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

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KEYWORDS: mortality; twin pregnancies; ultrasound; weight discordance

ABSTRACT

Objectives *The primary aim of this systematic review was to explore the strength of association between birth-weight (BW) discordance and perinatal mortality in twin pregnancy. The secondary aim was to ascertain the contribution of gestational age and growth restriction in predicting mortality in growth-discordant twins.*

Methods *MEDLINE, EMBASE, CINAHL and Clinical Trials.gov databases were searched. Only studies reporting on the risk of mortality in twin pregnancies affected compared with those not affected by BW discordance were included. The primary outcomes explored were incidence of intrauterine death (IUD), neonatal death (NND) and perinatal death. Outcome was assessed separately for monochorionic (MC) and dichorionic (DC) twin pregnancies. Analyses were stratified according to BW discordance cut-off (≥ 15%, ≥ 20%, ≥ 25% and ≥ 30%) and selected gestational characteristics, including incidence of IUD or NND before and after 34 weeks' gestation, presence of at least one small-for-gestational age (SGA) fetus in the twin pair and both twins being appropriate-for-gestational age. Risk of mortality in the larger* vs *smaller twin was also assessed. Meta-analyses using individual data random-effects logistic regression and meta-analyses of proportion were used to analyze the data.*

Results *Twenty-two studies (10 877 twin pregnancies) were included in the analysis. In DC pregnancies, a higher risk of IUD, but not of NND, was observed in twins with BW discordance ≥ 15% (odds ratio (OR) 9.8, 95% CI, 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) compared with those without weight discordance. For each cut-off of BW discordance explored in DC pregnancies, the smaller twin was at higher risk of mortality compared with the larger one. In MC twin pregnancies, excluding cases affected by twin–twin transfusion syndrome, twins with BW discordance ≥ 20% (OR 2.8, 95% CI, 1.3–5.8) or ≥ 25% (OR 3.2, 95% CI, 1.5–6.7) were at higher risk of IUD, compared with controls. MC pregnancies with ≥ 25% weight discordance were also at increased risk of NND (OR 4.66, 95% CI, 1.8–12.4) compared with those with concordant weight. The risk of IUD was higher when considering discordant pregnancies involving at least one SGA fetus. The overall risk of mortality in MC pregnancies was similar between the smaller and larger twin, except in those with BW discordance ≥ 20%.*

Conclusion *DC and MC twin pregnancies discordant for fetal growth are at higher risk of IUD but not of NND compared with pregnancies with concordant BW. The risk of IUD in BW-discordant DC and MC twins is higher when at least one fetus is SGA. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Birth-weight (BW) discordance is one of the major determinants of perinatal outcome in twin pregnancy, irrespective of chorionicity[1]. Although a certain degree of growth discordance may represent a normal physiological

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variation, a higher degree of discordance is known to be associated with increased perinatal mortality and morbidity[2–13]. In view of this association, it is routine obstetric practice to screen regularly twin pregnancies by ultrasound to evaluate the degree of intertwin fetal growth discordance[14].

Nevertheless, the actual role of discordant fetal growth in predicting perinatal mortality is still a matter of controversy. Although some studies have reported an increased risk of mortality in growth-discordant twins, others did not find any association[5–12]. Such inconsistencies could potentially be explained by heterogeneity in study design, inclusion of fetuses affected by anomalies and lack of stratification of the analysis according to gestational age at birth and chorionicity. Furthermore, several cut-offs of weight discordance have been suggested to be able to predict perinatal 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 has been reported to be independent of chorionicity, antenatal management of discordant twins should be tailored according to chorionicity in view of the higher risk of mortality and adverse neurological outcome observed in cases of cotwin 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 pregnancy. The secondary aim was to ascertain the contribution of gestational age and growth restriction in predicting mortality in discordant twins.

METHODS

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a-priori* designed protocol recommended for systematic reviews and meta-analyses[16–18]. MEDLINE, EMBASE, CINAHL and ClinicalTrials.gov databases were searched electronically on 18 December 2016 utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords and word variants for 'birth weight discordance' and 'outcome' (Table S1). The search and selection criteria were restricted to the 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 intrauterine death (IUD), neonatal death (NND) and perinatal death (PND). IUD was defined as the death of at least one twin at $\geq$ 20 weeks' gestation onwards, whereas NND was defined as the death of at least one of the newborns up to 28 days of age. PND was defined as the occurrence of IUD or NND.

Secondary outcomes were occurrence of IUD, NND and PND stratified according to gestational age at death $<$ or $\geq$ 34 weeks and BW of the twins (small-for-gestational age (SGA; twin pregnancy with BW of at least one twin $< 10^{th}$ percentile) or appropriate-for-gestational age (AGA; both twins with BW $\geq 10^{th}$ percentile)). Finally, we assessed the risk of IUD, NND and PND in the smaller *vs* larger twin.

All observed outcomes were reported separately for MC and dichorionic (DC) twins. The reason for this was that, although the association between discordant growth and mortality has been reported to be independent of chorionicity, this is still taken into account when 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 BW between the larger and the smaller twin and calculated by the following equation (larger actual BW − smaller actual BW)/larger actual BW)[1]. The analysis was stratified according to the most commonly reported cut-offs of BW discordance ($\geq$ 15%, $\geq$ 20%, $\geq$ 25% and $\geq$ 30%)[1].

Only studies reporting on the risk of mortality in BW-discordant *vs* BW-concordant twins and from which the raw numbers to calculate the risk of every explored outcome could be extrapolated were considered suitable for inclusion. Studies involving 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 higher-order multiple gestations reduced to twins, as well as studies reporting exclusively cases treated with intrauterine therapy (laser treatment or cord ligation), were excluded. Finally, studies involving cases with TTTS were also excluded. Only full-text articles were considered eligible for inclusion. Case reports, conference abstracts and case series with fewer than three 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.

Two authors (F.D., D.B.) reviewed all abstracts independently and agreement regarding potential relevance was reached by consensus. Full-text copies of those papers deemed relevant were obtained, and the same two reviewers extracted independently relevant data regarding study characteristics and pregnancy outcome. Inconsistencies were discussed and consensus was reached by the reviewers 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: selection of the study groups; comparability of the groups; and ascertainment of the outcome of interest[22]. Assessment of the selection of a study includes evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that an outcome of interest was not present at the start of the study. Assessment of the comparability of a study includes evaluation of the comparability of cohorts based on the design or analysis. Finally, ascertainment of the outcome of interest includes evaluation of the type of assessment for the outcome of interest, and 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

In this study, we evaluated the association between weight discordance and mortality (IUD, NND and PND) in twin pregnancy. The resulting meta-analyses were stratified according to chorionicity (MC or DC) and degree of weight discordance ($\geq 15\%$, $\geq 20\%$, $\geq 25\%$ or $\geq 30\%$). Furthermore, analyses were carried out five times including: (1) all pregnancies; (2) only pregnancies ≥ 34 weeks' gestation; (3) only pregnancies < 34 weeks' gestation; (4) only those pregnancies with at least one SGA twin; and (5) only those pregnancies with both twins being AGA.

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. The best performing methods for analysis of such cases are the Mantel–Haenszel odds ratio (OR) without zero-cell continuity corrections, logistic regression and an exact method[23,24]. Mantel–Haenszel ORs 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[25]. Therefore, to keep all studies in the analyses, we performed all meta-analyses using individual data random-effects logistic regression with single study as the cluster unit. The pooled datasets with individual data were reconstructed using published 2×2 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 OR 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 ORs may be of limited interest and sensitivity and specificity could be more informative. Thus, we computed the overall sensitivity and specificity (with 95% CI) for each comparison using the efficient-score method (corrected for continuity) described by Newcombe[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. Proportion meta-analyses were not meaningful when only one study could be included, and were performed using a random-effects model to account for the interstudy heterogeneity.

Potential publication bias was assessed either graphically, displaying the ORs of individual studies *vs* the logarithm of their standard errors (funnel plots), or formally, using Egger's regression asymmetry test[27]. As the power of formal testing for funnel-plot asymmetry is too low when fewer than 10 studies are included in a meta-analysis, we were able to evaluate the publication bias only for the meta-analyses reported in Figure S1[28].

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

RESULTS

General characteristics

The electronic search yielded 808 articles, of which 209 were assessed with respect to their eligibility for inclusion (Table S2) and 22 studies, involving 10 877 twin pregnancies, were eventually included in the systematic review (Figure 1, Table 1)[29–50].

In DC pregnancies, the prevalence of BW discordance $\geq 15\%$, $\geq 20\%$, $\geq 25\%$ and $\geq 30\%$ was 31.0% (95% CI, 29.0–33.1), 23.4% (95% CI, 22.4–24.5), 10.7%

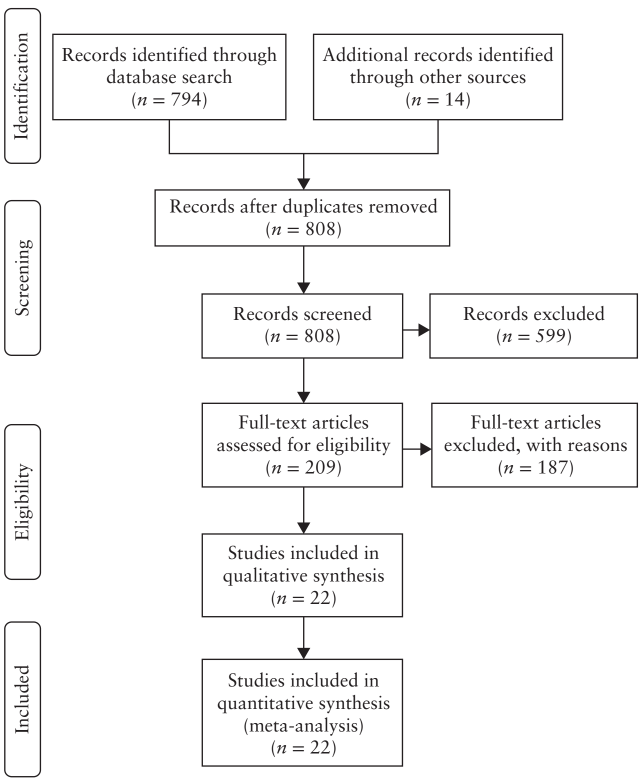

Figure 1 Flowchart summarizing inclusion in systematic review and meta-analysis of studies reporting on risk of mortality in twin pregnancies with *vs* those without birth-weight discordance.

Table 1 General characteristics of studies reporting on risk of mortality in twin pregnancies with *vs* those without birth-weight (BW) discordance included in systematic review and meta-analysis

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

Only first author of each study is given. *Numbers in parentheses are gestational weeks or postnatal age at death. †Age at neonatal death (NND) not reported. ‡One twin with estimated fetal weight < 10^{th} percentile for gestational age. DC, dichorionic; IUD, intrauterine death; MC, monochorionic; NS, not stated; PND, perinatal death; Prosp, prospective; Retro, retrospective.

(95% CI, 9.6–11.9) and 5.9% (95% CI, 4.8–7.0), respectively, whereas the corresponding prevalence in MC twins was 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), respectively.

It should be noted that, in view of the fact that some included studies were case–control series, the figures reported above may not represent the actual prevalence of the different cut-offs of BW discordance in twin pregnancies.

Results of the quality assessment of the included studies according to NOS are presented in Table S3. 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 the studies were their retrospective design, small sample size, varied gestational ages at scan, large heterogeneity in the definition of abnormal cut-offs for BW 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 it entirely possible for the robustness of the results to be affected by other cofactors.

Synthesis of the results

Dichorionic twin pregnancies

Birth-weight discordance ≥ 15%. Two studies (2001 pregnancies) explored the risk of mortality in DC twins 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); this was mainly due to the increased risk of IUD (OR 9.8, 95% CI, 3.9–29.4), whereas there was no increased risk of NND in DC twins with BW discordance ≥ 15% compared with those without (Table 2).

When stratifying the analysis according to gestational age at outcome, the risk of IUD after 34 weeks' gestation was higher in discordant compared with concordant twins (OR 6.2, 95% CI, 2.0–22.6), but there was no difference in the risk of NND. Furthermore, in BW-discordant twins compared with BW-concordant twins, the risk of IUD was higher when at least one twin was SGA (OR 12.0, 95% CI, 2.9–106), whereas there was no difference when both discordant twins were AGA ($P = 0.8$). Likewise, the risk of PND was higher in BW-discordant *vs* BW-concordant pregnancies with at least one SGA twin, with an OR of 9.2 (95% CI, 2.8–47.7) (Table 2).

Pooled proportions for the occurrence of mortality in discordant and concordant DC twin pairs, stratified according to BW discordance ≥ 15%, ≥ 20% and ≥ 25%, are reported in Table S4.

Birth-weight discordance ≥ 20%. Eleven studies, including 6795 twin pregnancies, explored the risk of mortality in DC twins with BW discordance ≥ 20% compared with controls[29,31,33,34,36,37,41,43,44,48,49]. The risk of PND was higher in BW-discordant *vs* BW-concordant twin pregnancies (OR 6.0, 95% CI, 3.5–10.1); this was due to the higher risk of IUD (OR 7.0, 95% CI, 4.2–11.8) rather than that of NND in the discordant cases (Table 3). The risk of IUD in twin pregnancies with BW discordance ≥ 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' gestation and in twin pairs with at least one SGA fetus (OR 12.7, 95% CI, 5.6–28.7) compared with pregnancies with concordant BW (Table 3).

Birth-weight discordance ≥ 25%. Five studies, including 2773 twin pregnancies, explored the risk of mortality in DC twins with BW discordance ≥ 25% compared with controls[31,37,45,47,50]. The risk of PND was higher in DC twins with a BW discordance compared with those with concordant BW (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 risk of NND between concordant and discordant DC twins (Table 4).

The association between BW discordance ≥ 25% and IUD in DC twins persisted when stratifying the analysis according to gestational age (OR 21.2, 95% CI, 7.2–69.7 for twins ≥ 34 weeks' gestation; OR 10.0, 95% CI, 2.7–44.8 for twins < 34 weeks' gestation) and when at least one SGA twin was present (OR 19.4, 95% CI, 6.4–78.4), but there was no difference when both twins were AGA (Table 4).

Birth-weight discordance ≥ 30%. Only one study explored the risk of mortality in non-anomalous twins affected by BW discordance ≥ 30%[31]. Compared with BW-concordant twins, the risk of PND was higher in discordant twin pregnancies with an OR of 13.8 (95% CI, 7.1–26.5) and this 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 5). The association between BW discordance ≥ 30% and IUD persisted when considering only twins born ≥ 34 weeks' gestation (OR 21.2, 95% CI, 6.8–63.9) or < 34 weeks' gestation (OR 13.6, 95% CI, 3.7–54.3) 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' gestation (OR 13.2, 95% CI, 1.3–66.8) and in pregnancies with at least one SGA twin (OR 13.1, 95% CI, 1.0–691) compared with concordant twins (Table 5).

Monochorionic twin pregnancies

Birth-weight discordance ≥ 15%. Only one study (302 twin pregnancies) explored the risk of mortality in MC twins with discordant *vs* those with concordant BW when a cut-off of 15% was applied[31]. When excluding pregnancies affected by TTTS, the overall risk of IUD, NND and PND was not significantly higher in pregnancies affected compared with those not affected by BW discordance. However, there was a higher risk of IUD ≥ 34 weeks' gestation (OR 10.5, 95% CI, 1.00–521) in discordant twins compared with controls and if a SGA twin was present (OR 8.0, 95% CI, 1.04–355), whereas there was no difference in the risk of NND (Table 6).

Birth-weight discordance ≥ 20%. Seven studies, including 1286 MC twin pregnancies, explored the risk of mortality in twins with BW discordance ≥ 20% compared with controls (Table 7)[29,31,34,39,44,46,48]. The risk of PND was higher in MC BW-discordant twins compared with controls, with an OR of 2.3 (95% CI, 1.2–4.5). The risk of IUD was higher in discordant compared with concordant twins (OR 2.8, 95% CI, 1.3–5.8), whereas there was no difference in the risk of NND between the two groups. When stratifying the analysis according to gestational age, the risk of IUD was higher in twins ≥ 34 weeks' gestation in pregnancies with BW discordance compared with those without (Table 7). Furthermore, there was an increased risk of IUD when at least one SGA fetus was present in the discordant pair.

Pooled proportions for the occurrence of mortality in discordant and concordant MC twin pairs, stratified according to BW discordance ≥ 20% and ≥ 25%, are reported in Table S5.

Birth-weight discordance ≥ 25%. Six studies (993 twin pregnancies) explored the risk of mortality in MC twin pregnancies when a 25% cut-off was applied to define BW discordance[31,35,38,42,45,47]. The risk of PND was higher in BW-discordant compared with BW-concordant MC twins, with an OR of 3.2 (95% CI, 1.9–5.4). The risk of IUD and NND was higher in discordant *vs* concordant

Table 2 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in dichorionic twins with birth-weight discordance ≥ 15% (discordant) *vs* dichorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies) (n)*	*Fetuses (n/N discordant vs n/N concordant)*	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	1[31] (1859)	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 wks	1[31] (1606)	12/459 *vs* 5/1147	6.13 (2.10–17.5)	< 0.001	70.6 (44.0–89.7)	71.9 (69.6–74.1)
Pregnancies < 34 wks	1[31] (253)	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[31] (839)	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 twins AGA	1[31] (1020)	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						
All pregnancies	1[31] (1859)	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 wks	1[31] (1606)	1/459 *vs* 5/1147	0.50 (0.06–4.28)	0.58	16.7 (0.4–64.1)	71.4 (69.1–73.6)
Pregnancies < 34 wks	1[31] (253)	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[31] (839)	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 twins AGA	1[31] (1020)	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						
All pregnancies	2[31,37] (2001)	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 wks	1[31] (1606)	13/459 *vs* 10/1147	3.31 (1.4–7.6)	0.005	56.5 (34.5–76.8)	71.8 (69.5–74.0)
Pregnancies < 34 wks	1[31] (253)	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[31] (839)	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 twins AGA	1[31] (1020)	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)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 3 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in dichorionic twins with birth-weight discordance ≥ 20% (discordant) *vs* dichorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies) (n)*	*Fetuses (n/N discordant vs n/N concordant)*	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	7[29,31,33,34,43,44,49] (5675)	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 wks	4[31,34,43,44] (3664)	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 wks	2[31,34] (972)	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[31,33] (1073)	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 twins AGA	4[29,31,33] (2448)	4/161 *vs* 24/2287	2.51 (0.85–7.40)	0.09		
NND						
All pregnancies	5[31,41,43,44,48] (3385)	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 wks	3[31,43,44] (2945)	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 wks	2[31,34] (328)	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[31,33] (1002)	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 twins AGA	2[31,43] (1178)	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						
All pregnancies	5[31,36,37,43,44] (4127)	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 wks	3[31,43,44] (2945)	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 wks	1[31] (253)	14/81 *vs* 11/172	3.06 (1.21–7.83)	0.007	56.0 (35.3–75.0)	70.6 (64.2–76.3)
≥ 1 SGA twin	1[31] (839)	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 twins AGA	1[31] (1020)	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)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. *Calculated using exact logistic regression, as logistic regression model was not possible due to zero events in exposed group. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 4 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in dichorionic twins with birth-weight discordance ≥ 25% (discordant) *vs* dichorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies)* (n)	*Fetuses* (n/N *discordant* vs n/N *concordant)*	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	2[31,45] (1965)	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 wks	1[31] (1608)	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 wks	1[31] (253)	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[31] (839)	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 twins AGA	1[31] (1020)	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						
All pregnancies	2[31,47] (2237)	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 wks	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 wks	1[31] (253)	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[31] (839)	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 twins AGA	1[31] (1020)	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						
All pregnancies	3[31,37,50] (2289)	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 wks	1[31] (1608)	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 wks	1[31] (253)	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[31] (839)	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 twins AGA	1[31] (1020)	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)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 5 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in dichorionic twins with birth-weight discordance ≥ 30% (discordant) *vs* dichorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies)* (n)	*Fetuses* (n/N *discordant* vs n/N *concordant)*	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	1[31] (1859)	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 wks	1[31] (1608)	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 wks	1[31] (253)	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[31] (903)	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 twins AGA	1[31] (1020)	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						
All pregnancies	1[31] (1859)	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 wks	1[31] (1608)	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 wks	1[31] (253)	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[31] (903)	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 twins AGA	1[31] (1020)	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						
All pregnancies	1[31] (1859)	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 wks	1[31] (1608)	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 wks	1[31] (253)	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[31] (903)	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 twins AGA	1[31] (1020)	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)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 6 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in monochorionic twins with birth-weight discordance ≥ 15% (discordant) *vs* monochorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies)* (n)	*Fetuses* (n/N *discordant* vs n/N *concordant*)	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	1[31] (302)	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 wks	1[31] (230)	4/66 *vs* 1/164	10.5 (1.00–521)	0.01	80.0 (29.9–98.9)	72.4 (66.0–78.1)
Pregnancies <34 wks	1[31] (73)	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[31] (152)	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 twins AGA	1[31] (150)	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						
All pregnancies	1[31] (302)	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 wks	1[31] (230)	0/66 *vs* 0/164	—	—	—	71.3 (64.9–77.0)
Pregnancies <34 wks	1[31] (73)	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[31] (152)	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 twins AGA	1[31] (150)	0/24 *vs* 0/126	—	—	—	84.0 (76.9–89.3)
PND						
All pregnancies	1[31] (302)	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)
Pregnancies ≥34 wks	1[31] (230)	4/66 *vs* 1/164	10.5 (1.0–521)	0.01	80.0 (29.9–98.9)	72.4 (66.0–78.1)
Pregnancies <34 wks	1[31] (73)	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[31] (152)	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 twins AGA	1[31] (150)	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)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 7 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in monochorionic twins with birth-weight discordance ≥ 20% (discordant) *vs* monochorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies)* (n)	*Fetuses* (n/N *discordant* vs n/N *concordant*)	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	6[29,31,34,39,44,46] (1286)	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 wks	3[31,34,44] (676)	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 wks	3[31,34,48] (411)	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[31] (151)	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 twins AGA	2[29,31] (400)	1/33 *vs* 9/367	1.37 (0.18–10.5)	0.775	10.0 (25.0–44.5)	91.8 (87.6–94.3)
NND						
All pregnancies	5[31,41,43,44,46] (659)	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 wks	3[31,43,44] (478)	1/167 *vs* 0/311	1.86 (0.05–∞)*	0.7	100 (5.5–100)	65.2 (60.7–69.4)
Pregnancies < 34 wks	2[31,48] (166)	2/44 *vs* 3/122	2.11 (0.3–14.3)	0.8	40.00 (5.3–85.3)	73.9 (66.4–80.5)
≥ 1 SGA twin	2[31,43] (194)	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 twins AGA	2[31,43] (192)	0/17 *vs* 0/175	—	—	—	91.1 (86.0–94.6)
PND						
All pregnancies	4[31,36,44,46] (746)	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 wks	2[31,44] (428)	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 wks	2[31,48] (166)	7/44 *vs* 11/122	1.01 (0.4–3.9)	0.799	38.89 (17.3–64.3)	75.0 (67.2–81.8)
≥ 1 SGA twin	1[31] (151)	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 twins AGA	1[31] (150)	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)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. *Calculated using exact logistic regression, as logistic regression model was not possible due to zero events in reference group. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 8 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in monochorionic twins with birth-weight discordance ≥ 25% (discordant) *vs* monochorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies)* (n)	*Fetuses* (n/N *discordant* vs n/N *concordant*)	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	5[31,35,38,42,45] (993)	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 wks	2[31,42] (405)	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 wks	3[31,38,42] (523)	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[31,35,45] (393)	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 twins AGA	1[31] (150)	0/1 *vs* 7/149	6.33 (0.24–169)	0.3	0.0 (0.0–43.9)	99.3 (95.6–100)
NND						
All pregnancies	6[31,32,35,38,42,47] (1203)	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 wks	1[31] (230)	0/22 *vs* 0/208	—	—	—	90.4 (85.7–93.8)
Pregnancies < 34 wks	2[31,38] (348)	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[31,35] (280)	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 twins AGA	1[31] (150)	0/1 *vs* 0/149	—	—	—	99.3 (95.8–100)
PND						
All pregnancies	5[31,35,37,38,42] (1021)	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 wks	1[31] (230)	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 wks	2[31,38] (348)	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[31,35] (280)	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 twins AGA	1[31] (150)	0/1 *vs* 7/149	6.33 (0.24–169)	0.3	0.0 (0.0–43.9)	99.3 (95.6–100)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 9 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in monochorionic twins with birth-weight discordance ≥ 30% (discordant) *vs* monochorionic twins without birth-weight discordance (concordant), overall and according to selected gestational characteristics

Gestational characteristic	*Studies[ref] (pregnancies)* (n)	*Fetuses* (n/N *discordant* vs n/N *concordant*)	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
IUD						
All pregnancies	1[31] (302)	4/29 *vs* 13/273	3.20 (0.70–11.4)	0.06	23.5 (7.8–50.2)	91.2 (87.2–94.1)
Pregnancies ≥ 34 wks	1[31] (230)	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 wks	1[31] (73)	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[31] (152)	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 twins AGA	1[31] (150)	0/1 *vs* 7/149	6.33 (0.24–169)	0.3	0.0 (0.0–43.9)	99.3 (95.6–100)
NND						
All pregnancies	1[31] (302)	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 wks	1[31] (230)	0/12 *vs* 0/218	—	—	—	94.8 (90.8–97.2)
Pregnancies < 34 wks	1[31] (73)	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[31] (152)	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 twins AGA	1[31] (150)	0/1 *vs* 0/149	—	—	—	99.3 (95.8–100)
PND						
All pregnancies	1[31] (302)	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 wks	1[31] (230)	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 wks	1[31] (73)	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[31] (152)	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 twins AGA	1[31] (150)	0/1 *vs* 7/149	6.33 (0.24–169)	0.3	0.0 (0.0–43.9)	99.3 (95.6–100)

When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study. AGA, appropriate-for-gestational age; SGA, small-for-gestational age; wks, weeks.

Table 10 Pooled odds ratios (OR) of likelihood of intrauterine (IUD), neonatal (NND) and perinatal (PND) death in smaller *vs* larger dichorionic and monochorionic twins, according to degree of birth-weight (BW) discordance

Outcome	*Studies[ref] (pregnancies) (n)*	*Fetuses (n/N smaller vs n/N larger)*	*Pooled OR (95% CI)*	P	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*
Dichorionic twins						
IUD						
BW discordance						
≥ 15%	1[31] (1138)	25/569 *vs* 0/569	53.3 (3.24–878)	0.005	100 (83.4–100)	51.1 (48.2–54.1)
≥ 20%	4[29,31,33,44] (2190)	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[31] (414)	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[31] (218)	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						
BW discordance						
≥ 15%	1[31] (1138)	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[31,44] (1838)	4/919 *vs* 0/919	5.30 (0.66–∞)*	0.12	100 (39.6–100)	50.1 (47.8–52.4)
≥ 25%	1[31] (414)	3/207 *vs* 0/207	7.10 (0.36–138)	0.2	100 (31.0–100)	50.4 (54.4–55.3)
≥ 30%	1[31] (218)	3/109 *vs* 0/109	7.20 (0.37–141)	0.2	100 (31.0–100)	50.7 (43.8–57.5)
PND						
BW discordance						
≥ 15%	1[31] (1138)	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[31,44] (1838)	4/919 *vs* 0/919	5.3 (0.66–∞)*	0.12	100 (39.6–100)	50.1 (47.8–52.4)
≥ 25%	1[31] (414)	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[31] (218)	17/109 *vs* 1/109	19.9 (2.98–841)	< 0.001	94.4 (70.6–99.7)	54.0 (46.8–61.0)
Monochorionic twins						
IUD						
BW discordance						
≥ 15%	1[31] (206)	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[31,44] (368)	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[31] (94)	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[31] (58)	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						
BW discordance						
≥ 15%	1[31] (206)	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[31,44,46] (422)	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[30,31] (188)	1/94 *vs* 1/94	1.00 (0.06–16.2)	0.99	50.0 (2.7–97.3)	50.0 (42.6–57.4)
≥ 30%	1[31] (58)	0/29 *vs* 0/29	—	—	—	50.0 (36.7–63.3)
PND						
BW discordance						
≥ 15%	1[31] (206)	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[31,36,44] (450)	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[31] (94)	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[31] (58)	3/29 *vs* 1/29	3.23 (0.24–175)	0.3	75.0 (21.9–98.7)	51.9 (38.0–65.5)

*Calculated using exact logistic regression, as logistic regression model was not possible due to zero events in reference group. When fewer than two studies could be included in a meta-analysis, OR was computed from raw data of the single study.

twins, with ORs of 3.2 (95% CI, 1.5–6.7) and 4.7 (95% CI, 1.8–12.4) (Table 8). The risk of IUD was higher when considering only discordant pregnancies containing at least one SGA fetus (OR 4.6, 95% CI, 1.7–12.8).

Birth-weight discordance ≥ 30%. Only one study, including 303 MC twin pregnancies, explored the risk of mortality in non-anomalous twins with BW discordance ≥ 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 ≥ 34 weeks compared with those without discordance, with an OR of 14.3 (95% CI, 1.1–136), whereas this association did not persist when considering only cases < 34 weeks' gestation (Table 9).

Smaller *vs* larger twin

The risk of mortality in the smaller *vs* larger twin in DC pregnancies according to degree of BW discordance is shown in Table 10. For each cut-off of BW discordance explored, the smaller twin was at higher risk of IUD but not of NND compared with the larger one.

The assessment of the risk of mortality between the smaller and the larger twin in MC twin pregnancies was limited by the small number of included cases and events. The risk of PND was higher in the smaller twin with BW discordance ≥ 20% (OR 4.2, 95% CI, 1.2–15.1) compared with the larger twin (Table 10). Pooled proportions for the occurrence of mortality in the smaller and larger twins are reported in Table S6.

DISCUSSION

The findings of this systematic review showed that DC and MC twin pregnancies with fetal growth discordance were generally at higher risk of IUD, but not of NND, compared with pregnancies with BW-concordant twins. The risk of IUD in discordant twins was higher when at least one fetus was SGA, whereas it was not increased when considering only AGA twins. When comparing the smaller twin with the larger twin, the risk of IUD was usually higher in the smaller twin than in the larger twin in DC pregnancy, whereas in MC pregnancy there was an increased risk of PND in the smaller twin *vs* the larger twin for a BW discrepancy $\geq 20\%$.

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 a 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. As not all included studies were case–control series reporting matched populations, it is possible that the presence and degree of association between BW discordance and mortality might have been affected by several cofactors that were not balanced between cases affected and those not affected by discrepancy in twin size, such as gestational age at birth, severity of growth restriction and maternal comorbidities.

Another limitation of this systematic review was the differences in the antenatal management of discordant twins between the included studies. Furthermore, the interval between the occurrence of IUD and birth was not reported in most of the included studies, which is a fundamental factor, as a larger interval between IUD and birth may affect significantly 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 gestational age at birth or detection of discordant growth and BW centile of the twins, thus considerably reducing the number of cases included in these subanalyses 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.

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

In the present systematic review, BW discordance was associated with an increased risk of IUD and such an association was independent of gestational age, with an increased risk of mortality both before and after 34 weeks' gestation. Conversely, twins discordant for fetal growth were not at higher risk of NND, except for MC pregnancies with a BW discrepancy $\geq 20\%$. The lack of association between BW discordance and NND confirms the finding in singleton pregnancies that 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 Doppler findings, should be considered when managing weight-discordant twins[52].

The association between discordant growth and mortality was stronger when considering twin pregnancies with at least one SGA fetus, whereas the risk was not increased when both discordant twins were AGA. It has been suggested recently that discordant growth in AGA twins may represent a risk factor for adverse perinatal outcome, irrespective of fetal weight[29]. However, in the present systematic review, we did not find an increased risk of either IUD or NND in AGA discordant twins, although the small number of cases included in this analysis may have underestimated this association. Therefore, these results should be interpreted with caution, as 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 still be considered at risk of adverse perinatal outcome and have close follow-up in order to detect signs of fetal compromise, such as abnormal growth trend and Doppler findings.

When comparing the smaller with the larger twin, a higher risk of IUD was observed in the smaller twin in DC twin pregnancies, whereas there was no difference in MC pregnancies. This difference could be explained by the different pathophysiology of discordant growth in MC compared with DC twin pregnancies; in DC twins, discordant growth is caused mainly by discordant placental size and function, whereas in MC twins, 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, which could partially explain why the risk of mortality was similar between the smaller and larger twins in MC pregnancies. Furthermore, due to the presence of such anastomoses, single IUD in a MC pair may lead to cotwin death in a considerable number of cases[15].

Large prospective studies aiming to assess the optimal management options and the outcome of weight-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.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Search strategy for PubMed, EMBASE and CINAHL for systematic review and meta-analysis

Table S2 Studies ($n = 187$) excluded from systematic review and meta-analysis and reasons for exclusion

Table S3 Quality assessment of included studies according to Newcastle–Ottawa Scale

Table S4 Pooled rates of intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in dichorionic twins with (discordant) and those without (concordant) birth-weight (BW) discordance, stratified according to degree of BW discordance and selected gestational characteristics

Table S5 Pooled rates of intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in monochorionic twins with (discordant) and those without (concordant) birth-weight (BW) discordance, stratified according to degree of BW discordance and selected gestational characteristics

Table S6 Pooled rates of intrauterine death (IUD), neonatal death (NND) and perinatal death (PND) in smaller *vs* larger dichorionic and monochorionic twins according to birth-weight (BW) discordance

Figure S1 Funnel plots of logarithm of odds ratios *vs* their standard errors for overall death in dichorionic twins with *vs* those without birth-weight (BW) discordance $\geq 20\%$ (a), in monochorionic twins with *vs* those without BW discordance $\geq 20\%$ (b) and monochorionic twins with *vs* those without BW discordance $\geq 25\%$.

