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Birthweight discordance and neonatal morbidity in twin pregnancies: a systematic review and meta-analysis

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ABSTRACT

Introduction: The aim of this systematic review was to quantify the association between birthweight discordance and neonatal morbidity in twin pregnancies. **Material and methods:** Medline, Embase and Cinahl databases were searched. Studies reporting the occurrence of morbidity in twins affected compared to those not affected by birthweight discordance were included. The primary outcome was composite neonatal morbidity (including neurological, respiratory, infectious morbidities, abnormal acid-base status and necrotizing enterocolitis). The secondary outcomes were the individual morbidities. Sub-group analysis according to chorionicity, gestational age at birth and fetal weight (smaller vs larger twin) was also performed. Random-effect head-to-head meta-analyses were used to analyze the data. **Results:** Twenty studies (10851 twin pregnancies) were included. The

risk of composite morbidity was significantly higher in the pregnancies with birthweight discordance ≥15% (odds ratio (OR) 1.4, 95% confidence interval (CI); 1.0 to 1.9), ≥20% (OR 2.2, 95% CI; 1.40 to 3.45), ≥25% (OR 2.5, 95% CI; 1.8 to 3.6) and ≥30% (OR 3.4, 95% CI; 2.2 to 3.2). In dichorionic twins, birthweight discordance ≥15% (OR 2.4, 95% CI; 1.65 to 3.46), ≥20% (OR 2.2, 95% CI; 1.3 to 3.8), ≥25% (OR 2.7, 95% CI; 1.4 to 5.1) and ≥30% (OR 3.6, 95% CI; 2.3 to 5.7) were all significantly associated with composite neonatal morbidity. Analysis of monochorionic twins was hampered by the very small number of included studies which precluded adequate statistical power. Monochorionic twins with a birthweight discordance ≥20% were at significantly higher risk of composite neonatal morbidity (OR 2.2, 95% CI; 1.1 to 4.9) compared to those presenting with lesser degree of discordance. When stratifying the analysis according to gestational age at birth and fetal size, twins with birthweight discordance ≥15%, 20%, 25% and 30% delivered at ≥34 weeks were at higher risk of neonatal morbidity compared to controls, while there was no difference in the risk of morbidity between the larger and the smaller twin in the discordant pair. **Conclusions:** Birthweight discordance is associated with neonatal morbidity in twin pregnancies. The strength of this association persists for dichorionic twins while it was not possible to extrapolate robust evidence on monochorionic twins due to the low power of the analysis due to the small number of included studies.

Keywords

birthweight discordance, dichorionic twins, monochorionic twins, neonatal morbidity, twin pregnancies, ultrasound.

Abbreviations

MC monochorionic

DC dichorionic

BW birthweight

TTTS twin to twin transfusion syndrome

NEC necrotizing enterocolitis

NICU Neonatal Intensive Care Unit

CI confidence interval

OR odds ratio

NOS Newcastle-Ottawa Scale

Key message

Birthweight discordance is associated with neonatal morbidity in twins, mainly due to the higher risk in dichorionic twins.

INTRODUCTION

Twin pregnancies are at increased risk of perinatal mortality and morbidity compared to singletons mainly due to preterm birth, growth restriction and complications unique of monochorionic (MC) gestations, such as twin to twin transfusion syndrome (TTTS).[1,2] Birthweight (BW) discordance is unique to twin and high-order multiple gestations. Although it may represent a normal physiological variation, high degrees of discrepancy in fetal growth have been associated with poor perinatal outcome.[3-13] In view of this association, clinicians commonly report the degree of estimated weight discordance detected on ultrasound.[8]

In a recent systematic review, we reported that both dichorionic (DC) and MC twin pregnancies discordant for fetal growth are at higher risk of intrauterine death, especially as a result of growth restriction.[3] Besides mortality, BW discordance has also been reported to be associated with an increased risk of neonatal morbidity such as respiratory distress syndrome, sepsis, intra-ventricular hemorrhage and admission to neonatal intensive care unit.[9-13]Despite this, small sample size of previously published studies, inclusion of cases affected by fetal anomalies or TTTS, heterogeneity in prenatal management and outcomes' measures do not allow to extrapolate a robust evidence on the strength of association between discordant weight and morbidity. Furthermore, several BW discordance cut-offs have been proposed to be related with poor neonatal outcome, but which one provides the optimal combination of sensitivity and specificity is not known.

The aim of this systematic review was to quantify the association between BW discordance and neonatal morbidity in twin pregnancies.

MATERIAL AND METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to a priori designed protocol recommended for systematic reviews and meta-analysis.[14-16] Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched electronically in February 2018, utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "birthweight discordance" and "outcome" (Supporting Information Appendix S1). The search and selection criteria were restricted to English language. Reference lists of relevant articles and reviews were hand searched for additional reports. Prisma and MOOSE guidelines were followed.[17-19] The study was registered with the PROSPERO database (Registration number: CRD42016043062).

Study selection, data collection and data items

The primary outcome was the risk of a composite score of neonatal morbidity, defined as the occurrence of at least one of the following outcomes:

- 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).
- Neurological morbidity (including seizures, intra-ventricular hemorrhage and periventricular leukomalacia of any grade detected on ultrasound scan).
- Severe neurological morbidity (including seizures, intra-ventricular hemorrhage grade III and IV and periventricular leukomalacia grades II and III detected on ultrasound scan).
- Infectious morbidity (including pneumonia, meningitis, culture-proven sepsis).
- Abnormal acid-base status, defined as pH< 7.2.
- Necrotizing enterocolitis (NEC) (any grade).

BW discordance was calculated using the following equation: BW discordance (%) = (larger twin´s actual weight – smaller twin´s actual weight)/ larger twin´s actual weight) x100.[1] We stratified the

analysis according to the most commonly reported cut-offs of BW discordance (≥15%, ≥20%, ≥25% and ≥30% respectively).

The secondary outcome was the risk of individual neonatal morbidities (respiratory, neurological, or infectious morbidity, abnormal acid base status, NEC and admission to neonatal intensive care unit) in weight discordant compared to concordant twins.

All the observed outcomes were reported for the entire population of twin pregnancies and for MC and DC twins separately. Furthermore, sub-group analyses considering the risk of perinatal morbidity only in pregnancies delivered from 34 weeks of gestation and in the smaller compared to the larger twin were performed. In MC twins, we aimed to report the risk of mortality after exclusion of cases affected by TTTS.

Only studies reporting the risk of morbidity in discordant vs concordant twins and from which the raw numbers to calculate the risk of every explored outcome could be extrapolated were considered suitable for the inclusion. Studies including cases with fetal structural or chromosomal anomalies were excluded in view of the known higher risk of mortality and morbidity. Studies reporting the outcome of high order multiple gestations reduced to twins as well as studies exclusively reporting cases treated with intra-uterine therapy (laser treatment or cord ligation) were excluded. Finally, studies including cases with TTTS were also excluded. The reason for this choice was based on the fact that TTTS is an independent predictor of adverse outcome in MC twins. Despite being a hemodynamic anomaly, a certain degree of weight discordance is commonly associated with TTTS. Therefore, including cases affected by TTTS would have biased the analysis on the actual association between weight discordance and morbidity by adding an additional risk factor for adverse perinatal outcome. Furthermore, cases affected by TTTS can be affected by other comorbidities (for example, selective fetal growth restriction or twin anemia polycythemia sequence) and are commonly delivered before term, which may represent additional sources of bias and would have not allow to elucidate the actual association between weight discordance and the explored outcomes. Only full text articles were considered eligible for the inclusion. Case reports, conference abstracts and case series with fewer than 3 cases were excluded to avoid publication bias. Furthermore, studies published before 2000 were not included as advances in the management of twin pregnancies make them less relevant.

Three authors (DDM, DB) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus. Full text copies of those papers were obtained and the same reviewers independently extracted relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed by the reviewers and consensus reached or by discussion with a third author (FDA). If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. For those articles in which information was not reported but the methodology was such that this information would have been recorded initially, the authors were contacted.

Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for case-control studies. According to NOS, each study is judged on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment outcome of interest.[20] Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that outcome of interest was not present at start of study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, the ascertainment of the outcome of interest includes the evaluation of the type of the assessment of the outcome of interest, length and adequacy of follow-up. According to NOS a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.[20]

Statistical analyses

We examined one continuous outcome (mean maternal gestational age at birth), and eight categorical outcomes: (1) respiratory morbidity; (2) infectious morbidity; (3) neurological morbidity, all cases; (4) neurological morbidity, severe cases only; (5) NEC; (6) acid-base imbalance (cutoff pH<7.2); (7) admission to neonatal intensive care unit; (8) composite morbidity (including all cases with one neurological, respiratory or infectious morbidity, NEC, or an acid-base imbalance).

First, we performed random-effect meta-analyses of proportions to estimate the pooled rates of each categorical outcome in twins with a discordant intrauterine growth pattern vs twins with a concordant pattern. Second, we used random-effect head-to-head meta-analyses to directly

compare: (a) the risk of each categorical outcome, and (b) the mean gestational age at birth among discordant versus concordant twins, expressing the results (a) as summary odds ratio (OR), (b) as mean difference, plus relative 95% confidence interval (CI). The statistical heterogeneity was evaluated through I^2 metric.

All of the above 16 proportion, nine head-to-head, and eight diagnostic tool meta-analyses were stratified according to the degree of weight discordance (≥15%; ≥20%; ≥25%; ≥30%) in discordant fetuses and were carried out three times: (a) including all twins; (b) including DC twins only; (c) including MC twins only.

We were able to assess publication bias graphically, through funnel plots, and formally, through Egger's regression asymmetry test 2, only in two meta-analyses, because the formal tests for funnel plot asymmetry cannot be used when the total number of publications included for each outcome is <10 (the power is too low to distinguish chance from real asymmetry) 3. RevMan 5.3 (The Cochrane Collaboration, 2014) and Stata version 13.1 (Stata Corp., College Station, TX, USA) were used to analyze the data.

RESULTS

General characteristics

3594 articles were identified, 208 were assessed with respect to their eligibility for inclusion (Supporting Information Appendix S1 and S2) and 25 studies were included in the systematic review (Table 1, Supporting Information Table S1).[9-13, 23-42] Among them, 22 studies (including 11.470 twin pregnancies) reported the occurrence of morbidity in twins affected compared to those not affected by BW discordance, while 3 exclusively the occurrence of morbidity in the smaller compared to larger twin.[30,32,39]

The prevalence of BW discordance ≥15%, 20%, 25% and 30% was 25.6% (95% CI; 24.2 to 27.0), 17.0% (95% CI; 16.1 to 18.0), 10.9% (95% CI; 9.6 to 12.2) and 4.3% (95% CI; 3.3 to 5.5), respectively. When stratifying the analysis according to chorionicity, the prevalence of BW discordance ≥15%, 20%, 25% and 30% was 28.6% (95% CI; 25.4 to 31.9), 16.9% (95% CI; 15.8 to 18.0), 10.9% (95% CI; 9.6 to 12.2) and 4.5% (95% CI; 3.4 to 5.9) in DC pregnancies, while the corresponding figures in MC twins were 17.3% (95% CI; 12.1 to 23.7), 18.4% (95% CI; 16.5 to 20.5), 14.5% (95% CI; 11.5 to 18.5) and 2.8% (95% CI; 0.9 to 6.4), respectively.

The results of the quality assessment of the included studies using NOS are presented in Table 2. Most of the included studies showed an overall good score regarding the selection and comparability of the study groups, and for ascertainment of the outcome of interest. The main weaknesses of these studies were their retrospective design, small sample size, different gestational ages at scan, large heterogeneity in the definition of abnormal cut-offs for discordance and lack of information on prenatal management of twins affected by weight discordance. Furthermore, not all the included studies were matched case-control series, thus making entirely possible for other co-factors to affect the robustness of the results. More importantly, the majority of the analyses on MC twins were affected by the very small number of included cases and even smaller number of events which might have reduced the statistical power of the analysis and the robustness of the results. Finally, sub-group analyses according to the gestational age at birth (< vs ≥34 weeks of gestation) and fetal weight (smaller vs larger twin) could not be stratified according to chorionicity in view of the lack of data on MC and DC twins separately.

Synthesis of the results

BW discordance ≥15%

Three studies (7468 twins) explored the risk of composite neonatal morbidity in twins compared to those without a BW discordance ≥15% (figure 1).[9,23,35] When considering all twin pregnancies, the risk of composite morbidities was higher in twins when compared to those without a BW discordance ≥15% (OR 1.4, 95% CI; 1.0 to 1.9; I^2=52%, p=0.05). The strength of this association persisted when considering only DC twins (OR 2.4, 95% CI; 1.7 to 3.5; I^2=58%, p<0.001), while there was no difference in MC twins (p=0.9). Likewise, there was no difference in the risk of respiratory morbidity in discordant vs concordant DC (P=0.12) and MC (p=0.7) twins (Table 3, Supporting Information Table S2). Only one study explored the risk of neurological and infectious morbidity and NEC reporting a higher risk in discordant DC while no difference in MC twins (Table 3). The risk of admission to Neonatal Intensive Care Unit (NICU) was significantly higher in twins with a BW discordance ≥15% (OR 1.7, 95% CI; 1.40 to 2.11; I^2=30%, p<0.001) compared to controls. However, only one study stratifies the analysis according to chorionicity, reporting a higher risk in DC, but not in MC pregnancies (Table 3).

BW discordance ≥20%

Sixteen studies (17178 twin) explored the risk of composite neonatal morbidity in discordant twins compared to those not presenting with BW discordance ≥20% (figure 1).[9-13,24-25,27-29,31,34,36-37,40] Overall, the risk of neonatal morbidity was significantly higher in discordant twins (OR 2.2, 95% CI; 1.40 to 3.45; I^2=87%, p<0.001) and persisted when stratifying the analysis according to chorionicity (Table 4). Conversely, the risk of respiratory morbidity was not affected by BW discordance. Both DC (OR 2.5, 95% CI; 1.3 to 4.9) and MC (OR 1.9, 95% CI; 1.02 to 3.57) twins with a BW discordance ≥20% were at significantly higher risk of neurological morbidity compared to twins presenting with lesser degree of size discordance. Furthermore, the strength of this association persisted when considering only severe neurological morbidity (OR 4.4, 95% CI; 1.8 to 11.2 and 4.5, 95% CI; 1.3 to 15.6 for DC and MC twins, respectively). The risk of infectious morbidity was not significantly different between discordant and concordant twins (p=0.2). However, this lack of association was due to the non-significant risk of such morbidity in MC twins (p=0.2), while the risk of infectious morbidity was significantly higher in DC twins with a BW discordance ≥20% (OR 2.2, 95% CI; 1.7 to 3.0; I^2=0%, p<0.001). Finally, the risk of admission to NICU was significantly higher in DC (OR 1.7, 95% CI; 1.1 to 2.5; I^2=79%, p<0.001) but not in MC (p=0.06) discordant twins compared to controls.

BW discordance ≥25%

Five studies (5486 twins) explored the risk of neonatal morbidity in discordant twins compared to those not presenting a BW discordance ≥25% (figure 1).[9,33,38,41-42] The risk of composite neonatal morbidity was significantly higher in twins with compared to those without a BW discordance ≥25% (OR 2.5, 95% CI; 1.8 to 3.6; I^2=28%, p<0.001) (Table 5). The increased risk of morbidity in twins with BW discordance ≥25% compared to controls was due to the higher incidence of respiratory (OR: 2.7, 95% CI; 1.9 to 3.8; I^2: 19%, p<0.001) and infectious (OR 2.4, 95% CI; 1.5 to 4.0; I^2:0%, p= 0.006) morbidity and admission to NICU (OR 3.2, 95% CI; 2.2 to 4.3; I^2: 0%, p<0.001), while there was no difference between cases and controls as regard as neurological morbidity and NEC.

When stratifying the analysis according chorionicity, discordant DC (OR 2.7, 95% CI; 1.4 to 5.1; I^2=58%, p=0.004) but not MC (p=0.5) twins were at higher risk of morbidity compared to non-discordant pregnancies. Likewise, the risk of respiratory (OR 2.8, 95% CI; 1.6 to 4.7; I^2=0, p<0.001) and neurological (OR 6.8, 95% CI; 2.5 to 19.0; I^2=0%, p<0.001) morbidity was significantly higher in

DC but not MC twins. However, the computation of such outcomes in MC twins was affected by the inclusion of only three studies, thus making the analysis not adequately powered.

Ascertainment of the strength of association between BW discordance ≥25% and infectious morbidity, NEC and admission to NICU was affected by the very small number of included studies with only one publication reporting such risk in DC and MC twins separately (Table 5). In DC pregnancies, the risk of infectious morbidity (OR 3.0, 95% CI; 1.7 to 5.5, p<0.001) and admission to NICU (OR 3.3, 95% CI; 2.1 to 5.2, p<0.001), but not that of NEC (p=0.08), was significantly higher in discordant compared to concordant twins, while there was no association between BW discordance ≥25% and any of these outcomes (Table 5).

BW discordance ≥30%

The computation of the strength of association between BW discordance ≥30% and morbidity was affected by the inclusion of only two studies (2660 twins) (Figure 1).[9,26] Overall twins with BW discordance ≥30% were at higher risk of composite morbidity compared to controls (OR 3.4, 95% CI; 2.2 to 3.2; I^2=0%, p<0.001) and this association persisted in DC (OR 3.6, 95% CI; 2.3 to 5.7; I^2=0%, p<0.001) but not in MC (p=0.9) twins (Table 6). Furthermore, the risk of admission to NICU was significantly higher in discordant compared to concordant twins (OR 3.3, 95% CI; 2.2 to 5.2; I^2=0%, p<0.001).

Only one study including only twin pregnancies delivered from 34 weeks of gestation tried to ascertain the association between BW discordance ≥30% and the other outcomes explored in the present systematic review. Overall, discordant DC twins were at higher risk of respiratory (OR 3.8, 95% CI; 1.4 to 10.1, p=0.007), neurological (OR 8.93, 95% CI; 2.4 to 33.5, p=0.001), infectious (OR 3.1, 95% CI; 1.3 to 7.9, p=0.008) but not of NEC (p=0.05) compared to those with less degree of size discordance, while there was no association between BW discordance ≥30% and any of the explored outcomes in MC twins.

Sub-group analyses: pregnancies delivered ≥34 weeks of gestation and smaller vs larger twin

Sub-group analyses according to gestational age at delivery (< vs ≥34 weeks of gestation) and fetal weight (smaller vs larger twin in the discordant pair) were affected by the small number of included studies and even smaller incidence of events, which reduced the power of the analysis and precluded a comprehensive assessment of the strength of association between BW discordance and perinatal outcome in DC and MC twin pregnancies separately. In view of such limitations, the analysis was restricted to all twin pregnancies and not stratified according to chorionicity.

When considering only pregnancies delivered from 34 weeks of gestation, BW discordance was ≥ 15% (OR 1.6, 95% CI; 1.2 to 2.1), ≥ 20% (OR 2.0, 95% CI; 1.4 to 3.0), ≥ 25% (OR 3.0, 95% CI; 1.9 to 4.8) and ≥ 30% (OR 3.7, 95% CI; 2.0 to 7.0) were all associated with composite perinatal morbidity (Supporting Information Table S3).

Finally, when exploring the risk of morbidity according to fetal weight (smaller vs larger twin in the discordant pair), there was no difference in the occurrence of the different morbidities explored in the present systematic review between the smaller and larger discordant twin although the analysis was affected by the small number of included studies (Supporting Information Table S4).

DISCUSSION

The findings from this systematic review showed that BW discordance was associated with neonatal morbidity in twin pregnancies. The risk of morbidity in discordant compared to concordant twins was higher when increasing the cut-off of discordance and was mainly related to both mild and severe neurological events. Conversely, the risk of respiratory morbidity was generally not affected by growth discrepancy, except for a discordance of ≥25% and ≥30% in DC pregnancy.

Stratification of the analysis according to chorionicity showed that neonatal morbidity was increased in discordant (≥15%, 20%, 25% and 30%) compared to concordant DC twins. In MC pregnancies, a significant association between morbidity and BW discordance was found only for a cut-off of 20%. However, the robustness of the results might have been affected by the low power of analysis due to small number of MC twins included.

Similarly, the small number of included studies did not allow a comprehensive assessment of the association between BW discordance and morbidity according to gestational age at birth (< vs ≥34 weeks of gestation) and fetal weight (smaller vs larger twin) for DC and MC twins separately. Overall, twins with BW discordance ≥15%, 20%, 25% and 30% delivered from 34 weeks of gestations were at higher risk of morbidity compared to controls, while there was no difference in the risk of morbidity between the larger and the smaller twin in the discordant pair.

The major limitations of this systematic review are small number of included studies, their retrospective, non-randomized design, differences between the included populations, and dissimilar approach to the antenatal management of discordant twin pregnancies. The findings were also subject to potential publication bias because of the nature of some of the outcomes evaluated (outcome rates with the left-side limited to a value of zero), which limits the reliability of funnel plots, and because of the scarce number of individual studies, which strongly limits the reliability of formal tests. Furthermore, in some of the included studies, the strength of association between BW discordance and morbidity might have been affected by several co-factors which were not balanced between affected and not affected cases since not all the included studies were case-control series reporting matched populations.

Another limitation of our systematic review is related to the lack of stratification of the analyses according to chorionicity in the majority of the included studies. In view of the small number of studies which reported the data according to chorionicity, the subgroup analysis in MC twin pregnancies is likely to be statistically underpowered. Furthermore, the differences in the protocols of antenatal management of discordant twins and lack of inclusion of cases affected by TTTS may have influenced the results. Some of the included studies did not specify the type of prenatal surveillance adopted and the threshold of discordance used for delivery, while others did not consider the gestational age at scan and the individual weight centile when exploring the association between weight discordance and morbidity. Twin pregnancies affected by high degrees of weight discordance are routinely delivered before term in order to avoid fetal loss; in this scenario, the incidence of most of the explored outcomes is likely to be increased due of the effect of prematurity. Gestational age at birth is the major determinant of perinatal outcome in singletons.[43]

Unfortunately, in sub-group analyses, pregnancies delivered from ≥34 weeks of gestation and the occurrence of the explored outcomes in the smaller compared to larger twins could not be stratified according to chorionicity due to the lack of data on MC and DC twins separately. It may be entirely possible that the observed higher risk of morbidity in size discordant twins may be the results of iatrogenic preterm delivery in order to reduce mortality rather than the consequence of weight discordance per se. The effect of growth restriction on morbidity represents another peculiar issue. In a previous systematic review, we showed that twin pregnancies complicated by growth discordance were at high risk of intra-uterine death compared to those not affected and that this association was mainly due to the presence of at least a growth restricted fetus in the twin pair. In the present review, the sub-analysis comparing the smaller vs larger twin showed a similar risk of morbidity although it was affected by the very small number of included studies.

Finally, in the overall analysis, the prevalence of some of the observed outcomes was lower compared to that previously reported in the published literature. This was partially due to the fact that some of the included studies reported morbidity only in pregnancy approaching to term, thus reducing the occurrence of the explored morbidities.

Despite these limitations, the present study represents the most up-to-date and comprehensive published estimate of the association between BW discordance and neonatal morbidity in twin pregnancies.

Prenatal management of twins affected by weight discordance is challenging. There is no randomized trial comparing the different management options in twins affected by discordant growth. Furthermore, there is no consensus yet on which threshold of discordance should be used to define a pregnancy as at risk of adverse outcome.

The findings of our systematic review showed that BW discordance is associated with morbidity in DC but not in MC twin pregnancies, when pregnancies affected by TTTS were excluded. The lack of association between size discordance and morbidity in MC twins might have been the consequence of the low power of the analysis due the very small number of included studies. Another likely explanation for the lack of association between high degrees of weight discordance and morbidity in

MC twins is the high rate of morbidity in the control group. This is not surprising, as MC twin pregnancies are at higher risk of adverse perinatal outcome, irrespective of the presence of discordance, and are delivered at earlier gestational age in case of suspected complications. Furthermore, perinatal outcome in MC twins is not only determined by the presence and degree of placental sharing but also by the direction and magnitude of blood flow through the placental anastomoses which may be responsible for acute transfusion events leading to sudden fetal death and subsequent increased risk of neurological morbidity for the surviving co-twins irrespective of the degree of weight discordance. Therefore, despite the lack of association reported by this review, MC pregnancies discordant for fetal growth should be considered at high risk of perinatal mortality and morbidity and undergo an intensive surveillance. In MC twin pregnancies, selective intra-uterine growth restriction is commonly used as a synonym of weight discordance. Selective intra-uterine growth restriction is defined as the presence of a twin with estimated fetal weight less than 10th percentile and it is commonly associated with a discrepancy in fetal weight ≥25%.[44] Therefore, prenatal detection of discordant growth in MC twins should prompt a careful Doppler evaluation of the umbilical artery Doppler flow pattern in order to stratify the risk of adverse pregnancy outcome.[45]

Despite the reported association, it is the authors' opinion that weight discordance per se should not be used as a primary indication for delivery in order to reduce mortality and morbidity. Iatrogenic preterm birth may increase the risk of morbidity. Although there are no specific guidelines on how often ultrasound surveillance should be performed, apart from severity of weight discordance, other factors such as gestational age, chorionicity and fetal Doppler should be considered for determining the timing of delivery in growth discordant twins.[45] However, BW discordance was associated with an increased risk of morbidity even when only pregnancies delivered from ≥34 weeks of gestation were included in the analysis suggesting that growth discrepancy is associated with adverse perinatal outcome even at later gestational ages.

The findings from this systematic review showed that there was no difference in the risk of morbidity between the smaller and the larger twin in the discordant pair. However, the analysis was biased by the small number of included studies which did not allow a meaningful stratification of the results according to the gestational age at birth, thus it may be entirely possible that the lack of association between morbidity and growth restriction in the discordant pair may be due to the effect of prematurity in determining the perinatal outcome of twin.

CONCLUSION

BW discordance is associated with neonatal morbidity in twins. The strength of this association persists for DC twins while it was not possible to extrapolate robust evidence on MC pregnancies due to the small number of included studies and subsequent low statistical power of this subgroup analysis. Large, prospective studies sharing objective protocols of antenatal management and post-natal follow-up are needed to elucidate the actual association between discordant growth and morbidity in DC and MC twin pregnancies separately and to ascertain whether iatrogenic delivery may improve neonatal outcome in growth discordant twins.

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Supporting Information legends

Table S1: Excluded studies and reason for the exclusion.

Table S2: Proportion meta-analyses: pooled rates of each categorical outcome in twins with (discordant) and without (concordant) birthweight discrepancy. All analyses were performed considering: (1) all twins; (2) monochorionic twins only; (3) dichorionic twins only, and were stratified by degree of birthweight discordance. For each outcome, the pooled rates were computed only when >1 study could be included in the corresponding meta-analysis.

Table S3: Results of the head-to-head meta-analyses comparing the risk of each categorical outcome considering only pregnancies delivered from 34 weeks of gestation, according to different degrees of birthweight (BW) discordance.

Table S4: Results of the head-to-head meta-analyses comparing the risk of each categorical outcome in the smaller vs larger twin according to different degrees of birthweight (BW) discordance.

Appendix S1. Search strategy.

Appendix S2. PRISMA flow-diagram.

Figure Legend

Figure 1. Pooled odd ratios (95% confidence intervals) for the risk of composite morbidity in twins affected compared to those not affected by different degree of birthweight (BW) discordance.

Table 1. General characteristics of the studies included in the systematic review.

Author	Year	Country	Study design	Period considered	Chorionicity	Morbidity	Twin pregnancies	Cut-off (s) explored
D'Antonio[9]	2017	United Kingdom	Retrospective	2000-2010	DC, MC	Respiratory, neurological, infectious abnormal acid/base status, admission to NICU	939	20%, 25%
Vedel[23]	2017	Denmark	Retrospective	2004-2008	DC, MC	Respiratory, neurological, infectious, admission to NICU, NEC	2733	15%
Fumagalli[10]	2016	Italy	Retrospective	2007-2011	DC, MC	Respiratory, neurological, infectious, admission to NICU, NEC	734	20%
Van de Waarsenburg[24]	2015	The Netherlands	Retrospective	2008-2011	DC, MC	Respiratory, neurological, infectious, NEC	274	20%
Domingues[11]	2015	Portugal	Retrospective	2003-2010	DC, MC	Respiratory, neurological, infectious, NEC, admission to NICU	485	20%
Zuckerwise[25]	2014	United States	Retrospective	2007-2010	MC	Admission to NICU	73	20%
Egic[26]	2014	Serbia	Retrospective	2009-2012	DC	Admission to NICU	391	30%
Gupta[27]	2014	India	Prospective	2005	DC, MC	Respiratory, neurological, infectious, NEC	120	20%
Harper[28]	2013	United States	Retrospective	1990-2008	DC, MC	Respiratory, neurological, abnormal acid/base status, admission to NICU	1145	20%
Suzuki[29]	2012	Japan	Retrospective	2002-2010	DC, MC	Abnormal acid base status	832	20%
Lopriore[30]	2012	The Netherlands	Retrospective	2002-2011	MC	Respiratory, neurological, infectious	47	25%
Breatnach[31]	2011	Ireland	Prospective	2007-2009	DC, MC	Respiratory, neurological, admission to NICU	963	18%

Haimovic[32]	2011	Israel	Retrospective	2002-2007	DC, MC	Respiratory, neurological, infectious, NEC, admission to NICU	81	15%
Alam Machado[12]	2009	Brazil	Retrospective	1998-2004	DC, MC	Respiratory, neurological, infectious	151	20%
Lopriore[33]	2008	The Netherlands	Retrospective	2002-2008	MC	Neurological	117	25%
Appleton[34]	2007	Portugal	Retrospective	1989-2002	DC, MC	Abnormal acid/base status, composite	230	20%
Kilic[35]	2006	Turkey	Retrospective	2003-2005	DC, MC	Respiratory, neurological, infectious, NEC	68	15%
Canpolat[13]	2006	Turkey	Retrospective	2000-2004	DC, MC	Respiratory, infectious, NEC	266	20%
Pongpanich[36]	2006	Thailand	Retrospective	2003-2004	DC, MC	Respiratory, admission to NICU	150	20%
Cordero[37]	2005	United States	Retrospective	1990-2004	MC	Respiratory, neurological, LOS	74	20%
Leduc[38]	2005	Canada	Retrospective	1994-2002	DC, MC	Neurological, admission to NICU	503	25%
Yinon[39]	2005	Israel	Retrospective	1995-2000	DC-MC	Respiratory, neurological, infectious, NEC	96	15%
Adegbite[40]	2004	United Kingdom	Retrospective	1991-1997	DC, MC	Neurological	154	20%
Nassar[41]	2003	Lebanon	Retrospective	1984-2000	DC, MC	Respiratory, neurological, infectious, NEC	679	25%
Dashe[42]	2000	United States	Retrospective	1990-1998	DC, MC	Respiratory, neurological, infectious, abnormal acid base status, admission to NICU	513	25%

DC, dichorionic; MC, monochorionic; NICU, Neonatal Intensive Care Unit; NEC, necrotizing enterocolitis;

Table 2. Quality assessment of the included studies according to Newcastle-Ottawa Scale (NOS) a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Author	Year	Selection	Comparability	Outcome
D'Antonio[9]	2017	★★★	★	★★
Vedel[23]	2017	★★	★	★★
Fumagalli[10]	2016	★★	★	★★
Van de Waarsenburg[24]	2015	★★	★	★★
Domingues[11]	2015	★★	★	★★
Zuckerwise[25]	2014	★★	★	★★
Egic[26]	2014	★★	★	★
Gupta[27]	2014	★★	★★	★★
Harper[28]	2013	★★	★	★★
Suzuki[29]	2012	★★	★	★★
Lopriore[30]	2012	★★	★	★
Breatnach[31]	2011	★★	★	★
Haimovic[32]	2011	★★	★	★
Alam Machado[12]	2009	★★	★	★
Lopriore[33]	2008	★★★	★★	★★
Appleton[34]	2007	★★	★	★★
Kilic[35]	2006	★★	★	★★

Canpolat[13]	2006	★★	★	★★
Pongpanich[36]	2006	★★	★	★★
Cordero[37]	2005	★★	★	★★
Leduc[38]	2005	★★	★	★★
Yinon[39]	2005	★★	★	★
Adegbite[40]	2004	★★	★	★
Nassar[41]	2003	★★	★★	★★
Dashe[42]	2000	★★	★	★★

Table 3. Results of the head-to-head meta-analyses comparing the risk of each categorical outcome in twins with birthweight discordance ≥15% (discordant twins) versus twins without birthweight discordance (concordant twins). All outcomes were compared considering: (1) all twins; (2) dichorionic twins only; (3) monochorionic twins only.

	N. studies (sample)	**Study references**	**Raw data[a] (n/N vs n/N)**	**Pooled odds ratio (95% confidence interval)**	**p**	**I^2 (%)**
1. *All twins*						
Composite morbidity	3 (7468)	9,23,35	161/1912 vs 325/5556	1.38 (1.00-1.91)	0.05	52
Respiratory morbidity	3 (7468)	9,23,35	118/1912 vs 262/5556	1.25 (1.00-1.58)	0.05	0
Neurological morbidity	2 (2002)	9,35	11/542 vs 14/1460	1.80 (0.80-4.04)	0.15	0
Severe neurological morbidity	1 (1878)	9	7/494 vs 8/1384	2.47 (0.89-6.45)	0.08	--
Infectious morbidity	3 (7468)	9,23,35	56/1912 vs 125/5556	0.91 (0.39-2.10)	0.8	80
Necrotizing enterocolitis	2 (2002)	9,35	5/542 vs 12/1460	0.79 (0.26-2.39)	0.7	0
pH <7.2	0	-	-	-	-	-
Admission to NICU	3 (7480)	9,23,35	818/1918 vs 1717/5562	1.72 (1.40-2.11)	<0.001	30
2. *Dichorionic twins*						
Composite morbidity	1 (1710)	9	55/434 vs 73/1276	2.39 (1.65-3.46)	<0.001	-
Respiratory morbidity	1 (1710)	9	16/434 vs 29/1276	1.65 (0.89-3.06)	0.12	-

Neurological morbidity	1 (1710)	9	7/434 vs 6/1276	3.47 (1.16-10.4)	0.03	-
Severe neurological morbidity	1 (1710)	9	7/434 vs 6/1276	3.47 (1.16-10.4)	0.03	-
Infectious morbidity	1 (1710)	9	35/434 vs 43/1276	2.52 (1.59-3.99)	<0.001	-
Necrotizing enterocolitis	1 (1710)	9	0/434 vs 3/1276	0.42 (0.02-8.12)	0.6	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	1 (1710)	9	63/434 vs 89/1276	2.26 (1.61-3.19)	<0.001	-
3. *Monochorionic twins*						
Composite morbidity	1 (358)	9	5/62 vs 26/296	0.91 (0.34-2.47)	0.9	-
Respiratory morbidity	1 (358)	9	1/62 vs 7/296	0.68 (0.08-5.60)	0.7	-
Neurological morbidity	1 (358)	9	0/62 vs 2/296	0.94 (0.04-19.9)	0.9	-
Severe neurological morbidity	1 (358)	9	0/62 vs 2/296	0.94 (0.04-19.9)	0.9	-
Infectious morbidity	1 (358)	9	1/62 vs 19/296	0.24 (0.03-1.82)	0.2	-
Necrotizing enterocolitis	1 (358)	9	1/62 vs 2/296	2.41 (0.22-27.0)	0.5	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	1 (358)	9	7/62 vs 28/296	1.22 (0.51-2.93)	0.7	--

NICU, Neonatal Intensive Care Unit.

[a]The first "n/N" refers to e.g. the number of discordant twins with composite morbidity (n) / the total number of discordant twins (N); the second "n/N" refers to e.g. the number of concordant twins with composite morbidity / the total number of concordant twins.

Table 4. Results of the head-to-head meta-analyses comparing the risk of each categorical outcome in twins with birthweight discordance ≥20% (discordant twins) versus twins without birthweight discordance (concordant twins). All outcomes were compared considering: (1) all twins; (2) dichorionic twins only; (3) monochorionic twins only.

	N. studies (sample)	**Study references**	**Raw data[a] (n/N vs n/N)**	**Pooled odds ratio (95% confidence interval)**	**p**	**I^2 (%)**
1. *All twins*						
Composite morbidity	14 (16878)	9-13, 24, 25, 27-29, 31, 36, 37, 40	420/2699 vs 1117/14179	2.12 (1.44-3.15)	0.0002	86
Respiratory morbidity	9 (13794)	9-13, 27, 28, 31, 37	277/2063 vs 784/11731	1.58 (0.98-2.58)	0.06	86
Neurological morbidity	9 (8028)	9-12, 27, 28, 31, 37, 40	45/1494 vs 98/6534	1.88 (1.00-3.56)	0.05	55
Severe neurological morbidity	5 (3464)	9, 12, 28, 37, 40	16/536 vs 15/2928	4.12 (1.66-10.2)	0.002	15
Infectious morbidity	7 (12742)	9-13, 27, 31	122/1948 vs 395/10794	1.60 (0.93-2.76)	0.09	80
Necrotizing enterocolitis	7 (7276)	9-13, 27, 31	18/1426 vs 29/5850	2.79 (1.48-5.27)	0.002	0
pH <7.2	4 (2684)	12, 27, 28	32/506 vs 61/2178	2.26 (1.40-3.65)	0.008	0
Admission to NICU	6 (13416)	9, 11, 25, 28, 31, 36	588/1792 vs 2176/11624	2.31 (1.64-3.27)	<0.001	86
2. *Dichorionic twins*						
Composite morbidity	8 (7414)	9-12, 28, 29, 31, 40	226/1340 vs 592/6074	2.24 (1.33-3.79)	0.003	85
Respiratory morbidity	6 (6046)	9-12, 28, 31	176/1074 vs 507/4972	1.88 (1.01-3.52)	0.05	88

Neurological morbidity	7 (6196)	9-12, 28, 31, 40	26/1114 vs 50/5082	2.49 (1.26-4.92)	0.009	36
Severe neurological morbidity	4 (2656)	9, 12, 28, 40	8/388 vs 10/2268	4.42 (1.75-11.2)	0.002	0
Infectious morbidity	5 (5288)	9-12, 31	77/1026 vs 159/4262	2.23 (1.68-2.96)	<0.001	0
Necrotizing enterocolitis	5 (5288)	9-12, 31	9/1026 vs 16/4262	2.54 (0.79-8.21)	0.12	31
pH <7.2	3 (1860)	12, 28, 29	9/302 vs 23/1558	2.24 (1.00-5.01)	0.05	0
Admission to NICU	4 (5610)	9, 11, 28, 31	274/832 vs 871/4778	1.65 (1.07-2.54)	0.02	79
3. *Monochorionic twins*						
Composite morbidity	9 (2118)	9-12, 25, 28, 29, 31, 37	121/450 vs 264/1668	2.14 (1.14-3.99)	0.02	74
Respiratory morbidity	7 (1526)	9-12, 28, 31, 37	82/298 vs 178/1228	1.74 (0.84-3.65)	0.14	74
Neurological morbidity	8 (1592)	9-12, 28, 31, 37, 40	19/314 vs 32/1278	1.91 (1.02-3.57)	0.04	4
Severe neurological morbidity	5 (794)	9, 12, 28, 37, 40	10/144 vs 7/650	4.49 (1.29-15.6)	0.02	20
Infectious morbidity	5 (1230)	9-12, 31	18/266 vs 61/1322	1.41 (0.81-2.46)	0.2	0
Necrotizing enterocolitis	5 (1230)	9-12, 31	4/230 vs 8/1000	2.35 (0.69-8.00)	0.2	0
pH <7.2	3 (594)	12, 28, 29	4/150 vs 12/444	1.08 (0.36-3.24)	0.9	0
Admission to NICU	5 (1620)	9, 11, 25, 28, 31	107/260 vs 306/1360	1.91 (0.97-3.76)	0.06	72

NICU = Neonatal Intensive Care Unit.

[a]The first "n/N" refers to e.g. the number of discordant twins with composite morbidity (n) / the total number of discordant twins (N); the second "n/N" refers to e.g. the number of concordant twins with composite morbidity / the total number of concordant twins.

Table 5. Results of the head-to-head meta-analyses comparing the risk of each categorical outcome in twins with birthweight discordance ≥25% (discordant twins) versus twins without birthweight discordance (concordant twins). All outcomes were compared considering: (1) all twins; (2) dichorionic twins only; (3) monochorionic twins only.

	N. studies (sample)	**Study references**	**Raw data [a] (n/N vs n/N)**	**Pooled odds ratio (95% confidence interval)**	**p**	**I^2 (%)**
1. *All twins*						
Composite morbidity	5 (5486)	9, 33, 38, 41, 42	81/572 vs 322/4914	2.54 (1.82-3.55)	<0.001	28.4
Respiratory morbidity	4 (5268)	9, 38, 41, 42	59/524 vs205/4744	2.66 (1.9-3.8)	<0.001	18.9
Neurological morbidity	5 (5486)	9, 33, 38, 41, 42	12/572 vs 54/4914	2.12 (0.55-8.20)	0.3	64
Severe neurological morbidity	5 (5486)	9, 33, 38, 41, 42	12/572 vs 54/4914	2.12 (0.55-8.20)	0.3	64
Infectious morbidity	3 (4262)	9, 41, 42	20/394 vs 101/3868	2.42 (1.47-4.02)	0.006	0
Necrotizing enterocolitis	3 (4262)	9, 41, 42	2/394 vs 65/3868	0.34 (0.09-1.33)	0.1	0
pH <7.2	0	-	-	-	-	-
Admission to NICU	2 (2904)	9, 42	51/232 vs 222/2672	3.15 (2.24-4.43)	<0.001	0
2. *Dichorionic twins*						
Composite morbidity	2 (2276)	9, 38	36/200 vs 152/2076	2.65 (1.38-5.12)	0.004	58

Respiratory morbidity	2 (2276)	9, 38	19/200 vs 73/2076	2.78 (1.64-4.72)	<0.001	0
Neurological morbidity	2 (2276)	9, 38	6/200 vs 10/2076	6.82 (2.45-19.0)	<0.001	0
Severe neurological morbidity	2 (2276)	9, 38	6/200 vs 10/2076	6.82 (2.45-19.0)	<0.001	0
Infectious morbidity	1 (1520)	9	15/120 vs 63/1400	3.03 (1.67-5.51)	<0.001	-
Necrotizing enterocolitis	1 (1520)	9	1/120 vs 1/1400	11.76 (0.73-189)	0.08	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	1 (1520)	9	29/120 vs 123/1400	3.31 (2.09-5.23)	<0.001	-
3. *Monochorionic twins*						
Composite morbidity	3 (826)	9, 33, 38	17/120 vs 57/706	1.56 (0.42-5.79)	0.5	56
Respiratory morbidity	2 (608)	9, 38	12/72 vs19/536	3.64 (0.81-16.3)	0.09	31
Neurological morbidity	3 (826)	9, 33, 38	2/120 vs 10/706	1.75 (0.29.10.4)	0.5	30
Severe neurological morbidity	3 (826)	9, 33, 38	2/120 vs 10/706	1.75 (0.29.10.4)	0.5	30
Infectious morbidity	1 (358)	9	2/22 vs 20/336	1.58 (0.34-7.24)	0.6	-
Necrotizing enterocolitis	1 (358)	9	0/22 vs 13/336	0.53 (0.03-9.25)	0.7	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	1 (358)	9	2/22 vs 33/336	0.92 (0.21-4.10)	0.9	-

NICU = Neonatal Intensive Care Unit. .

[a] The first "n/N" refers to e.g. the number of discordant twins with composite morbidity (n) / the total number of discordant twins (N); the second "n/N" refers to e.g. the number of concordant twins with composite morbidity / the total number of concordant twins.

Table 6. Results of the head-to-head meta-analyses comparing the risk of each categorical outcome in twins with birthweight discordance ≥30% (discordant twins) versus twins without birthweight discordance (concordant twins). All outcomes were compared considering: (1) all twins; (2) dichorionic twins only; (3) monochorionic twins only.

	N. studies (sample)	**Study references**	**Raw data [a] (n/N vs n/N)**	**Pooled odds ratio (95% confidence interval)**	**p**	**I^2 (%)**
1. *All twins*						
Composite morbidity	2 (2660)	9, 26	31/114 vs 238/2546	3.35 (2.17-3.18)	<0.001	0
Respiratory morbidity	1 (1878)	9	5/62 vs 48/1816	3.23 (1.24-8.42)	0.02	-
Neurological morbidity	1 (1878)	9	3/62 vs 18/1816	7.64 (2.10-27.8)	0.002	-
Severe neurological morbidity	1 (1878)	9	3/62 vs 18/1816	7.64 (2.10-27.8)	0.002	-
Infectious morbidity	1 (1878)	9	8/62 vs 92/1816	2.78 (1.28-6.01)	0.009	-
Necrotizing enterocolitis	1 (1878)	9	0/62 vs 6/1816	2.23 (0.12-39.9)	0.6	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	2 (2660)	9, 26	33/114 vs 264/2546	3.34 (2.18-5.12)	<0.001	0
2. *Dichorionic twins*						
Composite morbidity	2 (2302)	9, 26	30/104 vs 208/2198	3.61 (2.31-5.66)	<0.001	0
Respiratory morbidity	1 (1520)	9	5/52 vs 40/1468	3.80 (1.43-10.1)	0.007	-
Neurological morbidity	1 (1520)	9	3/52 vs 10/1468	8.93 (2.38-33.5)	0.001	-

Severe neurological morbidity	1 (1520)	9	3/52 vs 10/1468	8.93 (2.38-33.5)	0.001	-
Infectious morbidity	1 (1520)	9	7/52 vs 71/1468	3.06 (1.33-7.03)	0.008	-
Necrotizing enterocolitis	1 (1520)	9	1/52 vs 3/1468	9.58 (0.98-93.6)	0.05	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	2 (2302)	9, 26	32/104 vs 230/2198	3.63 (2.34-5.63)	<0.001	0
3. *Monochorionic twins*						
Composite morbidity	1 (358)	9	1/10 vs 30/348	1.18 (0.14-9.61)	0.9	-
Respiratory morbidity	1 (358)	9	0/10 vs 8/348	1.91 (0.10-35.3)	0.7	-
Neurological morbidity	1 (358)	9	0/10 vs 2/348	6.60 (0.30-147)	0.2	-
Severe neurological morbidity	1 (358)	9	0/10 vs 2/348	6.60 (0.30-147)	0.2	-
Infectious morbidity	1 (358)	9	1/10 vs 21/348	1.73 (0.21-14.3)	0.6	-
Necrotizing enterocolitis	1 (358)	9	0/10 vs 3/348	4.70 (0.23-96.9)	0.3	-
pH <7.2	0	-	-	-	-	-
Admission to NICU	1 (358)	9	1/10 vs 34/348	1.03 (0.13-8.35)	0.9	-

NICU = Neonatal Intensive Care Unit. OR = Odds Ratio. CI = Confidence Interval.

[a]The first "n/N" refers to e.g. the number of discordant twins with composite morbidity (n) / the total number of discordant twins (N); the second "n/N" refers to e.g. the number of concordant twins with composite morbidity / the total number of concordant twins.