168 (19.4)	0.530
Mean gestational age at birth in weeks (SD)[b]	36.4 (1.3)	36.7 (1.3)	0.011		36.4 (1.3)	36.7 (1.3)	0.062
Median weight at birth in grams (IQR)[c]	2423.8 (2153.8-2673.5)	2598.0 (2350.0-2840.0)	<0.001		2302.5 (2059.0-2621.3)	2590.0 (2343.6-2835.0)	<0.001
Median birthweight decile (IQR)[c]	3.35 (1.6-5.7)	4.70 (2.6-6.6)	<0.001		2.67 (1.5-4.9)	4.69 (2.6-6.6)	<0.001
Small for gestational age affecting one or both, n (%)[a]	116 (82.8)	305 (38.2)	<0.001		67 (94.4)	354 (40.8)	<0.001
Neonatal morbidity, n (%)[a]	43 (30.7)	116 (14.5)	<0.001		28 (39.4)	131 (15.1)	<0.001
Admission to the neonatal intensive care unit, n (%)[a]	50 (35.7)	137 (17.1)	<0.001		31 (43.7)	156 (18.0)	<0.001

BW = birthweight; NICU = neonatal intensive care unit; SD = standard deviation.
a Chi-squared test. B: T-test. c: Mann-Whitney U Test
*Combined outcome of: respiratory morbidity, infectious morbidity, neurological morbidity, hypoglycemia, hypothermia, jaundice, need for phototherapy, necrotizing enterocolitis, retinopathy.

Table 4. Odd ratios (OR) for the risk of neonatal morbidity and admission to the neonatal intensive care unit (NICU) in twin pregnancies with different thresholds of birthweight discordance.

	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P Value		Unadjusted OR (95% CI)	P value	Adjusted* OR (95% CI)	P value
BW discordance threshold	***Neonatal morbidity***					***Admission to NICU***			
≥5%	1.20 (0.82-1.74)	0.354	1.06 (0.68-1.65)	0.785		1.37 (0.96-1.96)	0.087	1.08 (0.71-1.66)	0.712
≥10%	1.32 (0.94-1.86)	0.108	1.02 (0.66-1.57)	0.945		1.40 (1.02-1.93)	0.040	1.00 (0.66-1.52)	0.987
≥15%	1.94 (1.35-2.78)	<0.001	0.77 (0.48-1.23)	0.273		1.96 (1.39-2.75)	<0.001	0.83 (0.53-1.30)	0.414
≥20%	2.61 (1.73-3.93)	<0.001	1.78 (1.05-3.03)	0.032		2.68 (1.81-3.97)	<0.001	1.68 (1.00-2.81)	0.049
≥25%	3.66 (2.20-6.11)	<0.001	2.56 (1.33-4.95)	0.005		3.54 (2.15-5.83)	<0.001	2.14 (1.12-4.07)	0.021
≥30%	4.97 (2.41-10.29)	<0.001	3.78 (2.12-9.87)	0.007		5.27 (2.55-10.90)	<0.001	5.01 (2.67-9.98)	0.001

*: Adjusted for chorionicity, birthweight, gestational age at birth and SGA status.

Table 5. Summary estimates of sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-) of each birthweight discordance threshold to predict neonatal morbidity in twin pregnancies*.

BW discordance threshold	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
≥17.6% (optimal)	35.22 (27.8-43.2)	83.21 (80.4-85.8)	29.95 (23.5-37.1)	86,30 (83.6-88.7)	2.10 (1.6-2.7)	0.78 (0.68-0.87)	2.69 (1.8-4.0)
≥5%	71.70 (74.0-78.6)	32.05 (28.8-35.5)	17.70 (14.8-20.9)	84.75 (80.1-88.7)	1.06 (0.93-1.16)	0.88 (0.67-1.14)	1.19 (0.8-1.7)
≥10%	50.94 (42.9-59.0)	56.03 (52.5-59.5)	19.10 (15.5-23.2)	84.85 (81.5-87.8)	1.16 (0.97-1.36)	0.88 (0.73-1.02)	1.32 (0.9-1.9)
≥15%	37.74 (30.2-45.8)	76.15 (73.0-79.1)	24.39 (19.2-30.3)	85.71 (82.9-88.2)	1.58 (1.20-1.99)	0.82 (0.71-0.92)	1.94 (1.3-2.8)
≥20%	27.04 (20.3-34.7)	87.56 (85.0-89.8)	30.71 (23.2-39.1)	85.48 (82.9-87.9)	2.17 (1.57-2.96)	0.83 (0.75-0.91)	2.61 (1.7-4.0)
≥25%	17.61 (12.0-24.4)	94.49 (92.7-96.0)	39.44 (28.0-51.8)	84.91 (82.4-87.2)	3.19 (2.04-4.94)	0.87 (0.80-0.93)	3.66 (2.1-6.3)
≥30%	9.43 (5.4-15.1)	97.95 (96.7-98.8)	48.39 (30.2-66.9)	84.14 (81.6-86.5)	4.60 (2.34-8.96)	0.92 (0.87-0.96)	4.97 (2.2-11.0)

* Combined outcome of: respiratory morbidity, infectious morbidity, neurological morbidity, hypoglycemia, hypothermia, jaundice, need for phototherapy, necrotizing enterocolitis, retinopathy. BW = birthweight; CI = Confidence Interval.

Supplementary Table 1. Incidence of the individual components of neonatal morbidity.

Morbidity	Twins (n/N)	Proportion (95% CI)
Composite neonatal morbidity	159/939	16.9 (14.6-19.5)
Respiratory morbidity	55/939	5.9 (4.4-7.6)
Infectious morbidity	100/939	10.7 (8.7-12.8)
Neurological morbidity	15/939	1.6 (0.9-2.6)
Hypoglycaemia	33/939	3.5 (2.4-4.9)
Hypothermia	8/939	0.9 (0.4-1.7)
Jaundice	61/939	6.5 (5.0-8.3)
Need for phototherapy	43/939	4.6(3.3-6.1)
Necrotizing enterocolitis	6/939	0.6 (0.2-1.4)
Retinopathy	1/939	0.1 (0.003-0.6)

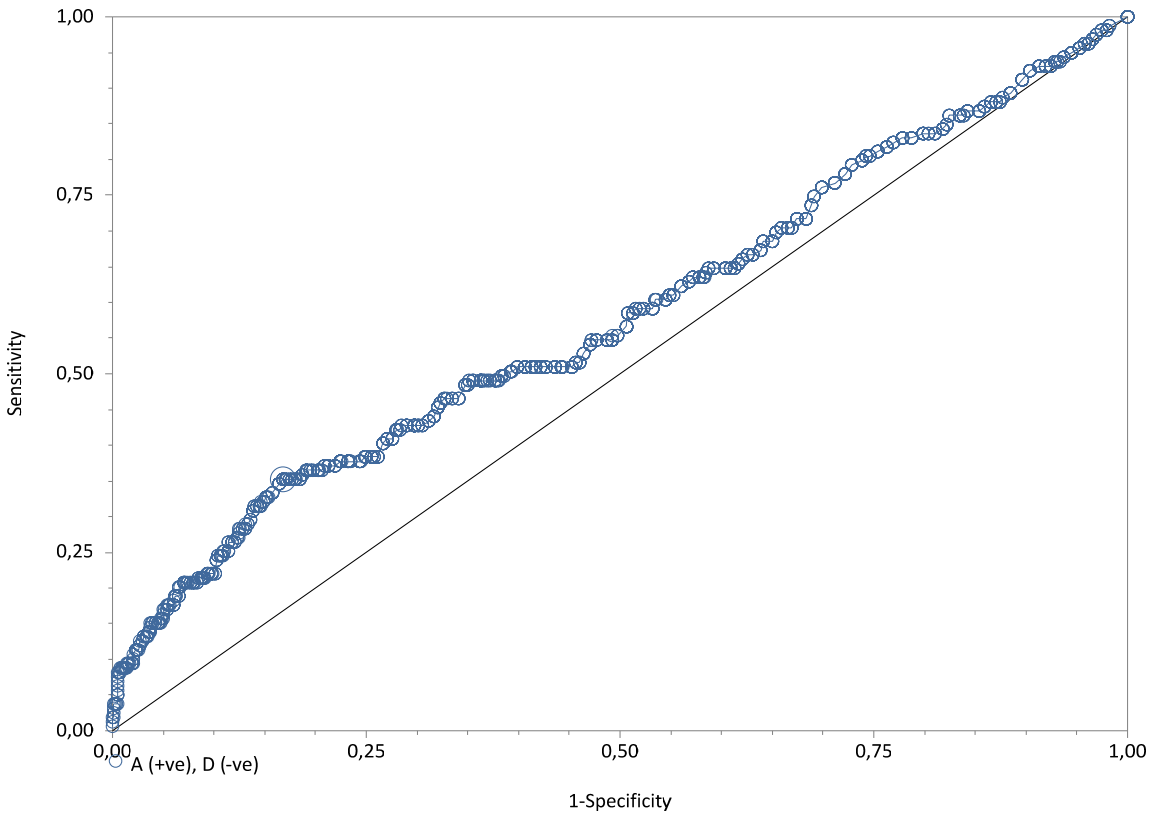

Figure 1

Receiver–operating characteristics curve for intertwin birthweight discordance

STORK contributors

Arash Bahamie, St Peter's Hospital
Amar Bhide, St George's University of London
Anne Deans, Frimley Park Hospital
Michael Egbor, St Helier's Hospital
Cheryl Ellis, Epsom General Hospital
Hina Gandhi, East Surrey Hospital
Rosol Hamid, Mayday University Hospital
Renata Hutt, Royal Surrey County Hospital
Adetunji Matiluko, St Helier's Hospital
Kim Morgan, Frimley Park Hospital
Faz Pakarian, Worthing Hospital
Aris Papageorghiou, St George's University of London
Elisabeth Peregrine, Kingston Hospital
Lesley Roberts, Royal Surrey County Hospital