Weight discordance and perinatal mortality in twin pregnancies: a systematic review and meta-analysis

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Short title: Weight discordance and mortality in twins

Keywords: twin pregnancies, weight discordance, mortality, ultrasound

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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.18966

ABSTRACT

Objectives: The primary aim of this systematic review was to explore the strength of association between birthweight (BW) discordance and perinatal mortality in twin pregnancies; the secondary aim was to ascertain the contribution of gestational age and growth restriction in determining mortality in growth discordant twins.

Methods: Medline, Embase, Cinahl and Clinicaltrials.gov databases were searched. Only studies reporting the risk of mortality in twin pregnancies affected compared to those not affected by weight discordance were included. The weight discordance cut-offs considered were ≥15%, ≥20%, ≥25%, ≥30%. Meta-analyses using individual data random-effect logistic regression and meta-analyses of proportion were used to analyse the data.

Results: Twenty-two studies (10877 twin pregnancies) were included. In DC pregnancies, the overall risk of IUD, but not of NND, was higher in twins with ≥15% (OR: 9.8, 3.9-29.4), ≥20% (OR: 7.0, 95% CI 4.15-11.8), ≥25% (OR: 17.4, 95% CI 8.3-36.7) and ≥30% (OR: 22.9, 95% CI 10.2-51.6) BW discordance compared to controls. For each cut-off of BW discordance explored, the smaller twin was at higher risk of mortality compared to the larger one.

In MC twin pregnancies, twins discordant ≥20% (OR: 2.8, 95% CI 1.3-5.8) or ≥25% (OR: 3.2, 95% CI 1.49-6.67) were at higher risk of IUD, compared to controls once cases affected by twin-to twin transfusion syndrome were excluded. Twin pregnancies with ≥25% weight discordance were also at risk of NND (OR: 6.77, 95% CI 2.25-20.4). The risk of IUD was higher when considering only discordant pregnancies containing at least an SGA fetus. The overall risk of mortality was not different between the smaller and larger twin except for a weight discordance of ≥20%

Conclusion: DC and MC twin pregnancies discordant for fetal growth are at higher risk of IUD but not NND compared to concordant twins. The risk of IUD in discordant DC and MC twins is higher when at least one fetus is SGA.

INTRODUCTION

Birthweight (BW) discordance is one of the major determinants of perinatal outcome in twin pregnancies irrespective of chorionicity[1]. Although certain degree of growth discordance may represent a normal physiological variation, perinatal mortality and morbidity are known to be increased with higher degrees of discordance[2-13]. In view of this association, it is routine obstetric practice to regularly screen twin pregnancies by ultrasound to evaluate the degree of inter-twin fetal growth discordance, given its overall good diagnostic accuracy in identifying these disorders[14].

Despite this, there are still controversies on the actual role of discordant fetal growth in determining perinatal mortality. Although some studies have reported an increased risk for mortality in growth-discordant twins, others did not find any association. Heterogeneity in the study design, inclusion of fetuses affected by anomalies and lack of stratification of the analysis according to gestational age at birth and chorionicity are likely to explain such inconsistencies. Furthermore, a multitude of weight discordance cut-offs have been suggested to be associated with mortality, but it is yet to be established which one provides the best combination of sensitivity and specificity.

Finally, although the association between BW discordance and mortality outcome has been reported to be independent of chorionicity, antenatal management of discordant twins should be tailored according to chorionicity in view of higher risk of mortality and adverse neurological outcome observed in case of co-twin death in monochorionic (MC) pregnancies[15].

The primary aim of this systematic review was to explore the strength of association between BW discordance and perinatal mortality in twin pregnancies; the secondary aim was to ascertain the contribution of gestational age and growth restriction in determining mortality in discordant twins.

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[16-18]. Medline, Embase, Cinahl and Clinicaltrials.govdatabases were searched electronically on the 18.12.2016 utilizing combinations of the relevant medical subject heading (MeSH) terms, key words, and word variants for "birthweight discordance" and "outcome" (Supplementary Table 1). 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[19-21].

The study was registered with the PROSPERO database (Registration number: CRD42016043062).

Study selection, data collection and data items

The primary outcomes explored in the present systematic review were:

- Intra-uterine death (IUD)
- Neonatal death (NND)
- Perinatal death (PND)

IUD was defined as the death of at least one twin from 20 weeks of gestation onwards, while NND as the death of at least one of the new-borns up to 28 days of life, and perinatal death (PND) was defined as the occurrence of IUD and NND.

The secondary outcomes were the occurrence of IUD, NND and PND stratified according to the gestational age at death and birthweight of the twins. For the purpose of this analysis, twin pregnancies were divided into those in which IUD (or NND in case twins were delivered) occurred before and after 34 weeks of gestation and into SGA (twin pregnancy with BW of at least one twin <10 percentile and appropriate for gestational age (AGA) (both twins with BW ≥10 percentile). Finally, we assessed the risk of IUD, NND and PND in the smaller vs larger twin.

All the observed outcomes were reported for MC and DC twins separately. The reason for this choice was based upon the fact that, although the association between discordant growth and mortality has been reported to be independent from chorionicity, it is taken into account while managing twins with discordant growth. Furthermore, in MC twins, we reported the risk of mortality after exclusion of cases affected by twin-to-twin transfusion syndrome (TTTS).

BW discordance was defined as the percentage of discrepancy in birthweight between the large and the smaller twin and calculated by the following equation (larger actual weight –smaller actual weight)/ larger actual weight)[1]. We stratified the analysis according to the most commonly reported cut-offs of BW discordance (≥15%, ≥20%, ≥25% and ≥30%).

Only studies reporting the risk of mortality 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 anomalies were excluded in view of the higher risk of mortality in twins affected by structural or chromosomal anomalies. Studies reporting the outcome of high order multiple gestations reduced to twins as well 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. 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 management of twin pregnancies make them less relevant.

Two authors (FD, DB) reviewed all abstracts independently. Agreement regarding potential relevance was reached by consensus; full text copies of those papers were obtained and the same two 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. 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[22]. 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[22].

Statistical analysis

Overall, we evaluated the association between weight discordance and mortality (IUD, NND and PND) in twin pregnancies. The resulting meta-analyses were stratified according to chorionicity (MC or DC) and degree of weight discordance (≥15%; ≥20%; ≥25%; or ≥30%). Furthermore, all analyses were carried out four times: (a) including all pregnancies; (b) including only pregnancies ≥34 weeks; (c) including only pregnancies <34 weeks; (d) including only those pregnancies with ≥1 SGA twin; (e) including only those pregnancies with both AGA twins.

Some of the included observational case-control studies reported zero events in one or both compared groups, and the exposed and unexposed groups were frequently unbalanced. In such a case, the best performing methods are the Mantel-Haenszel odds ratio without zero-cell continuity corrections, logistic regression and an exact method[23,24]. Mantel-Haenszel odds ratios cannot be computed in studies reporting zero events in both groups, the exclusion of which may however cause a relevant loss of information and the potential inflation of the magnitude of the pooled exposure effect. Therefore, to keep all studies in the analyses, we performed all meta-analyses using individual data random-effect logistic regression with single study as the cluster unit. The pooled datasets with individual data were reconstructed using published 2X2 tables. When one of the overall pooled arms showed no events, we used exact logistic regression. If a meta-analysis included only one study in the comparison, the related odds ratio was computed from the raw data of the single study.

Some of the comparisons showed an extreme imbalance in the success rate between the groups being compared. Besides the computational issues, in such cases the odds ratios may be of limited interest and sensitivity and specificity could be more informative. We thus computed the overall sensitivity and specificity (and related 95% confidence intervals) for each comparison using the efficient-score method (corrected for continuity) described by Newcombe[25,26].

Finally, we performed meta-analyses of proportions to estimate the pooled rates of IUD, NND and PND of discordant twins, concordant twins, SGA twins and AGA twins, respectively. Proportion meta-analyses were not meaningful when only one study could be included, and were performed using a random-effect model to account for the inter-study heterogeneity.

The potential publication bias was assessed either graphically, displaying the odds ratios of individual studies vs the logarithm of their standard errors (funnel plots), and formally, using Egger's regression asymmetry test[27]. As the power of formal testing for funnel plot asymmetry is too low when less than 10 studies are included into a meta-analysis, we were able to evaluate the publication bias only for the meta-analyses reported in Supplementary Graphs 1-3[28].

All analyses were carried out using STATA, version 13.1 (Stata Corp., College Station, TX, 2013).

RESULTS

General characteristics

808 articles were identified, 210 were assessed with respect to their eligibility for inclusion (Supplementary Table 2) and 22 studies were included in the systematic review (Table 1, Figure 1) (14-25) [29-51]. These 22 studies included 10877 twin pregnancies.

In DC pregnancies, the prevalence of BW discordance ≥15%, 20%, 25% and 30% was 31.0% (95% CI 29.0-33.1), 23.4% (95% CI 22.4-24.5), 10.7% (95% CI 9.6-11.9) and 5.9% (95% CI 4.8-7.0) respectively, while the corresponding figures in MC twins were 44.2% (95% CI 39.1-49.4), 26.7% (95% CI 24.7-28.7), 16.5% (95% CI 14.6-18.5) and 12.6% (95% CI 8.6-17.6).

However, in view of the fact that some included studies were case controlled series, the figures reported here may not represent the actual prevalence of the different cut-offs of birthweight discordance in twin pregnancies.

Results of quality assessment of the included studies using Newcastle-Ottawa Scale (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.

Synthesis of the results

DC twin pregnancies

BW discordance ≥15%

Two studies (2001 pregnancies) explored the risk of mortality in twin with a BW discordance ≥15%[31,37]. The risk of PND was higher in discordant vs concordant twins with an OR of 3.6 (95% CI 2.0-6.5) and this was mainly due to the increased risk of IUD (OR: 9.8, 3.9-29.4) while there was no risk of NND in DC twins with BW discordance ≥15% compared to controls (Table 3).

When stratifying the analysis according to the gestational age, the risk of IUD after 34 weeks of gestation was higher in discordant compared to concordant twins (OR: 6.2, 95% CI 2.0-22.6), but there was no difference in the risk of NND.

Furthermore, the risk of IUD was higher when at least one twin was SGA (OR: 12.0, 95% CI 2.9-106), while there was no difference in appropriately grown discordant twins (p= 0.8). Likewise, the risk of NND was higher in discordant SGA twins compared to SGA concordant twins, with an OR of 9.2 (95% CI 2.8-47.7) (Table 3). Proportions for the occurrence of mortality in discordant and concordant twin pairs are reported in Supplementary Table 3.

BW discordance ≥20%

Eleven studies including 6795 twin pregnancies explored the risk of mortality in discordant twins ≥20%compared to controls[29,31,33,34-37,41,43,44,48,49]. The risk of PND was higher in DC twin pregnancies with a BW ≥20%, (OR 6.0, 95% CI 3.5-10.1) and this was due to the higher risk of IUD (OR: 7.0, 95% CI 4.2-11.8) rather than NND (Table 4). The risk of IUD in twin pregnancies with a BW≥20% was higher both before (OR: 5.4, 95% CI 2.1-13.8) and after (OR: 7.3, 95% CI 3.2-16.2) 34 weeks of gestation and in twin pairs containing at least an SGA fetus (OR: 12.7, 95% CI 5.6-28.7) (Table 4).

BW discordance ≥25%

Five studies including 2773 twin pregnancies explored the risk of mortality in discordant twins (≥25%) compared to controls[31,37,45,47,50]. The risk of PND was higher in DC twins with a BW discordance compared to controls (OR: 8.4, 95% CI 4.9-14.3). The association between discordant growth ≥25% and PND was due to the higher risk of IUD (OR: 17.4, 95% CI 8.3-36.7), as there was no difference in NND between concordant and discordant DC twins (Table 5).

The association between BW discordance ≥25% and IUD in DC twins persisted when stratifying the analysis according to the gestational age (OR: 21.2, 95% CI 7.2-69.7 for twins ≥34 and OR:10.0, 95% CI 2.7-44.8 for twins <34 weeks of gestation, respectively) and when at least an SGA twin was present (OR: 19.4, 95% CI 6.4-78.4),but there was no difference when both twins were AGA (Table 5).Pooled proportions for the occurrence of mortality in discordant and concordant twin pairs are reported in Supplementary Table 3.

BW discordance ≥30%

Only one study explored the risk of mortality in non-anomalous twins affected by BW discordance ≥30%[31]. The risk of PND was higher in discordant twin pregnancies with an OR of 13.8 (95% CI 7.1-26.5) and it was due to the higher risk of IUD (OR: 22.9, 95% CI 10.2-51.6), as there was no difference in NND (Table 6). The association between BW discordance ≥30% and IUD persisted when considering only twins born ≥34 (OR: 21.2, 95% CI 6.8-63.9) or <34 (OR: 13.6, 95% CI 3.7-54.3) weeks of gestation and when at least one SGA fetus was present in the twin pair (OR: 10.7, 95% CI 4.1-31.3). There was no difference in IUD when considering only AGA twins. The risk of

NND was higher in discordant twins < 34 weeks and in those SGA (OR of 13.2, 95% CI 1.3-66.8 and 13.1, 95% CI 1.0-691 respectively) (Table 6).

MC twin pregnancies

BW discordance ≥15%

One study (302 twin pregnancies) explored the risk of mortality in discordant vs concordant MC twins when a cut-off of 15% was applied to define discordance[31]. When excluding pregnancies affected by TTTS, the overall risk of either IUD, NND and PND was not significantly higher in pregnancies affected compared to those not affected by BW discordance. However, there was a higher risk of IUD ≥34 weeks of gestation (OR: 10.5, 95% CI 1.00-521) in discordant twins compared to controls and in case a SGA twin was present (OR: 8.0, 95% CI 1.04-355), while there was no difference in the risk of NND (Table 7). Proportions for the occurrence of mortality in discordant and concordant twin pairs are reported in Supplementary Table 4.

BW discordance ≥20%

Six studies including 1286 MC twin pregnancies explored the risk of mortality in twins with BW ≥20% compared to controls (Table 8) [29,31,34,39,44,46]. The risk of PND was higher in MC discordant twins compared to controls with an OR of 2.3 (95% CI 1.2-4.5). The risk of IUD was higher in discordant compared to concordant twins (OR: 2.8, 95% CI 1.3-5.8), while there was no difference in the risk of NND between the two groups. When stratifying the analysis according to the gestational age, the risk of IUD was higher in twins ≥34 weeks of gestation (Table 8). Furthermore, there was an increased risk of IUD when at least one SGA fetus was present in the discordant pair.

BW discordance ≥25%

Five studies (993 MC twin pregnancies) explored the risk of mortality when a 25% cut-off was applied to define discordance[31,35,38,42,45]. The risk of PND was higher in discordant compared to concordant MC twin pairs with an OR of 3.2 (95% CI 1.9-5.4). The risk of IUD and NND was higher in discordant twins with an OR of 3.2 (95% CI 1.49-6.67) and 4.7 (95% CI 1.8-12.4) (Table 9). The risk of IUD was higher when considering only discordant pregnancies containing at least an SGA fetus (OR: 4.6, 95% CI 1.68-12.8), while there was no difference in the occurrence of NND. Pooled proportions for the occurrence of mortality in discordant and concordant twin pairs are reported in Supplementary Table 4.

BW discordance ≥30%

Only one study including 303 MC twin pregnancies explored the risk of mortality in non-anomalous discordant twins ≥30%[31]. In view of the small number of included cases and even smaller number of events it was not possible to perform a meaningful risk stratification. The risk of IUD was higher in discordant twin pregnancies compared to controls, with an OR of 14.3 (95% CI 1.1-136), while this association did not persist when considering only cases < 34 weeks of gestation (Table 10).

Smaller vs larger twin

Table 11 shows the risk of mortality in the smaller vs larger twin in DC pregnancies. For each cut-off of BW discordance explored in the present review, the smaller twin was at higher risk of IUD but not NND compared to the larger one.

The assessment of the risk of mortality between the smaller and the larger twin in MC twins was affected by the small number of included cases and events. The risk of PND was higher in the smaller twin with ≥20% risk of discordance (OR: 4.2, 95% CI 1.7-15.1) (Table 12). Pooled proportions for the occurrence of mortality in the smaller and larger twins are reported in Supplementary Table 5 and 6.

DISCUSSION

Main findings

The findings from this systematic review showed that DC and MC twin pregnancies discordant for fetal growth were generally at higher risk of IUD but not NND compared to concordant twins. The risk of IUD in discordant twins was higher when at least one fetus was SGA, while it was not increased when considering only AGA twins. When comparing the smaller and the larger twin, the risk of IUD was usually higher in the smaller than in the larger twins in DC, while in MC there was an increased risk of PND in the smaller twin for a discrepancy ≥20%.

Strengths and limitations

The small number of cases in some of the included studies, their retrospective non-randomized design, different definitions of IUD and NND among the included studies, dissimilarity of the populations (due to various inclusion criteria), use of estimated fetal weight as a proxy for BW discordance in some of the included studies and lack of standardized criteria for the antenatal management of discordant twin pregnancies represent the major limitations of this systematic review. Assessment of the potential publication bias was also problematic because of the nature of the outcome 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. Not all the included studies were case-control series reporting matched populations and it might be entirely possible that the presence and degree of association between BW discordance and mortality might have been affected by several co-factors which were not balanced between cases affected and not affected by discrepancy in twin size, such as gestational age at birth, severity of growth restriction and maternal co-morbidities.

Another major limitation of this systematic review was the differences in the antenatal management of discordant twins. Furthermore, the interval between the occurrence of IUD and birth was not reported in the large majority of the included studies; this is fundamental because a larger interval between IUD and birth may significantly affect the degree of weight discordance and consequently the magnitude of its effect on the outcomes explored in the present review. Finally, the majority of the included studies did not stratify the analysis according to the gestational age at birth or detection of discordant growth and birthweight centile of the twins, thus considerably reducing the number of cases included in these sub-analyses and, consequently, their power.

Despite these limitations, the present review represents the most comprehensive published estimate of the investigated outcomes in twin pregnancies affected by discordant growth.

Implications for clinical practice

Management of twin pregnancies affected by weight discordance is challenging. There is no randomized trial assessing the different management options (expectant management vs delivery) when a discrepancy in fetal size is detected during pregnancy. Furthermore, there is still no consensus on which cut-off of discordance should be adopted in clinical practice.

In the present systematic review, BW discordance was associated with an increased risk of IUD and such association was independent from gestational age, with increased risk of mortality either before and after 34 weeks of gestation. Conversely, twins discordant for fetal growth were not at higher risk of NND, except for a discrepancy of ≥20% in MC pregnancies. The generally lack of association between BW discordance and NND confirms the findings from singleton pregnancies, where gestational age at birth represents the main risk factor for neonatal mortality[51]. In this scenario, weight discordance per se should not be used as a primary indication for delivery, and other factors such as gestational age at assessment, chorionicity and fetal Dopplers should be considered when managing discordant twins[52].

The association between discordant growth and mortality was stronger when considering twin pregnancies containing at least one SGA fetus, while the risk was not increased when both twins were AGA. It has been recently suggested that discordant growth in appropriately grown twins may represent a risk factors for adverse perinatal outcome, irrespective of fetal weight[29]. In the present systematic review, we did not find an increased risk of either IUD and NND in appropriately grown discordant twins, although the small number of cases included in this analysis might have underestimated this association. Therefore, these results should be interpreted with caution and further evidence is needed to ascertain whether discordant AGA twins should be considered at high risk of perinatal compromise. Until then, AGA discordant twins should be still considered at risk of adverse perinatal outcome and worth of close follow-ups in order to detect signs of fetal compromise, such as abnormal growth trend and Doppler.

When comparing the smaller and larger twin, the risk of IUD was higher in the smaller twin in DC twins while there was no difference in MC pregnancies. The pathophysiology of discordant growth is different in MC and DC twin pregnancies; while in DC discordant growth is mainly caused by discordant placental size and function, in MC 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, and this might partially explain why the risk of mortality was similar between the smaller and larger twin. Furthermore, due to the presence of such anastomoses, single IUD in a MC pair may lead to co-twin death in a considerable number of cases[15].

Large prospective studies aiming at assessing the optimal management options and the outcome of discordant twins according to the degree of weight discrepancy, gestational age at assessment, Doppler findings and chorionicity are needed to elucidate the actual association between discordant growth and perinatal mortality in twin pregnancies.

Accepted Article

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Table 1. General characteristics of the included studies. Gestational age (in case of IUD) or days at outcome is reported between parentheses.

Author	Year	Country	Study design	Period considered	Chorionicity	Twin pregnancies	Mortality	Cut-off (s) explored
Harper[29]	2013	United States	Retrospective	1990-2008	DC, MC	1145	IUD (≥ 24w)	20%
Lopriore[30]	2012	The Netherlands	Retrospective	2002-2011	MC	47	NND (NS)	25%
D'Antonio[31]	2012	United Kingdom	Retrospective	2000-2010	DC, MC	2161	IUD (≥ 24w), NND (28d)	15%; 20%; 25%; 30%
Nakayama[32]	2012	Japan	Retrospective	2004-2010	MC	198	NND (28d)	25%
Suzuki[33]	2012	Japan	Retrospective	2002-2010	DC, MC	832	IUD (≥ 22w)	20%
Mahony[34]	2011	Ireland	Retrospective	1997-2006	DC, MC	1094	IUD (≥ 24w)	20%
Weisz[35]	2011	Israel	Prospective	2004-2008	MC	128	IUD (≥ 24w), NND (NS)	25%
Breatnach[36]	2011	Ireland	Prospective	2007-2009	DC, MC	963	PND (≥ 24w to 28d)	18%
Diaz-Garcia[37]	2010	France/Spain	Retrospective	2004-2007	DC, MC	283	PND (≥ 22w to 8d)	15%; 20%; 25%
Smith[38]	2010	United States	Retrospective	2001-2008	MC	270	IUD (≥ 24w), NND (NS)	25%
De Paepe[39]	2010	United States	Retrospective	2001-2009	MC	216	IUD	20%
Shrim[40]	2010	Canada/Israel	Retrospective	2001-2007	MC	93	IUD (≥ 25w), NND (28d)	20%
Alam Machado[41]	2009	Brazil	Retrospective	1998-2004	DC, MC	151	NND (7d)	20%
Lewi[42]	2008	Belgium/Germany/Spain	Prospective	2002-2007	MC	178	IUD (≥ 24w), NND (NS)	25%
Appleton[43]	2007	Portugal	Retrospective	1989-2002	DC, MC	230	IUD (≥ 34w), NND (NS)	20%
Hack[44]	2007	The Netherlands	Retrospective	1995-2004	DC, MC	1305	IUD (≥ 20w), NND (7d)	20%
Acosta-Rojas[45]	2007	Spain	Prospective	NS	DC, MC	219	IUD (≥ 20w), NND (28d)	25%*
Cordero[46]	2005	United States	Retrospective	1990-2004	MC	74	IUD (≥ 20w), NND (1d)	20%
Leduc[47]	2005	Canada	Retrospective	1994-2002	DC, MC	503	NND (1m)	25%
Adegbite[48]	2004	United Kingdom	Retrospective	1991-1997	DC, MC	154	NND (NS)	20%
Geipel[49]	2002	Germany	Retrospective	1998-2001	DC	256	IUD (≥ 24w)	20%
Victoria[50]	2001	United States	Retrospective	1993-1995	MC, DC	377	PND (≥ 24w) [a]	25%

*: and 1 twin EFW <10th pc for GA.
W: weeks of gestation; d: days; m: months; NS: not stated
a: time at neonatal death not reported

Table 2. Quality assessment of the included studiesaccording 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
Harper[29]	2013	★★	★	★★
Lopriore[30]	2012	★★	★	★★
D'Antonio[31]	2012	★★	★	★★
Nakayama[32]	2012	★★	★	★★
Suzuki[33]	2012	★★	★	★★
Mahony[34]	2011	★★	★	★★
Weisz[35]	2011	★★	★	★
Breatnach[36]	2011	★★	★★	★★
Diaz-Garcia[37]	2010	★★	★	★★
Smith[38]	2010	★★	★	★★
De Paepe[39]	2010	★★	★	★
Shrim[40]	2010	★★	★	★
Alam Machado[41]	2009	★★★	★★	★★
Lewi[42]	2008	★★	★	★★
Appleton[43]	2007	★★	★	★★
Hack[44]	2007	★★	★	★★
Acosta-Rojas[45]	2007	★★	★	★★
Cordero[46]	2005	★★	★	★★
Leduc[47]	2005	★★	★	★
Adegbite[48]	2004	★★	★★	★★
Geipel[49]	2002	★★	★	★★
Victoria[50]	2001	★★	★	★★

Table 3. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in dichorionic twins with birthweight discordance ≥15% (discordant twins) versus dichorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	Fetuses (n/N vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
IUD in discordant vs concordant twins						
- All pregnancies	1 (1859)[31]	(25/569 vs 6/1290)	9.83 (3.90-29.4)	<0.001	80.6 (61.9-91.9)	70.2 (68.1-72.3)
- Pregnancies ≥34 weeks	1 (1618)[31]	(12/459 vs 5/1159)	6.20 (2.01-22.6)	<0.001	70.6 (44.0-88.6)	72.1 (69.8-74.3)
- Pregnancies <34 weeks	1 (253)[31]	(13/110 vs 8/143)	2.26 (0.83-6.53)	0.07	61.9 (38.7-81.0)	58.2 (51.5-64.6)
- ≥ 1 SGA twin	1 (839)[31]	(22/411 vs 2/428)	12.0 (2.92-106)	<0.001	91.7 (71.5-98.5)	52.3 (48.8-55.7)
- Both AGA twins	1 (1020)[31]	(3/158 vs 4/862)	4.15 (0.60-24.7)	0.8	42.9 (11.8-79.8)	84.7 (82.3-86.8)
NND in discordant vs concordant twins						
- All pregnancies	1 (1859)[31]	(4/569 vs 13/1290)	0.69 (0.16-2.26)	0.5	23.5 (7.8-50.2)	69.3 (67.2-71.4)
- Pregnancies ≥34 weeks	1 (1618)[31]	(1/459 vs 5/1159)	0.50 (0.01-4.52)	0.5	16.7 (0.9-63.5)	71.6 (69.3-73.8)
- Pregnancies <34 weeks	1 (253)[31]	(3/110 vs 1/143)	3.98 (0.31-210)	0.2	75.0 (21.9-98.7)	57.0 (50.6-63.2)
- ≥ 1 SGA twin	1 (839)[31]	(3/411 vs 1/428)	3.14 (0.25-165)	0.3	75.0 (21.9-98.7)	51.1 (47.7-54.6)
- Both AGA twins	1 (1020)[31]	(1/158 vs 12/862)	0.45 (0.01-3.09)	0.4	7.7 (0.4-37.9)	84.4 (81.9-86.6)
PND in discordant vs concordant twins						
- All pregnancies	2 (2001)[31,37]	(30/621 vs 19/1380)	3.64 (2.03-6.52)	<0.001	61.2 (46.2-64.4)	69.7 (67.6-71.7)
- Pregnancies ≥34 weeks	1 (1618)[31]	(13/459 vs 10/1159)	1.75 (0.79-3.76)	0.12	56.5 (34.9-76.1)	72.0 (69.7-74.2)
- Pregnancies <34 weeks	1 (253)[31]	(16/110 vs 9/143)	2.53 (1.01-6.78)	0.03	64.0 (42.6-81.3)	58.8 (52.1-65.2)
- ≥ 1 SGA twin	1 (839)[31]	(25/411 vs 3/428)	9.17 (2.76-47.7)	<0.001	89.3 (70.6-97.2)	52.4 (48.9-55.9)
- Both AGA twins	1 (1020)[31]	(4/158 vs 16/862)	1.37 (0.33-4.33)	0.6	20.0 (6.6-44.3)	84.6 (82.8-86.7)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 4. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in dichorionic twins with birthweight discordance ≥20% (discordant twins) versus dichorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	Fetuses (n/N vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
IUD in discordant vs concordant twins						
- All pregnancies	7 (5675)[29,31,33,34,43,44,49]	(40/1331 vs 24/4344)	7.0 (4.15-11.8)	<0.001	62.5 (49.5-74.0)	77.0 (75.9-78.0)
- Pregnancies ≥34 weeks	4 (3664)[31,34,43,44]	(20/1036 vs 10/2628)	7.25 (3.24-16.2)	<0.001	66.7 (47.1-82.1)	72.0 (70.5-73.5)
- Pregnancies <34 weeks	2 (972)[31,34]	(13/225 vs 7/747)	5.37 (2.09-13.8)	<0.001	65.0 (40.9-83.7)	77.7 (74.9-80.3)
- ≥ 1 SGA twin	2 (1073)[31,33]	(40/367 vs 7/706)	12.7 (5.60-28.7)	<0.001	85.1 (71.1-96.3)	68.1 (65.2-70.9)
- Both AGA twins	4 (2448)[29,31,33]	(4/161 vs 24/2287)	2.51 (0.85-7.40)	0.09		
NND in discordant vs concordant twins						
- All pregnancies	5 (3385)[31,41,43,44,48]	(8/1021 vs 29/2364)	0.90 (0.40-2.04)	0.8	21.6 (10.4-38.7)	69.7 (68.2-71.3)
- Pregnancies ≥34 weeks	3 (2945)[31,43,44]	(1/892 vs 8/2053)	0.29 (0.04-2.30)	0.2	11.1 (0.6-49.3)	69.7 (67.9-71.3)
- Pregnancies <34 weeks	2 (328)[31,34]	(4/101 vs 15/227)	0.59 (0.19-1.84)	0.4	21.1 (7.0-46.1)	68.6 (63.1-73.7)
- ≥ 1 SGA twin	2 (1002)[31,33]	(3/292 vs 3/710)	2.45 (0.49-12.2)	0.3	50.0 (13.9-86.1)	71.0 (68.0-73.8)
- Both AGA twins	2 (1178)[31,43]	(0/82 vs 15/1096)	0.63 (0.0-3.75)*	0.7	0.0 (0.0-25.3)	92.9 (91.3-94.3)
PND in discordant vs concordant twins						
- All pregnancies	5 (4127)[31,36,37,43,44]	(38/1176 vs 25/2951)	5.98 (3.53-10.1)	<0.001	60.3 (47.2-72.2)	72.0 (70.6-73.4)
- Pregnancies ≥34 weeks	3 (2945)[31,43,44]	(16/892 vs 16/2053)	3.34 (1.56-7.15)	0.002	50.0 (32.2-67.8)	70.0 (68.2-71.6)
- Pregnancies <34 weeks	1 (253)[31]	(14/81 vs 11/172)	3.06 (1.21-7.83)	0.007	0.56 (35.3-75.0)	70.6 (64.2-76.3)
- ≥ 1 SGA twin	1 (839)[31]	(24/270 vs 4/569)	13.9 (4.70-55.5)	<0.001	85.7 (66.4-95.3)	69.7 (66.3-72.3)
- Both AGA twins	1 (1020)[31]	(3/65 vs 17/955)	2.67 (0.49-9.58)	0.11	15.0 (3.9-38.9)	93.8 (92.1-95.2)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age.

* Exact logistic regression, as no logistic regression model was possible due to zero event in the exposed group. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 5. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in dichorionic twins with birthweight discordance ≥25% (discordant twins) versus dichorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	Fetuses (n/N vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
IUD in discordant vs concordant twins						
- All pregnancies	2 (1965)[31,45]	(21/212 vs 11/1753)	17.4 (8.27-36.7)	<0.001	65.6 (46.8-80.8)	90.1 (88.7-91.4)
- Pregnancies ≥34 weeks	1 (1608)[31]	(12/149 vs 6/1459)	21.2 (7.20-69.7)	<0.001	66.7 (41.2-85.6)	91.4 (89.9-92.7)
- Pregnancies <34 weeks	1 (253)[31]	(10/58 vs 4/195)	9.95 (2.69-44.8)	<0.001	71.4 (42.0-90.4)	80.0 (74.2-84.7)
- ≥ 1 SGA twin	1 (839)[31]	(20/187 vs 4/652)	19.4 (6.35-78.4)	<0.001	83.3 (61.8-94.5)	79.5 (76.5-82.2)
- Both AGA twins	1 (1020)[31]	(1/20 vs 6/1000)	8.72 (0.18-77.1)	0.4	14.3 (0.8-58.0)	98.1 (97.0-98.8)
NND in discordant vs concordant twins						
- All pregnancies	2 (2237)[31,47]	(3/247 vs 17/1990)	1.42 (0.42-4.90)	0.6	15.0 (4.0-38.9)	89.0 (87.6-90.3)
- Pregnancies ≥34 weeks	1 (1608)	(1/149 vs 5/1459)	1.96 (0.04-17.7)	0.5	16.7 (0.9-63.5)	90.8 (89.5-92.1)
- Pregnancies <34 weeks	1 (253)[31]	(2/58 vs 9/195)	0.74 (0.07-3.72)	0.7	18.2 (3.2-52.2)	76.9 (70.9-81.9)
- ≥ 1 SGA twin	1 (839)[31]	(3/187 vs 1/652)	10.6 (0.84-558)	0.9	75.0 (21.9-98.7)	78.0 (75.0-80.7)
- Both AGA twins	1 (1020)[31]	(0/20 vs 13/1000)	0.0 (0.0-15.0)	0.6	0.0 (0.0-28.3)	98.0 (96.9-98.7)
PND in discordant vs concordant twins						
- All pregnancies	3 (2289)[31,37,50]	(28/252 vs 30/2037)	8.36 (4.90-14.3)	<0.001	48.3 (35.1-61.7)	90.0 (88.6-91.2)
- Pregnancies ≥34 weeks	1 (1608)[31]	(2/149 vs 11/1459)	1.79 (0.19-8.32)	0.4	15.4 (2.7-46.3)	90.8 (89.2-92.1)
- Pregnancies <34 weeks	1 (253)[31]	(12/58 vs 13/195)	3.65 (1.41-9.27)	0.002	48.0 (28.3-68.2)	79.8 (73.9-84.7)
- ≥ 1 SGA twin	1 (839)[31]	(23/187 vs 5/652)	18.1 (6.59-61.8)	<0.001	82.1 (62.4-93.2)	79.8 (76.8-82.5)
- Both AGA twins	1 (1020)[31]	(1/20 vs 19/1000)	2.72 (0.06-19.0)	0.3	5.0 (0.3-26.9)	98.1 (97.0-98.8)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 6. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in dichorionic twins with birthweight discordance ≥30% (discordant twins) versus dichorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	Fetuses (n/N vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
IUD in discordant vs concordant twins						
- All pregnancies	1 (1859)[31]	(17/109 vs 14/1750)	22.9 (10.2-51.6)	<0.001	54.8 (36.3-72.2)	95.0 (93.8-95.9)
- Pregnancies ≥34 weeks	1 (1608)[31]	(8/72 vs 9/1536)	21.2 (6.84-63.9)	<0.001	47.1 (23.9-71.5)	96.0 (94.9-96.9)
- Pregnancies <34 weeks	1 (253)[31]	(9/37 vs 5/216)	13.6 (3.70-54.3)	<0.001	64.3 (35.6-86.0)	88.3 (83.4-91.9)
- ≥ 1 SGA twin	1 (903)[31]	(16/170 vs 7/733)	10.7 (4.07-31.3)	<0.001	69.6 (47.0-85.9)	45.0 (39.1-51.0)
- Both AGA twins	1 (1020)[31]	(0/3 vs 7/1017)	0.0 (0.0-211)	0.9	0.0 (0.0-43.9)	99.7 (99.1-99.9)
NND in discordant vs concordant twins						
- All pregnancies	1 (1859)[31]	(3/109 vs 14/1750)	3.51 (0.64-12.8)	0.8	17.6 (4.7-44.2)	94.2 (93.1-95.2)
- Pregnancies ≥34 weeks	1 (1608)[31]	(1/72 vs 5/1536)	4.32 (0.09-39.2)	0.15	16.7 (0.9-63.5)	95.6 (94.4-96.5)
- Pregnancies <34 weeks	1 (253) [31]	(2/37 vs 9/216)	13.2 (1.33-66.8)	<0.001	18.2 (3.2-52.2)	85.5 (80.3-89.6)
- ≥ 1 SGA twin	1 (903)[31]	(3/170 vs 1/733)	13.1 (1.04-691)	0.004	75.0 (21.9-98.7)	81.4 (78.7-83.9)
- Both AGA twins	1 (1020)[31]	(0/3 vs 13/1017)	0.0 (0.0-107)	0.8	0.0 (0.0-28.3)	99.7 (99.1-99.9)
PND in discordant vs concordant twins						
- All pregnancies	1 (1859)[31]	(20/109 vs 28/1750)	13.8 (7.06-26.5)	<0.001	41.7 (27.9-56.7)	95.1 (93.7-96.0)
- Pregnancies ≥34 weeks	1 (1608)[31]	(9/72 vs 14/1536)	15.5 (5.67-40.0)	<0.001	39.1 (20.5-61.2)	96.0 (94.9-96.9)
- Pregnancies <34 weeks	1 (253)[31]	(11/37 vs 14/216)	6.41 (2.34-16.9)	<0.001	44.0 (25.0-64.7)	88.6 (83.6-92.2)
- ≥ 1 SGA twin	1 (903)[31]	(19/170 vs 8/733)	12.2 (4.96-32.8)	<0.001	70.4 (49.6-85.5)	82.8 (80.1-85.2)
- Both AGA twins	1 (1020)[31]	(0/3 vs 20/1017)	0.0 (0.0-66.9)	0.8	0.0 (0.0-20.0)	99.7 (99.0-99.9)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 7. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in monochorionic twins with birthweight discordance ≥15% (discordant twins) versus monochorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	**Fetuses (n/N vs n/N)**	**Pooled OR (95% CI)**	**p**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
IUD in discordant vs concordant twins						
- All pregnancies	1 (302)[31]	(9/103 vs 8/199)	2.29 (0.75-7.02)	0.09	52.9 (28.5-76.1)	67.0 (61.2-72.4)
- Pregnancies ≥34 weeks	1 (230)[31]	(4/66 vs 1/164)	10.5 (1.00-521)	0.010	80.0 (29.9-98.9)	72.4 (66.0-78.1)
- Pregnancies <34 weeks	1 (73)[31]	(5/37 vs 7/36)	0.65 (0.15-2.69)	0.5	41.7 (16.5-71.4)	47.5 (34.8-60.6)
- ≥ 1 SGA twin	1 (152)[31]	(9/79 vs 1/73)	7.97 (1.04-355)	0.02	90.0 (54.1-99.5)	50.7 (42.2-59.1)
- Both AGA twins	1 (150)[31]	(0/24 vs 7/126)	0.0 (0.0-2.83)	0.2	0.0 (0.0-43.9)	83.2 (75.9-88.7)
NND in discordant vs concordant twins						
- All pregnancies	1 (302)[31]	(1/103 vs 1/199)	1.94 (0.02-153)	0.6	50.0 (2.7-97.3)	66.0 (60.3-71.3)
- Pregnancies ≥34 weeks	1 (230)[31]	(0/66 vs 0/164)	--	--	--	71.3 (64.9-77.0)
- Pregnancies <34 weeks	1 (73)[31]	(1/37 vs 1/36)	0.97 (0.01-78.5)	0.9	50.0 (2.7-97.3)	49.3 (37.3-61.3)
- ≥ 1 SGA twin	1 (152)[31]	(1/79 vs 1/73)	0.92 (0.01-73.4)	0.9	50.0 (2.7-97.3)	48.0 (39.8-56.3)
- Both AGA twins	1 (150)[31]	(0/24 vs 0/126)	--	--	--	84.0 (76.9-89.3)
PND in discordant vs concordant twins						
- All pregnancies	1 (302)[31]	(10/103 vs 9/199)	2.26 (0.8-2.5)	0.09	52.6 (28.9-75.6)	67.1 (61.3-72.6-69.2)
- Pregnancies ≥34 weeks	1 (230)[31]	(4/66 vs 1/164)	10.5 (1.0-521)	0.010	80.0 (29.9-98.9)	72.4 (66.0-78.1)
- Pregnancies <34 weeks	1 (73)[31]	(5/37 vs 7/36)	0.68 (0.17-2-56)	0.5	42.9 (18.8-70.4)	47.5 (34.5-60.8)
- ≥ 1 SGA twin	1 (152)[31]	(9/79 vs 1/73)	5.14 (1.03-49.5)	0.02	83.3 (50.9-97.1)	50.7 (42.2-59.2)
- Both AGA twins	1 (150)[31]	(0/24 vs 7/126)	0.0 (0.0-2.83)	0.2	0.0 (0.0-43.9)	83.2 (75.9-88.7)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 8. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in monochorionic twins with birthweight discordance ≥20% (discordant twins) versus monochorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	**Fetuses (n/N vs n/N)**	**Pooled OR (95% CI)**	**p**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
IUD in discordant vs concordant twins						
- All pregnancies	6 (1286)[29,31,34,39,44,46]	(15/323 vs 17/963)	2.75 (1.31-5.76)	0.007	46.9 (29.5-65.0)	75.4 (72.9-77.7)
- Pregnancies ≥34 weeks	3 (676)[31,34,44]	(7/206 vs 5/470)	3.27 (1.03-10.4)	0.045	58.3 (28.6-83.5)	70.0 (66.4-73.5)
- Pregnancies <34 weeks	3 (411)[31,34,48]	(5/98 vs 8/313)	0.84 (0.3-2.8)	0.787	38.46 (13.9-78.4)	76.6 (72.2-80.7)
- ≥ 1 SGA twin	1 (151)[31]	(7/57 vs 3/94)	4.1 (1.1-17.1)	0.04	70.0 (34.8-93.3)	64.5 (56.1-72.2)
- Both AGA twins	2 (400)[29,31]	(1/33 vs 9/367)	1.37 (0.18-10.5)	0.775	10.0 (25.0-44.5)	91.79 (87.6-94.3)
NND in discordant vs concordant twins						
- All pregnancies	5 (659)[31,41,43,44,46]	(7/237 vs 7/422)	2.00 (0.66-6.10)	0.2	50.0 (24.0-76.0)	64.0 (60.5-68.0)
- Pregnancies ≥34 weeks	3 (478)[31,43,44]	(1/167 vs 0/311)	1.86 (0.05-∞)*	0.7	100 (5.5-100)	65.2 (60.7-69.4)
- Pregnancies <34 weeks	2 (166)31,48	(2/44 vs 3/122)	2.11 (0.3-14.3)	0.8	40.00 (5.3-85.3)	73.91 (66.4-80.5)
- ≥ 1 SGA twin	2 (194)[31,43]	(1/65 vs 1/129)	2.00 (0.12-32.5)	0.6	50.0 (2.7-97.3)	66.7 (59.5-73.2)
- Both AGA twins	2 (192)[31,43]	(0/17 vs 0/175)	--	--	--	91.1 (86.0-94.6)
PND in discordant vs concordant twins						
- All pregnancies	4 (746)31,36,44,46	(20/251 vs 20/495)	2.27 (1.15-4.48)	0.019	50.0 (34.1-65.9)	67.3 (63.7-70.7)
- Pregnancies ≥34 weeks	2 (428)[31,44]	(6/152 vs 4/276)	2.79 (0.78-10.1)	0.12	60.0 (27.4-86.3)	65.1 (60.3-69.6)
- Pregnancies <34 weeks	2(166)[31,48]	(7/44 vs 11/122)	1.01 (0.4-3.9)	0.799	38.89 (17.3-64.3)	75.00 /67.2-81.8)
- ≥ 1 SGA twin	1 (151)[31]	(8/57 vs 4/94)	3.67 (0.92-17.4)	0.3	66.7 (35.4-88.7)	64.7 (56.1-72.5)
- Both AGA twins	1 (150)[31]	(0/10 vs 7/140)	0.0 (0.0-7.89)	0.5	0.0 (0.0-43.9)	93.0 (87.2-96.4)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age;
* Exact logistic regression, as no logistic regression model was possible due to zero event in the reference group. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 9. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in monochorionic twins with birthweight discordance ≥25% (discordant twins) versus monochorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	**Fetuses (n/N vs n/N)**	**Pooled OR (95% CI)**	**p**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
IUD in discordant vs concordant twins						
- All pregnancies	5 (993)[31,35,38,42,45]	(11/142 vs 22/851)	3.15 (1.49-6.67)	0.003	33.3 (18.6-51.9)	86.4 (83.9-88.4)
- Pregnancies ≥34 weeks	2 (405)[31,42]	(2/47 vs 4/358)	3.95 (0.69-22.7)	0.12	33.3 (6.0-75.9)	88.7 (85.1-91.6)
- Pregnancies <34 weeks	3 (523)[31,38,42]	(7/91 vs 13/432)	1.75 (0.64-4.82)	0.3	35.0 (16.3-59.1)	83.3 (79.7-86.4)
- ≥ 1 SGA twin	3 (393)[31,35,45]	(8/75 vs 8/318)	4.63 (1.68-12.8)	0.003	50.0 (25.5-74.5)	82.2 (77.9-85.9)
- Both AGA twins	1 (150)[31]	(0/1 vs 7/149)	6.33 (0.24-169)	0.3	0.0 (0.0-43.9)	99.3 (95.6-100)
NND in discordant vs concordant twins						
- All pregnancies	6 (1203)[31,32,35,38,42,47]	(7/182 vs 6/1021)	4.66 (1.8-12.4)	0.002	53.9 (25.1-80.8)	85.3 (83.2-87.3)
- Pregnancies ≥34 weeks	1 (230)[31]	(0/22 vs 0/208)	--	--	--	90.4 (85.7-93.8)
- Pregnancies <34 weeks	2 (348)[31,38]	(2/66 vs 4/282)	2.17 (0.39-12.1)	0.4	33.3 (6.0-75.9)	81.3 (76.6-85.2)
- ≥ 1 SGA twin	2 (280)[31,35]	(3/66 vs 1/214)	10.1 (1.04-99.2)	0.046	75.0 (21.9-98.7)	77.2 (71.7-81.9)
- Both AGA twins	1 (150)[31]	(0/1 vs 0/149)	--	--	--	99.3 (95.8-100)
PND in discordant vs concordant twins						
- All pregnancies	5 (1021)[31,35,37,38,42]	(28/170 vs 44/851)	3.16 (1.87-5.36)	<0.001	38.9 (27.8-51.1)	85.0 (82.6-87.2)
- Pregnancies ≥34 weeks	1 (230)[31]	(2/22 vs 3/208)	6.83 (0.53-62.4)	0.7	2.2 (0.8-5.3)	40.0 (7.3-82.9)
- Pregnancies <34 weeks	2 (348)[31,37]	(6/66 vs 17/282)	1.02 (0.86-2.86)	0.9	26.1 (11.1-48.7)	81.5 (76.8-85.5)
- ≥ 1 SGA twin	2 (280)[31,35]	(3/66 vs 1/214)	10.1 (1.04-99.2)	0.046	75.0 (21.9-98.7)	77.2 (71.7-81.9)
- Both AGA twins	1 (150)[31]	(0/1 vs 7/149)	6.33 (0.24-169)	0.3	0.0 (0.0-43.9)	99.3 (95.6-100)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age; When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 10. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in monochorionic twins with birthweight discordance ≥30% (discordant twins) versus monochorionic twins without birthweight discordance (concordant twins), overall and by selected gestational characteristics.

	N. studies (sample)	Fetuses (n/N vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
IUD in discordant vs concordant twins						
- All pregnancies	1 (302)[31]	(4/29 vs 13/273)	3.20 (0.70-11.4)	0.04	23.5 (7.8-50.2)	91.2 (87.2-94.1)
- Pregnancies ≥34 weeks	1 (230)[31]	(2/12 vs 3/218)	14.3 (1.05-136)	<0.001	40.0 (7.3-83.0)	95.6 (91.7-97.7)
- Pregnancies <34 weeks	1 (73)[31]	(2/17 vs 10/56)	0.61 (0.06-3.40)	0.6	16.7 (2.9-49.1)	75.4 (62.4-85.2)
- ≥ 1 SGA twin	1 (152)[31]	(4/28 vs 6/124)	3.28 (0.62-14.9)	0.07	40.0 (13.7-72.6)	83.1 (75.7-88.7)
- Both AGA twins	1 (150)[31]	(0/1 vs 7/149)	6.33 (0.24-169)	0.3	0.0 (0.0-43.9)	99.3 (95.6-100)
NND in discordant vs concordant twins						
- All pregnancies	1 (302)[31]	(0/29 vs 1/273)	3.08 (0.12-77.3)	0.5	0.0 (0.0-94.5)	90.4 (86.3-93.3)
- Pregnancies ≥34 weeks	1 (230)[31]	(0/12 vs 0/218)	--	--	--	94.8 (90.8-97.2)
- Pregnancies <34 weeks	1 (73)[31]	(0/17 vs 2/56)	0.0 (0.0-6.52)	0.4	0.0 (0.0-80.2)	76.1 (64.2-85.1)
- ≥ 1 SGA twin	1 (152)[31]	(0/28 vs 2/124)	0.0 (0.0-8.69)	0.5	0.0 (0.0-80.2)	81.3 (74.0-87.0)
- Both AGA twins	1 (150)[31]	(0/1 vs 0/149)	--	--	--	99.3 (95.8-100)
PND in discordant vs concordant twins						
- All pregnancies	1 (302)[31]	(4/29 vs 14/273)	2.96 (0.66-10.4)	0.06	22.2 (7.4-48.1)	91.2 (87.1-94.1)
- Pregnancies ≥34 weeks	1 (230)[31]	(2/12 vs 3/218)	14.3 (1.05-136)	<0.001	40.0 (7.3-83.0)	95.6 (91.7-97.7)
- Pregnancies <34 weeks	1 (73)[31]	(2/17 vs 12/56)	0.49 (0.05-2.63)	0.4	14.3 (2.5-43.8)	74.6 (61.3-84.6)
- ≥ 1 SGA twin	1 (152)[31]	(4/28 vs 8/124)	2.42 (0.49-9.88)	0.16	33.3 (11.3-64.6)	82.6 (75.4-88.5)
- Both AGA twins	1 (150)[31]	(0/1 vs 7/149)	6.33 (0.24-169)	0.3	0.0 (0.0-43.9)	99.3 (95.6-100)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Table 11. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in smaller (SGA) versus larger (AGA) dichorionic twins, stratified by degree of birthweight discordance.

	N. studies (sample)	**Fetuses (n/N vs n/N)**	**Pooled OR (95% CI)**	**p**	**Sensitivity (95% CI)**	**Specificity (95% CI)**
IUD in SGA vs AGA twins						
Birthweight discordance:						
- ≥15%	1 (1138)[31]	(25/569 vs 0/569)	53.3 (3.24-878)	0.005	100 (83.4-100)	51.1 (48.2-54.1)
- ≥20%	4 (2190)[29,31,33,44]	(28/1095 vs 2/1095)	14.8 (3.51-62.6)	<0.001	96.6 (80.4-99.8)	50.6 (48.5-52.8)
- ≥25%	1 (414)[31]	(20/207 vs 1/207)	22.0 (3.44-917)	<0.001	95.2 (74.1-99.8)	52.4 (47.3-57.4)
- ≥30%	1 (218)[31]	(13/109 vs 1/109)	14.6 (2.10-627)	<0.001	92.6 (64.2-99.6)	52.9 (45.8-59.9)
NND in SGA vs AGA twins						
Birthweight discordance:						
- ≥15%	1 (1138)[31]	(3/569 vs 1/569)	3.01 (0.24-158)	0.3	75.0 (21.9-98.7)	50.1 (47.1-53.0)
- ≥20%	2 (1838)[31,44]	(4/919 vs 0/919)	5.30 (0.66--∞)*	0.12	100 (39.6-100)	50.1 (47.8-52.4)
- ≥25%	1 (414)[31]	(3/207 vs 0/207)	7.10 (0.36-138)	0.2	100 (31.0-100)	50.4 (54.4-55.3)
- ≥30%	1 (218)[31]	(3/109 vs 0/109)	7.20 (0.37-141)	0.2	100 (31.0-100)	50.7 (43.8-57.5)
PND in SGA vs AGA twins						
Birthweight discordance:						
- ≥15%	1 (1138)[31]	(28/569 vs 1/569)	29.4 (4.82-1203)	<0.001	96.6 (80.4-99.8)	51.2 (48.2-54.2)
- ≥20%	2 (1838)[31,44]	(4/919 vs 0/919)	5.30 (0.66--∞)*	0.12	100 (39.6-100)	50.1 (47.8-52.4)
- ≥25%	1 (414)[31]	(23/207 vs 1/207)	25.8 (4.08-1065)	<0.001	95.8 (76.9-99.8)	52.8 (47.7-57.8)
- ≥30%	1 (218)[31]	(17/109 vs 1/109)	19.9 (2.98-841)	<0.001	94.4 (70.6-99.7)	54.0 (46.8-61.0)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age.
* Exact logistic regression, as no logistic regression model was possible due to zero event in the reference group. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

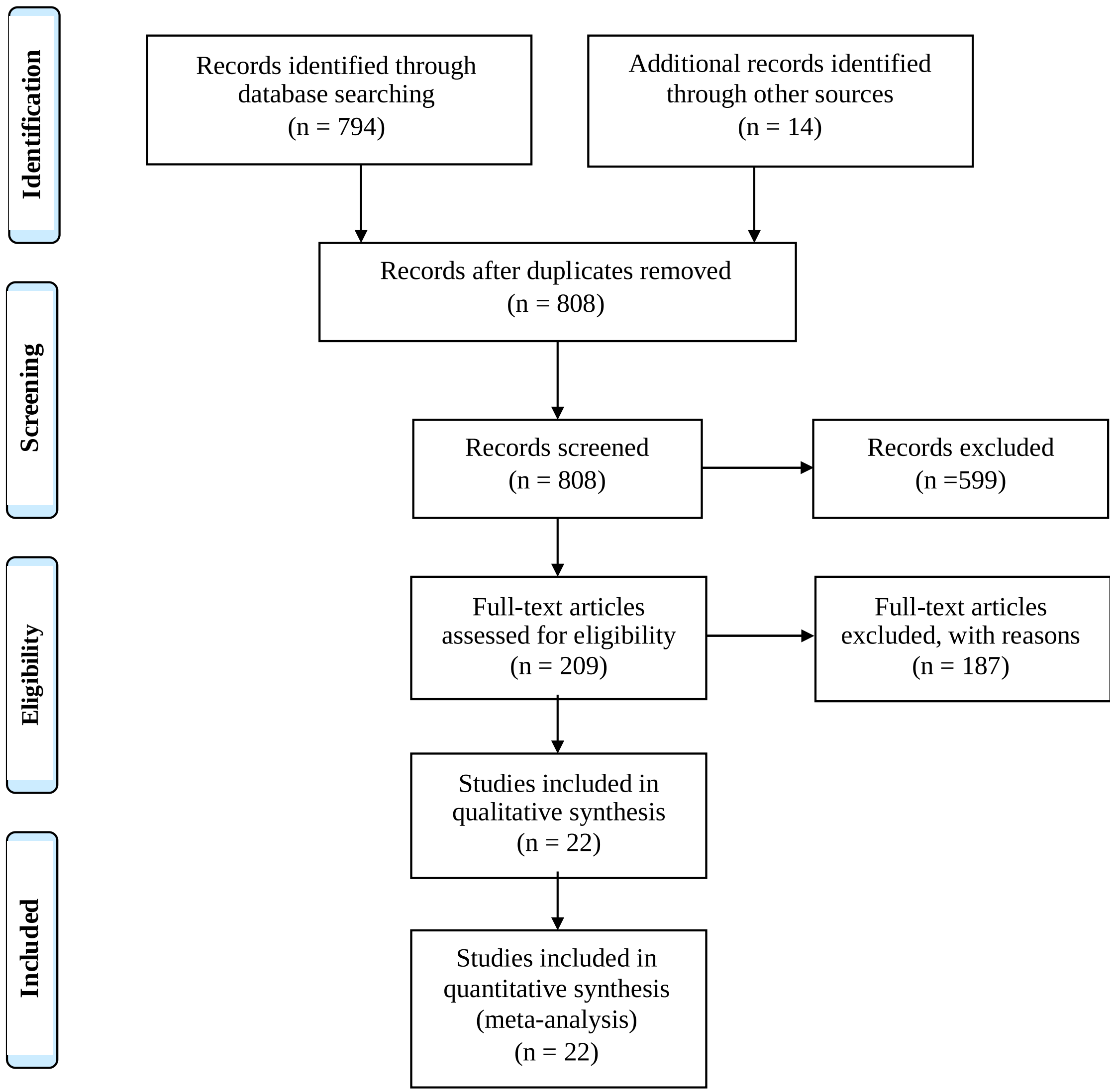
Table 12. Pooled odds ratios showing the likelihood of: intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in smaller (SGA) versus larger (AGA) monochorionic twins, stratified by degree of birthweight discordance.

	N. studies (sample)	Fetuses (n/N vs n/N)	Pooled OR (95% CI)	p	Sensitivity (95% CI)	Specificity (95% CI)
IUD in SGA vs AGA twins						
Birthweight discordance:						
- ≥15%	1 (206)[31]	(7/103 vs 2/103)	3.68 (0.67-37.0)	0.09	87.5 (46.7-99.3)	51.5 (44.3-58.6)
- ≥20%	2 (368)[31,44]	(8/184 vs 2/184)	3.87 (0.78-19.3)	0.06	80.0 (44.4-97.5)	50.8 (45.5-56.1)
- ≥25%	1 (94)[31]	(6/47 vs 1/47)	6.73 (0.75-316)	0.8	85.7 (42.0-99.2)	52.9 (41.9-63.6)
- ≥30%	1 (58)[31]	(3/29 vs 1/29)	3.23 (0.24-175)	0.3	75.0 (21.9-98.7)	51.9 (38.0-65.5)
NND in SGA vs AGA twins						
Birthweight discordance:						
- ≥15%	1 (206)[31]	(1/103 vs 0/103)	3.03 (0.12-75.2)	0.5	100 (5.5-100)	50.2 (43.2-57.3)
- ≥20%	3 (422)[31,44,46]	(5/211 vs 3/211)	1.74 (0.39-7.68)	0.5	62.5 (25.9-89.8)	50.2 (45.3-55.2)
- ≥25%	2 (188)[30,31]	(1/94 vs 1/94)	1.0 (0.06-16.2)	0.99	50.0 (2.7-97.3)	50.0 (42.6-57.4)
- ≥30%	1 (58)[31]	(0/29 vs 0/29)	--	--	--	50.0 (36.7-63.3)
PND in SGA vs AGA twins						
Birthweight discordance:						
- ≥15%	1 (206)[31]	(7/103 vs 2/103)	3.68 (0.67-37.0)	0.09	87.5 (46.7-99.3)	51.5 (44.3-58.6)
- ≥20%	3 (450)[31,36,44]	(12/225 vs 3/225)	4.19 (1.16-15.1)	0.028	80.0 (51.4-94.7)	51.0 (46.2-55.8)
- ≥25%	1 (94)[31]	(6/47 vs 1/47)	6.73 (0.75-316)	0.8	85.7 (42.0-99.2)	52.9 (41.9-63.6)
- ≥30%	1 (58)[31]	(3/29 vs 1/29)	3.23 (0.24-175)	0.3	75.0 (21.9-98.7)	51.9 (38.0-65.5)

OR = Odds Ratio; CI = Confidence Interval; SGA = Small for gestational age; AGA = Appropriate for gestational age. When <2 studies could be included in a meta-analysis, the OR was computed from the raw data of the single study.

Figure Legend

Figure 1. Systematic review flowchart


Identification
Screening
Eligibility
Included
Records identified through database searching (n = 794)
Additional records identified through other sources (n = 14)
Records after duplicates removed (n = 808)
Records screened (n = 808)
Records excluded (n =599)
Full-text articles assessed for eligibility (n = 209)
Full-text articles excluded, with reasons (n = 187)
Studies included in qualitative synthesis (n = 22)
Studies included in quantitative synthesis (meta-analysis) (n = 22)