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Crown–rump length discordance and adverse perinatal outcome in twin pregnancies: systematic review and meta-analysis

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KEYWORDS: adverse perinatal outcome; birth-weight discordance; crown–rump length discordance; dichorionic twins; meta-analysis; monochorionic twins

ABSTRACT

Objective *The aim of this systematic review was to explore the relationship between crown–rump length (CRL) discordance detected at 11–14 weeks of gestation and adverse outcome in twin pregnancy and to assess its predictive accuracy.*

Methods *A protocol designed* a priori *following MOOSE guidelines and recommended for systematic review and meta-analysis was used. The outcomes observed were: total fetal and perinatal loss, fetal loss at < 24 weeks, fetal loss at ≥ 24 weeks, birth-weight (BW) discordance, preterm delivery (PTD) at < 34 weeks and fetal anomalies. The analysis was performed for all twins and for dichorionic (DC) and monochorionic (MC) twins separately.*

Results *A total of 2008 articles were identified and 17 studies were included in the systematic review. Twin pregnancies with CRL discordance ≥ 10% were at significantly higher risk of perinatal loss (RR, 2.80; 95% CI, 1.25–6.27;* P = *0.012), fetal loss at ≥ 24 weeks (RR, 4.07; 95% CI, 1.47–11.23;* P = *0.006), BW discordance (RR, 2.24; 95% CI, 1.89–2.64;* P < *0.001) and PTD at < 34 weeks (RR, 1.49; 95% CI, 1.23–1.80;* P < *0.001) but not of fetal loss at < 24 weeks (*P = *0.130). A meta-analysis of fetal anomalies was not possible because fewer than two studies explored this outcome. However, when used alone to screen for adverse pregnancy outcome, the predictive accuracy of CRL discordance was low for each of the outcomes explored.*

Conclusion *CRL discordance is associated with an increased risk of adverse pregnancy outcome. However, the accuracy of CRL discordance in predicting adverse outcome is poor and thus limits its routine use in clinical practice.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Twin pregnancies are at increased risk of perinatal mortality and morbidity compared to singleton pregnancies, mainly due to preterm birth, growth discordance, fetal anomalies and complications related to monochorionicity such as twin-to-twin transfusion syndrome[1–4]. Early ultrasound assessment is crucial in providing appropriate prenatal care. Determination of chorionicity in early pregnancy provides the first stratification of perinatal risk and guides monitoring for early detection of specific complications[2,5,6]. Significant discordance in crown–rump length (CRL) is associated with higher risk of adverse perinatal outcomes such as fetal loss, weight discordance, fetal anomalies and preterm delivery[7–18]. It has been hypothesized that impaired fetal growth in early pregnancy and the presence of underlying fetal chromosomal or structural anomalies may explain this phenomenon[19]. As a consequence of this association, CRL discordance is commonly a reason for counseling parents concerning adverse pregnancy outcome. However, the value of CRL discordance as a screening parameter and the magnitude of discordance considered to be a significant predictor of pregnancy complications continue to be a matter for debate. The aims of this systematic review were to explore the relationship between CRL discordance detected at the 11–14-week scan and adverse pregnancy outcome in twin pregnancies and to assess its predictive accuracy in clinical practice.

METHODS

Search strategy

A protocol was designed *a priori* according to recommendations for systematic review and meta-analysis[20–24].

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MEDLINE (since inception), EMBASE (since inception), CINAHL (since inception) and The Cochrane Library (since inception), including The Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and The Cochrane Central Register of Controlled Trials (CENTRAL), were searched electronically on 9 August 2013. Combinations of the following relevant medical subject heading (MeSH) terms, keywords and word variants were used: 'crown rump length', 'embryo', 'fetal size', 'fetal growth', 'multiple pregnancies', 'twin pregnancies', 'miscarriage', 'abortion', 'pregnancy loss', 'fetal death', 'fetal loss', 'stillbirth', 'twin-to-twin transfusion syndrome', 'small for gestational age', 'intrauterine growth restriction', 'selective intrauterine growth restriction', 'fetal growth restriction', 'weight discordance', 'preterm birth', 'chromosomal abnormalities', 'aneuploidy' and 'structural abnormalities' (Appendix S1). Reference lists of relevant articles and reviews were hand-searched for additional reports. The search was limited to English language. The study was registered with the PROSPERO database (Registration number: CRD42013005234, http://www.crd.york.ac.uk/PROSPERO).

Data extraction and quality assessment

All abstracts were reviewed independently by two authors (F.D. and A.K.). Agreement concerning potential relevance was reached by consensus and full text copies of relevant papers were obtained. Two authors (F.D. and A.K.) independently extracted relevant data regarding study characteristics and pregnancy outcome.

Only papers reporting an association between CRL discrepancy at the 11–14-week scan and adverse perinatal outcome were included, irrespective of the discordance cut-off reported (Table 1). Furthermore, a meta-analysis including only pregnancies with CRL discordance ≥ 10% was performed. The rationale for this cut-off was the fact that it was the one most commonly reported, usually representing the 90th–95th centile of the population analyzed. Quality of the studies was assessed using criteria from the STROBE statement[21]. Inconsistencies were discussed among authors and consensus was reached. If more than one study was published for the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations. We contacted authors of articles in which information was not reported to obtain data that, according to their methodology, was recorded initially. Only full-text articles were considered eligible for inclusion; case reports, conference abstracts and case series with fewer than three cases were also excluded to avoid publication bias.

Study selection and outcomes analyzed

The outcomes observed were: total fetal and perinatal loss, fetal loss at < 24 weeks, fetal loss at ≥ 24 weeks, birth-weight (BW) discordance, preterm delivery (PTD) at < 34 weeks and fetal anomalies. Studies were assessed according to the following criteria: population, outcome and study design. Only studies exploring the relationship between different adverse pregnancy outcomes in twins with CRL discrepancy detected at the 11–14-week scan were considered suitable for inclusion.

The rationale behind this decision relies on the fact that twin pregnancies are not routinely scanned before 11 weeks of gestation. Furthermore, our recent systematic review already explored the relationship between CRL discordance detected in the early stages of development and subsequent fetal loss[25].

Perinatal loss was defined as the sum of fetal and perinatal deaths of one or both twin(s) up to 28 days after birth. BW discordance was defined as discordance in growth of ≥ 20% between the two fetuses. Fetal anomalies were defined as the presence of structural abnormalities detected at the first-trimester scan or later during pregnancy. Preterm birth was defined as delivery at < 34 weeks of gestation. These outcomes were explored for all twins and separately for monochorionic (MC) and dichorionic (DC) twins when possible.

Statistical analysis

Between-study heterogeneity was explored using the I^2 statistic which represents the percentage of between-study variation due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, whereas I^2 values ≥ 50% indicate a substantial level of heterogeneity. A fixed-effects model was used if substantial statistical heterogeneity was not present. Random-effects models were also used to test the robustness of results[26]. Results were reported as relative risks (RR) for each outcome observed in twins with a given cut-off for CRL discordance compared to those with lesser degrees of discordance. For the purpose of this analysis we chose a cut-off of ≥ 10%.

In order to assess the predictive accuracy of CRL discordance in twin pregnancies, sensitivity, specificity, positive likelihood ratio (LR+), negative likelihood ratio (LR−) and diagnostic odds ratio (DOR) were calculated according to reconstructed two-by-two tables. Summary estimates of sensitivity, specificity, LR+, LR− and DOR for the overall predictive accuracy of CRL discrepancy ≥ 10% were calculated using the DerSimonian–Laird random-effects model, with DOR defined as the ratio between the odds of the test being positive if the subject has a disease and the odds of the test being positive if the subject does not have the disease[27].

Potential publication biases were assessed graphically by using funnel plot and statistically by using Begg's and Egger's tests. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was below 10. In this case, the power of the tests is too low to distinguish chance from real asymmetry[28]. Statistical analysis was performed using StatsDirect (StatsDirect LtD, Altrincham, UK) and Meta-Disc 1.4 (www.hrc.es/investigacion/metadisc_en.htm, Ramón y Cajal Hospital, Madrid, Spain) statistical software. A P-value < 0.05 was considered statistically significant.

Table 1 Summary of studies included in the systematic review of crown–rump length discordance (CRL disc.) and adverse perinatal outcome in twin pregnancies

Study	*Study design*	*Chorionicity*	*CRL disc. cut-off(s) (%)**	*Pregnancies* (n)	*Discordant twins* (n)	*Outcome(s) observed*	*Study findings*
Johansen[17] (2014)	Retro.	MC and DC	10	1993	188	FL (< 24 weeks or > 24 weeks), NND, PTD, BW disc. (≥ 20%)	CRL disc. associated with PTD, BW disc. in DC and MC twins; however, predictive accuracy of CRL disc. low
D'Antonio[29] (2013)	Retro.	MC and DC	10†	2155	235	FL (< 24 weeks), stillbirth (>24 weeks), NND, BW disc. (>25%), PTD (< 34 weeks)	CRL disc. not predictive of any adverse outcome irrespective of cut-off used once chromosomal abnormalities are ruled out
O'Connor[30] (2013)	Prosp.	MC and DC	20	260	2	BW disc. (≥ 18%), PTD	CRL disc. not predictive of any adverse outcome
Weissman-Brenner[31] (2012)	Retro.	MC and DC	12	396	50	BW disc. (> 24% and > 30%)	CRL disc. associated with BW disc. in DC twins
Fratelli[32] (2011)	Retro.	MC	5–20	135	19	FL (< 24 weeks), stillbirth (> 24 weeks)	CRL disc. not associated with or predictive of adverse pregnancy outcome
Matias[33] (2011)	Prosp.	MC	NS	237	NS	BW disc.	CRL disc. not independently associated with BW disc.
Fajardo-Exposito[34] (2011)	Prosp.	MC and DC	15	46	3	BW disc. (≥ 15%),	CRL disc. not associated with BW disc.
Fareeduddin[14] (2010)	Retro.	DC	9	78	24	PTD (37 weeks)	CRL disc. associated with PTD
Dias[35] (2010)	Retro.	MC and DC	10.1–12.1‡	660	63	FL, BW disc. (≥ 15% and 25%)	CRL disc. associated with but not predictive of FL and BW disc.
Bhide[13] (2009)	Retro.	MC and DC	10.4–12.2‡	507	NS	FL, BW disc. (≥ 20%)	CRL disc. associated with FL in MC and BW disc. in DC twins; however, its predictive accuracy low
Lewi[36] (2008)	Prosp.	MC	12 (mm)	200	NS	BW disc. (≥ 20–25%), FL	CRL disc. predictive of adverse outcome in MC twins
Kagan[37] (2007)	Prosp.	MC	10–14	512	43	FL (before and after 18 weeks' gestation)	CRL disc. associated with but not highly predictive of early FL in MC twins
El Kateb[38] (2007)	Prosp./ Retro.	MC	10	239	7§	BW disc. (> 20%), perinatal mortality	CRL disc. associated with perinatal loss in MC twins
Bartha[9] (2005)	Retro.	MC and DC	1 (SD)	59	18	FL, perinatal loss, BW disc. (≥ 20%), structural anomalies, PTD	CRL disc. associated with BW disc., IUGR and PTD
Salomon[11] (2005)	Prosp.	MC and DC	11.4–14.3‡	182	NS	BW disc., aneuploidy, FL, structural abnormalities, BW disc. (> 20%)	CRL disc. > 95th centile indicates major growth delay in one twin, which could indicate presence of aneuploidy
Kalish[7] (2004)	Retro.	DC	11	159	18	FL, structural or chromosomal abnormalities, PTD	CRL disc. associated with structural or chromosomal abnormalities
Kalish[8] (2003)	Retro.	DC	11 (3 days)	130	12	BW disc. (> 20), FL or anomalies	CRL disc. associated with BW disc.

Only the first author of each study is given. *Unless specified otherwise. †Cut-off for CRL discordance used in the meta-analysis. ‡Corresponding to the 90th and 95th centiles of discordance in the population analyzed. §Incidence of CRL discordance available only for a proportion of the entire population analyzed. BW, birth-weight; DC, dichorionic; disc., discordance; FL, fetal loss; IUGR, intrauterine growth restriction; MC, monochorionic; NND, neonatal death; NS, not stated; Prosp., prospective; PTD, preterm delivery; Retro., retrospective.

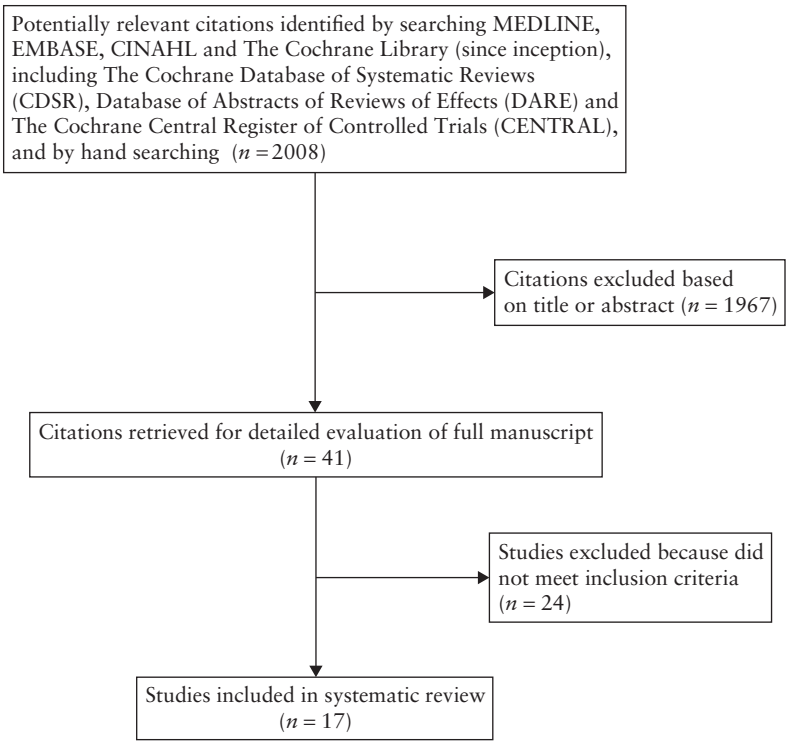


Figure 1 Flowchart showing the selection of studies included in this systematic review.

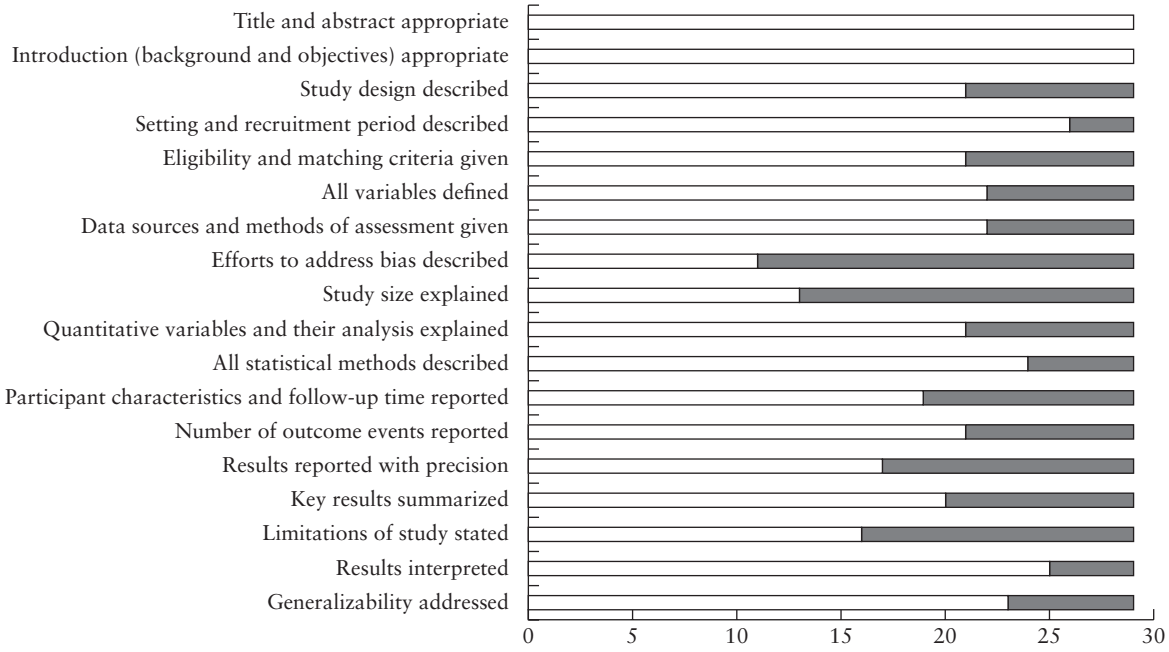


Figure 2 Summary of quality assessment[20–24] of the 17 studies analyzed in this systematic review. □, yes; ■, no.

RESULTS

A total of 2008 articles were identified; 41 were assessed with respect to their eligibility for inclusion (Appendix S2) and a total of 17 studies were included (Figure 1)[7–9,11,13,14,17,29–38]. General characteristics of the studies included are reported in Table 1. Several cut-offs for CRL discordance and different definitions of pregnancy outcome were reported by different authors. Most studies were of good quality, although only a small proportion tried to assess bias and included an explanation of the sample size (Figure 2). The risks of an adverse outcome in pregnancies with a CRL discordance ≥ 10% and the predictive accuracy of CRL discordance at the 11–14-week scan are shown for each adverse outcome included (Tables 2 and 3).

Table 2 Relative risk (RR) for the outcomes investigated in this systematic review of twin pregnancies with crown–rump length discordance ≥ 10% detected at the 11–14-week scan compared to those with lesser degrees of discordance

Outcome	*Studies* (n)	*Population* (n)	*RR (fixed model)*	I^2	*RR (random model)*
All losses	5	4898	1.95 (1.38–2.76)	74.8	2.80 (1.25–6.27)
Fetal loss < 24 weeks	3	2833	2.27 (1.18–4.37)	52.5	2.36 (0.78–7.19)
Fetal loss ≥ 24 weeks	2	2344	4.07 (1.47–11.23)	—	4.16 (1.49–11.60)
Birth-weight discordance	4	4619	2.24 (1.89–2.64)	43.3	2.33 (1.83–9.61)
Preterm delivery	3	4360	1.49 (1.23–1.80)	0	1.51 (1.24–1.83)
Fetal anomalies	—	—	—	—	—

Values in parentheses are 95% CI.

Table 3 Predictive accuracy of crown–rump length discordance ≥ 10% detected at the 11–14-week scan for the different outcomes analyzed in this systematic review

Outcome	*Sensitivity (%)*	*Specificity (%)*	*Positive likelihood ratio*	*Negative likelihood ratio*	*Diagnostic odds ratio*
All losses	17.6 (12.6–23.5)	90.3 (89.4–91.1)	2.59 (1.2–5.4)	0.92 (0.84–1.02)	2.92 (1.2–6.9)
Fetal loss < 24 weeks	20.2 (10.3–33.6)	89.6 (88.4–90.7)	2.06 (0.8–6.1)	0.92 (0.76–1.11)	2.30 (0.7–8.0)
Fetal loss ≥ 24 weeks	34.4 (13.1–61.7)	89.0 (87.7–90.3)	3.16 (1.6–6.3)	0.75 (0.53–1.06)	4.23 (1.5–12.0)
Birth-weight discordance	20.7 (17.6–24.0)	91.2 (90.3–92.1)	2.49 (1.9–3.3)	0.86 (0.80–0.93)	2.92 (2.0–4.3)
Preterm delivery	13.7 (11.2–16.5)	91.2 (90.2–92.1)	1.54 (1.2–1.9)	0.95 (0.93–0.98)	1.63 (1.3–2.1)
Fetal anomalies	—	—	—	—	—

Values in parentheses are 95% CI.

Perinatal mortality

The risk of perinatal loss was significantly higher in twin pregnancies with a CRL discordance ≥ 10% compared to those with lesser degrees of discordance (RR, 2.80; 95% CI, 1.25–6.27; $P = 0.012$) (Figure 3). The predictive accuracy of CRL discrepancy at the 11–14-week scan for perinatal loss was low (sensitivity, 17.6% (95% CI, 12.6–23.5); specificity, 90.3% (95% CI, 89.4–91.1); LR+, 2.59 (95% CI, 1.2–5.4); LR–, 0.92 (95% CI, 0.84–1.02); DOR, 2.92 (95% CI, 1.2–6.9)) (Figure 4). When analysis was performed separately for MC and DC twin pregnancies, the risk of perinatal loss in pregnancies with a CRL discordance of ≥ 10% was significantly higher regardless of chorionicity, although the predictive accuracy was poor (Tables S1 and S2).

Fetal loss at < 24 weeks

We did not find a significant association between CRL discordance at the 11–14-week scan and the risk of fetal loss at < 24 weeks of gestation ($P = 0.130$) (Figure 3). The predictive accuracy of CRL discordance for early fetal loss was low (sensitivity, 20.2% (95% CI, 10.3–33.6); specificity, 89.6 (95% CI, 88.4–90.7); LR+, 2.06 (95% CI, 0.8–6.1); LR–, 0.92 (95% CI, 0.76–1.11)) (Figure 4). CRL discordance was significantly associated with fetal loss at < 24 weeks of gestation in MC twins but it was not possible to perform a meta-analysis in DC twins (Tables S1 and S2).

Fetal loss at ≥ 24 weeks

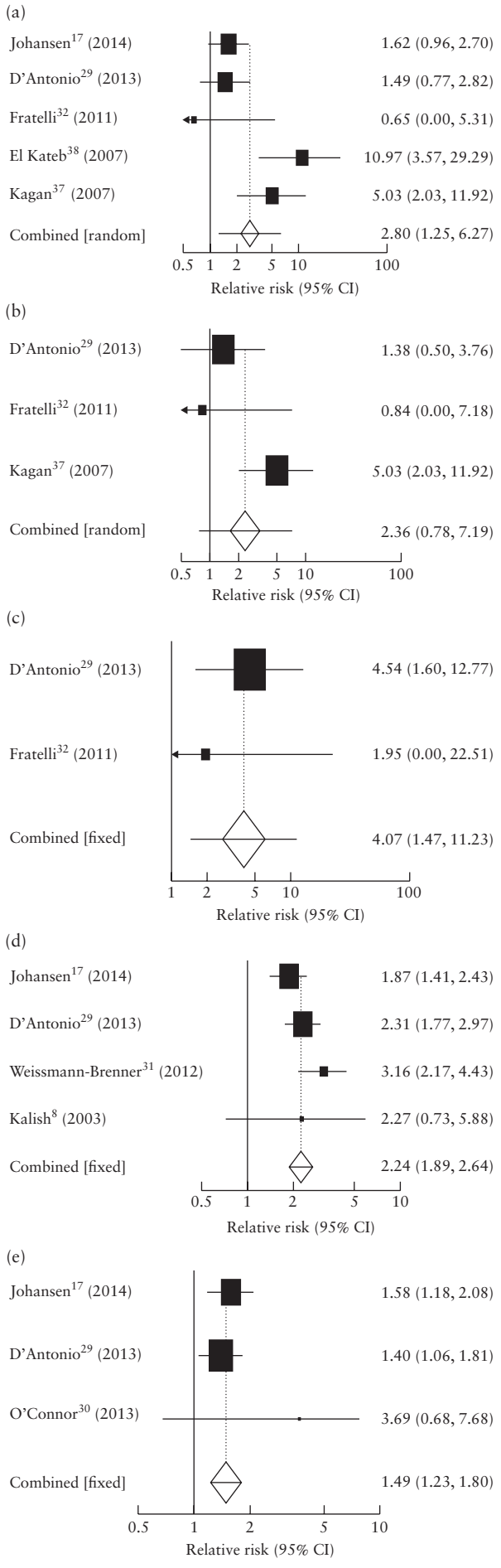
Only two studies were included in the meta-analysis for the outcome of fetal loss ≥ 24 weeks. CRL discordance was significantly associated with fetal loss at ≥ 24 weeks (RR, 4.07; 95% CI, 1.47–11.23; $P = 0.006$) (Figure 3)[29,32]. The predictive accuracy of CRL discordance was poor for fetal loss at ≥ 24 weeks (sensitivity, 34.4% (95% CI, 13.1–61.7); specificity, 89.0% (95% CI, 87.7–90.3); LR+, 3.16 (95% CI, 1.6–6.3); LR–, 0.75 (95% CI, 0.53–1.06); DOR, 4.23 (95% CI, 1.5–12.0)) (Figure 4). In MC pregnancies CRL discordance was not significantly associated with late fetal loss, but it was not possible to perform a meta-analysis in DC twins because only one study explored this outcome[29].

Birth-weight discordance

CRL discordance was significantly associated with BW discordance (RR, 2.24; 95% CI, 1.89–2.64; $P < 0.001$) (Figure 3). However, the predictive accuracy of CRL discordance detected at the 11–14-week scan was poor for BW discordance (sensitivity, 20.7% (95% CI, 17.6–24.0); specificity, 91.2% (95% CI, 90.3–92.1); LR+, 2.49 (95% CI, 1.9–3.3); LR–, 0.86 (95% CI, 0.80–0.93); DOR, 2.92 (95% CI, 2.0–4.3)) (Figure 4). When the analysis was restricted according to chorionicity, both DC and MC twins with a CRL discordance ≥ 10% were at significantly higher risk of BW discordance, although the predictive accuracy was low (Tables S1 and S2).

Preterm delivery

CRL discordance was significantly associated with PTD at < 34 weeks (RR, 1.49; 95% CI, 1.23–1.80; $P < 0.001$) (Figure 3). The predictive accuracy of CRL discordance detected at 11–14 weeks was poor for PTD at < 34 weeks (sensitivity, 13.7% (95% CI, 11.2–16.5); specificity, 91.2% (95% CI, 90.2–92.1); LR+, 1.54 (95% CI, 1.2–1.9); LR–, 0.95 (95% CI, 0.93–0.98); DOR, 1.63



(95% CI, 1.3–2.1)) (Figure 4). The risk of PTD in DC twin pregnancies with CRL discordance ≥ 10% was significantly higher than in those with lesser degrees of discordance (RR, 2.20; 95% CI, 1.77–2.74; $P = 0.017$), while there was no statistical difference with respect to this outcome in MC twins ($P = 0.099$) (Table S1). However, even in DC twins, the predictive accuracy of CRL discordance was poor (Table S2).

Fetal structural anomalies

Only one study explored the risk of fetal anomalies in twin pregnancies with CRL discordance detected at 11–14 weeks of gestation; thus, it was not possible to perform a meta-analysis on this outcome[7].

DISCUSSION

Twin pregnancies with CRL discordance of ≥ 10% at 11–14 weeks of gestation are at a significantly higher risk of fetal and perinatal loss, BW discordance and PTD. These findings were similar when the analysis was categorized according to chorionicity. However, when used alone as a screening parameter for adverse pregnancy outcome, the predictive accuracy of CRL discordance was low for each of these outcomes, irrespective of twin chorionicity.

A recent systematic review explored the predictive accuracy of early CRL discordance at < 10 weeks[25]. In this review, the predictive accuracy of CRL discordance at 7–10 weeks of gestation was high (sensitivity, 87.4%; specificity, 95.2%) for fetal loss at < 14 weeks. Our results suggest that predictive accuracy using CRL discordance is poor for fetal losses occurring later in pregnancy, i.e. stillbirth and perinatal loss. These results were consistent when restricting the analysis to CRL discordance recorded at the 11–14-week scan.

CRL discordance at 11–14 weeks of gestation is commonly a reason to counsel parents concerning the possibility of an adverse pregnancy outcome. However, optimal management of the pregnancy in cases with CRL discordance is undetermined. The results of this review indicate that, although CRL discordance carries a significantly higher risk of an adverse pregnancy outcome, predictive accuracy is poor, thus limiting its use in clinical practice as a screening parameter. In view of this association a longitudinal assessment of fetal growth is warranted, to detect the presence of growth discordance which is significantly and independently associated with perinatal mortality in twin pregnancies[3]. Although data from the published literature did not permit a meta-analysis on the risk

Figure 3 Forest plots showing relative risks for the five categories of adverse outcome investigated in this systematic review of twin pregnancies with crown–rump length discordance ≥ 10% detected at the 11–14-week scan. Only the first author of each study is given. Adverse outcomes: (a) all fetal losses; (b) fetal loss < 24 weeks; (c) fetal loss ≥ 24 weeks; (d) birth-weight discordance; (e) preterm birth.

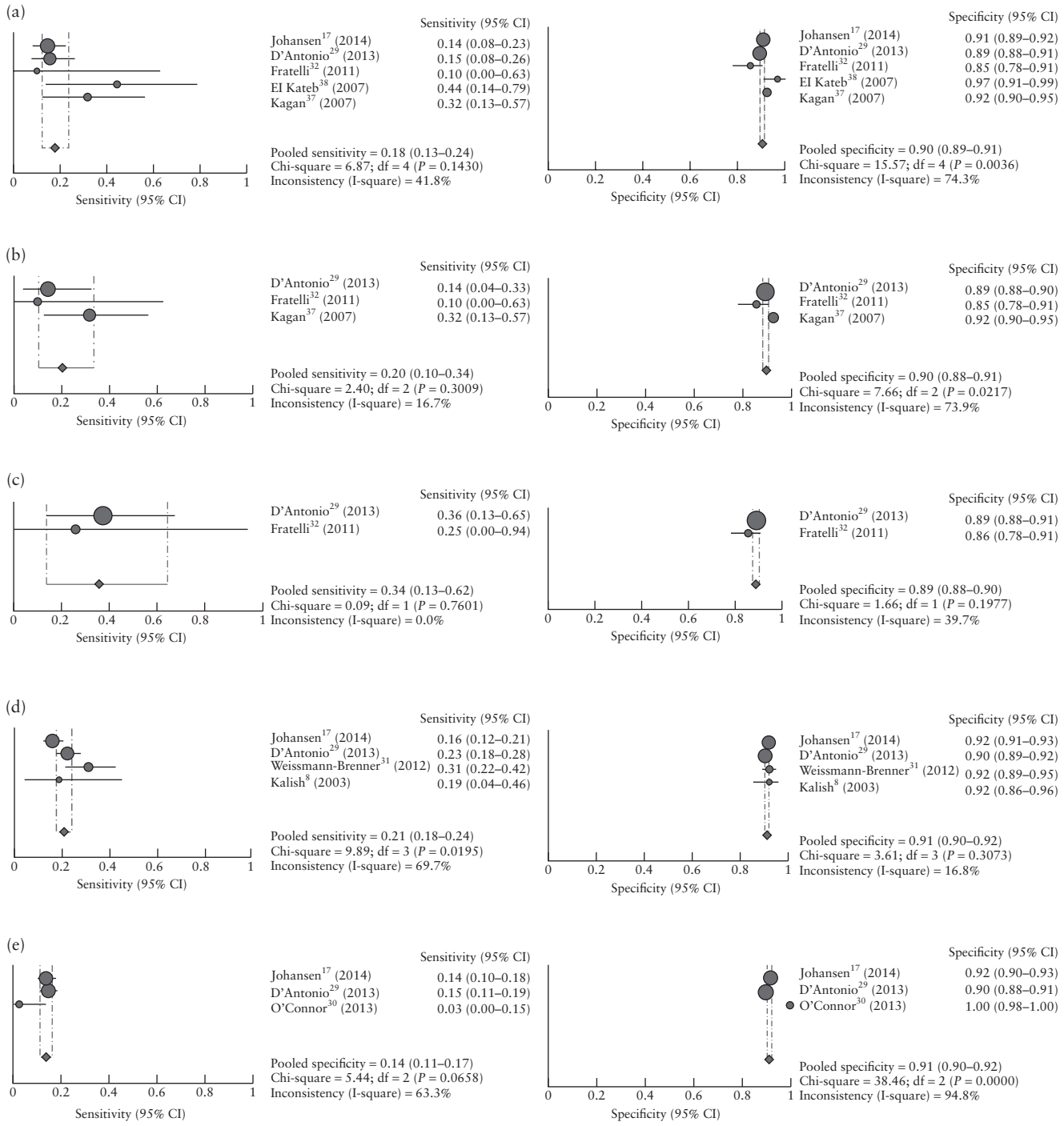


Figure 4 Forest plots showing sensitivity and specificity of crown–rump length discordance ≥ 10% detected at the 11–14-week scan for the five categories of adverse outcome in twin pregnancies investigated in this systematic review. Only the first author of each study is given. Adverse outcomes: (a) all fetal losses; (b) fetal loss < 24 weeks; (c) fetal loss ≥ 24 weeks; (d) birth-weight discordance; (e) preterm delivery.

of chromosomal and structural abnormalities, the choice of a prenatal invasive test might be a reasonable option, especially if additional first-trimester ultrasound markers of aneuploidy are detected at the first-trimester scan.

Fetuses with chromosomal abnormalities have been reported to have a smaller than expected CRL and twin pregnancies affected by aneuploidy are recognized to have significant CRL discordance[39,40]. Future research should aim to evaluate the role of CRL discordance detected between 11 and 14 weeks of gestation in predicting chromosomal and structural abnormalities in the context of recent advances in first-trimester combined screening and non-invasive prenatal diagnosis[41].

The data from this meta-analysis reveal the relative risks and the diagnostic accuracy of CRL discordance for different adverse pregnancy outcomes. Several cut-offs of CRL discrepancy have been reported and the association between CRL discordance and an adverse outcome is highly dependent on the threshold adopted. The decision to limit analysis to only those pregnancies with

discordance ≥ 10%, although introducing a selection bias, was justified by the fact that this threshold was that most commonly used to represent the higher centiles of discordance in twin pregnancies (Table 1). Furthermore, different definitions of fetal and perinatal loss, BW discordance and PTD have been reported in different studies; it was thus impossible to include more studies in the meta-analysis for each of the outcomes explored. The small number of studies for each outcome, the over representation of monochorionic twins and the exclusion of studies from which crude data could not be extracted are other major limitations of this systematic review.

In conclusion, CRL discordance is associated with a higher risk of adverse pregnancy outcome. However, the predictive accuracy of CRL discordance is low and, therefore, the results of this review do not suggest its use in clinical practice as a screening parameter for adverse pregnancy outcome. Further large studies are needed to evaluate the strength of association between discordance in CRL and chromosomal or structural abnormalities. Longitudinal assessment of fetal growth is warranted for timely detection of significant discordance in BW.

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SUPPORTING INFORMATION ON THE INTERNET

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

Appendix S1 Search strategy (databases and terms).

Appendix S2 Excluded studies and reasons for exclusion.

Table S1 Relative risk of adverse outcomes in twin pregnancies with crown–rump length discordance at the 11–14-week scan, according to chorionicity.

Table S2 Predictive accuracy of crown–rump length discordance at the 11–14-week scan, according to chorionicity.