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Systematic Review

Association between chorionicity and preterm birth in twin pregnancies: a systematic review involving 29 864 twin pregnancies

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Background The perinatal mortality and morbidity among twins vary by chorionicity. Although it is considered that monochorionicity is associated with an increased risk of preterm birth in twin pregnancies, no systematic review exists evaluating this association.

Objectives This systematic review was undertaken to assess the association between preterm birth and chorionicity in twin pregnancies.

Search strategy We searched the electronic databases from January 1990 to July 2019 without language restrictions.

Selection criteria All studies on twin pregnancies where chorionicity and preterm birth were evaluated were included.

Data collection and analysis Findings are reported as odds ratios with 95% confidence intervals. The estimates are pooled using random-effects meta-analysis.

Main results From 13 156 citations, we included 39 studies (29 864 pregnancies). Monochorionicity was significantly associated with increased risk of preterm birth at ≤28, ≤32, ≤34 and <37 weeks in women asymptomatic and symptomatic for preterm labour (odds ratio [OR] 2.14, 95% CI 1.52–3.02, I^2 = 46%, OR 1.55, 95% CI 1.27–1.89 I^2 = 68%, OR 1.47, 95% CI 1.27–1.69, I^2 = 60%, OR 1.66, 95% CI 1.43–1.93, I^2 = 65%, respectively). Among those asymptomatic for preterm labour, significantly increased odds of preterm birth were seen for monochorionicity at gestations ≤34 weeks (OR 1.85, 95% CI 1.42–2.40, I^2 = 25%) and <37 weeks (OR 1.75, 95% CI 1.22–2.53, I^2 = 61%). Sensitivity analysis showed significantly increased odds of spontaneous preterm birth at ≤34 and <37 weeks for monochorionicity (OR 1.25, 95% CI 1.01–1.55, I^2 = 0% and OR 1.41, 95% CI 1.13–1.78, I^2 = 0%).

Conclusions Monochorionicity is significantly associated with preterm birth at all gestations.

Keywords Chorionicity, multiple pregnancy, preterm birth, preterm labour, twins, ultrasound predictors.

Tweetable abstract In twin pregnancies, monochorionicity is associated with an increased risk of preterm birth at all gestations.

Linked article This article is commented on by C Andrew Combs, p. 797 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16516.

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Introduction

Twin pregnancies are associated with a significantly higher rate of perinatal morbidity and mortality compared with singleton pregnancies.[1] The major contributing factor to this problem is prematurity.[2] A four-fold higher risk of mortality is seen among twins due to preterm birth. The number of twin gestations has increased dramatically over the past few decades due to the expansion of assisted reproductive technology and increase in maternal age at conception.[3] Therefore, tools to predict preterm birth in twin pregnancies are necessary to identify those at risk of

preterm birth at an early stage so that necessary preventive measures can be taken.

The perinatal mortality and morbidity among twins vary significantly by chorionicity. Several studies have shown that monochorionicity imparts greater risk of preterm birth, stillbirth, perinatal mortality and neonatal intensive care unit admission compared with dichorionic twins.[4–7] The particular challenges of monochorionic pregnancies arise from the shared placenta and the placental vascular anastomoses that are almost universal, leading to complications such as twin-twin transfusion syndrome (TTTS), selective growth restriction, twin reversed arterial perfusion sequence, twin anaemia-polycythaemia sequence and single intrauterine death.[8]

Although it is well established that monochorionic twin pregnancies are associated with an increased risk of preterm birth, no systematic reviews exist evaluating the relation between chorionicity and preterm birth in twin pregnancies. Available studies vary in sample sizes, and risk estimates are imprecise. We hence undertook this systematic review to assess the risk of preterm birth in twin pregnancies for chorionicity.

Methods

We conducted a comprehensive review using a prospective protocol and complied with standard reporting guidelines. The PROSPERO ID of the protocol for this study is CRD42019147871. This protocol was registered for a review on ultrasound predictors of preterm birth in twin pregnancies. Due to the large volume of data on each of the predictors, we aim to publish a series of systematic reviews, one of which is this review on chorionicity.

Search strategy and study selection criteria

The electronic databases MEDLINE, Embase, CINAHL and LILACS were searched without language restrictions, to identify potentially eligible studies on preterm birth in twin pregnancies which were published from 1 January 1990 to July 2019. The search terms 'twin pregnancy', 'multiple pregnancies' were used and combined with terms for outcomes such as 'preterm', 'prematurity', 'preterm birth' or 'premature birth'. Additionally, terms for predictors which include 'chorionicity', 'monochorionic', 'dichorionic' were included and combined with the above terms. Where applicable, we 'exploded' the search terms. Appendix S1 outlines the full search strategy. A manual search of the reference lists of all primary studies and previously published systematic reviews was performed to supplement the database search.

A two-stage process was followed in study selection. Initially, we screened the titles and abstracts of the total hits from the database search to identify relevant citations for full-text evaluation. The full texts of the selected citations were then screened and the ones satisfying the inclusion criteria were included. This process was carried out independently by two reviewers, (SM and CD) and any disagreements were resolved by consensus after discussion with another reviewer (ST).

We included studies involving both monochorionic and dichorionic twin pregnancies with spontaneous or iatrogenic preterm birth at ≤28, ≤32, ≤34 or <37 weeks of gestation. Case reports, case series, in vitro studies and animal studies were excluded. We accepted the primary study authors' definitions, stratifications or thresholds for the selected factors assessed. No minimal sample size was required for inclusion.[9] Any method for estimation of gestational age was accepted.

There was no involvement of patients in the development of this systematic review, and a core outcome set was not used. There was no funding source for this study.

Study quality assessment and data extraction

The Newcastle Ottawa Scale (NOS) was used to assess the methodological quality of the included studies, by two independent reviewers (SM and CD).[9] The risk of bias in the selection, comparability and outcome assessment of cohorts were evaluated, and stars allotted for adherence to the pre-specified criteria. Studies that scored four stars for selection, two stars for comparability between the cohorts and three stars for the ascertainment of outcome were regarded to have a low risk of bias. Studies that had two or three stars for selection, one for comparability and two for outcome ascertainment were considered to have a medium risk of bias. Any study with a score of one for selection or outcome ascertainment, or zero for any of the three domains was considered to have a high risk of bias.[10]

Data were extracted in duplicate by two reviewers (SM and CD) and recorded on a customised data extraction sheet (Annexure 1). Dichotomous data were extracted to 2 × 2 tables. Authors were contacted by email for relevant data if insufficient data were reported in the original article. If multiple studies were published for the same outcomes from the same cohort of subjects, only the most recent study was included.

Statistical analysis

The estimates of the individual studies were calculated using random-effects meta-analysis, and the summary estimates were presented as odds ratios (OR) with 95% confidence intervals (CI). Heterogeneity was assessed with the I^2 statistics. Sensitivity analysis was performed for spontaneous preterm birth and preterm birth, excluding twin-twin transfusion syndrome. A visual exploration of funnel plot asymmetry to detect small-study effects was performed where more than ten studies were available.[11] REVMAN[12] and STATA 13.0.[13] were used for all analyses.

Results

From 13 156 citations, we included 39 studies (29 864 pregnancies). Figure 1 depicts the process of selecting studies.

Characteristics of the included studies

Of the 39 studies, 29 were retrospective cohorts,[4,14–41] eight were prospective cohorts[42–49] and two were cohorts nested within randomised controlled trials.[50,51] Thirty-two studies were conducted in high-income countries (USA 6, UK 6, Portugal 5, Italy 4, Denmark 3, Korea 2, Germany 1, Austria 1, Israel 1, Taiwan 1, Poland 1, Canada 1, France 1, Sweden 1, Netherlands 1), five in upper-middle-income countries (Brazil 2, China 2, Iran 1) and two in a middle-income country (Pakistan). All the studies were published after the year 2000. Sample sizes ranged from 70[42] to 3862.[24]

Nearly 64% of the studies (25/39) explicitly excluded complicated twin pregnancies such as twin-twin transfusion syndrome (12 studies),[18,20,26,28,35,37,38,41,45,47,49,51] monoamniotic pregnancies (16 studies),[4,17,18,20,22,28,31,33,37–39,45,47,48,50,51] fetal chromosomal abnormalities (9 studies),[14,17,20,29,34,35,37,38,51] major fetal structural anomalies (15 studies),[14,17,18,20,26,28,29,35,37,38,45,46,49–51] selective fetal reduction (6 studies),[14,18,31,36,38,51] selective intrauterine growth restriction (1 study),[41] twin anaemia-polycythaemia sequence (1 study)[41] and twin reversed arterial perfusion sequence (2 studies).[28,41]

Seven of the 39 studies (18%) reported on pregnancies which are asymptomatic for preterm labour[20,22,34,38,45,50,51] whereas 31 studies reported on pregnancies which were both symptomatic and asymptomatic for preterm labour.[4,14–19,21,23,24,26–33,35–37,39–44,46–49] Seven studies (18%) reported on treatment or prophylaxis for preterm labour.[36,37,39,42,48,50,51] Around 80% (31/39) of the studies

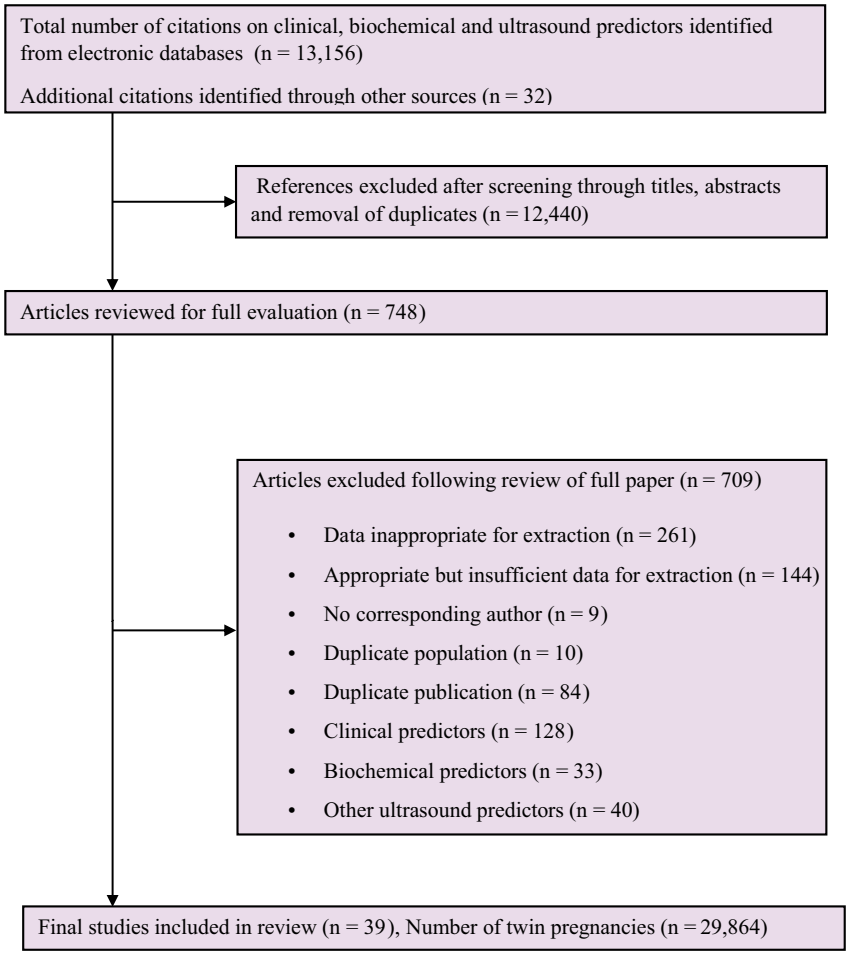

Figure 1. Study selection process in the systematic review of association between chorionicity and preterm birth in twin pregnancies.

reported on both spontaneous and iatrogenic preterm birth[4,14–36,38,39,41,42,46,47,49], and 26% of the studies (10/39) reported on spontaneous preterm birth.[23,37,38,40,43–45,48,50,51] Eleven studies reported on preterm birth ≤28 weeks (28%),[4,18,20,23,26,32,38,41,44,47,48] 23 studies on preterm birth ≤32 weeks (59%),[4,14–16,19,20,23–25,27–29,32,36–39,41,45,47–50] 22 studies on preterm birth ≤34 weeks (56%)[4,15,18–20,24,26–28,30–32,38,40,43–48,50,51] and two-thirds of the studies on preterm birth <37 weeks (67%).[4,15–17,19,21–23,25–29,32–36,38,39,42,44,46–48,51] Characteristics of the included studies are given in Table S1.

Quality of the included studies

Quality of the included studies is shown in Figure 2. In all, 97% of the studies were low risk for study selection (38/39),[4,14–38,40–51] 10% (4/39) were low risk for comparability[28,32,40,49] and all studies were low risk for study outcome (100%).[4,14–51] One study had a medium risk of bias for study selection (3%),[39] 32 studies for comparability[4,14,15,17,20–27,29–31,33–39,41–48,50,51] and none of the studies had a medium risk of bias for outcome. None of the studies had a high risk of bias for selection or outcome; however, three studies were of high risk for comparability.[16,18,19]

Chorionicity as a predictor of preterm birth among women symptomatic and asymptomatic for preterm labour

Monochorionicity was studied as a predictor of preterm birth at ≤28 weeks in 11 studies (10 484 pregnancies),[4,18,20,23,26,32,38,41,44,47,48] ≤32 weeks in 23 studies (19 783 pregnancies),[4,14–16,19,20,23–25,27–29,32,36–39,41,45,47–50] ≤34 weeks in 22 studies (21 181 pregnancies)[4,15,18–20,24,26–28,30–32,38,40,43–48,50,51] and <37 weeks in 26 studies (15 997 pregnancies).[4,15–17,19,21–23,25–29,32–36,38,39,42,44,46–48,51] A significantly high odds of preterm birth was seen for monochorionic twin pregnancies at all four gestations studied among women symptomatic and asymptomatic for preterm birth, as summarised in Table 1.

Chorionicity as a predictor of preterm birth among women asymptomatic for preterm labour

In women who were asymptomatic for preterm labour, significantly increased odds of preterm birth was seen at gestations ≤34 weeks (OR 1.85, 95% CI 1.42–2.40, I^2 = 25%)[20,38,45,50,51] and <37 weeks (OR 1.75, 95% CI 1.22–2.53, I^2 = 61%).[22,34,38,51] However, the odds of preterm birth was not found to be significantly increased at ≤28 weeks[20,38] or ≤32 weeks,[20,38,45,50] as shown in Table 1.

Sensitivity analysis

Sensitivity analysis was performed for spontaneous preterm birth and for preterm birth among studies that had excluded twin-twin transfusion syndrome. Monochorionicity was significantly associated with an increased risk of spontaneous preterm birth at ≤34 weeks (OR 1.25, 95% CI 1.01–1.55, I^2 = 0%) and <37 weeks (OR 1.41, 95% CI 1.13–1.78, I^2 = 0%) as evaluated in eight studies (3048 pregnancies)[38,40,43–45,48,50,51] and five studies (1999 pregnancies),[23,38,44,48,51] respectively. However, the odds of spontaneous preterm birth were not significantly increased at gestations ≤28 weeks as assessed in three studies (1641 pregnancies),[38,44,48] and at ≤32 weeks as assessed in five studies (2465 pregnancies).[37,38,45,48,50] Table 2 and Figure S2 show the pooled odds ratios for spontaneous preterm birth.

Among studies where twin-twin transfusion syndrome was excluded, we identified six studies that reported on any preterm birth at ≤28 weeks (8315 pregnancies),[18,20,26,38,41,47] eight studies at ≤32 weeks (8658 pregnancies),[20,28,37,38,41,45,47,49] eight studies at ≤34 weeks (9342 pregnancies)[18,20,26,28,38,45,47,51] and six studies at <37 weeks (4650 pregnancies).[26,28,35,38,47,51] The results of our sensitivity analysis demonstrated that monochorionicity was associated with

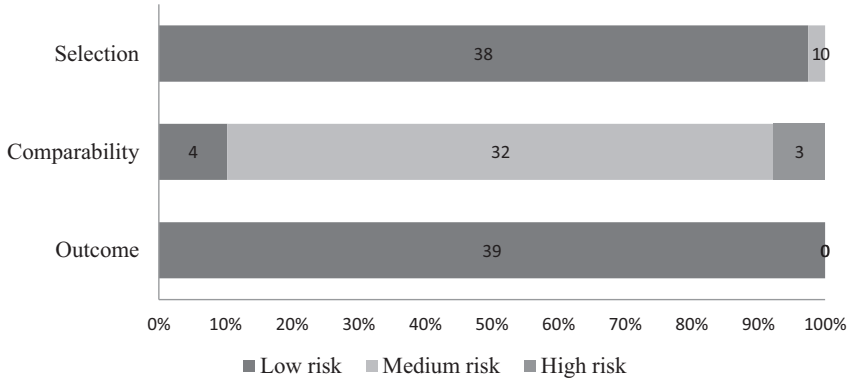

Figure 2. Quality assessment using the Newcastle Ottawa Scale in the systemic review of association between chorionicity and preterm birth in twin pregnancies.

Table 1. Pooled odds ratios (OR) for preterm birth (PTB) in the systematic review of association between chorionicity and preterm birth in twin pregnancies

Predictor	Outcome: PTB	No. of studies	Monochorionicity		Dichorionicity		OR (95% CI)	*P*-value	I^2 (%)
			No. of PTB	No. of women	No. of PTB	No. of women			
Symptomatic and asymptomatic women									
Monochorionicity versus dichorionicity	≤28 wk	11	121	2372	206	8112	2.14 (1.52–3.02)	0.0001	46
	≤32 wk	23	680	4571	1575	15,211	1.55 (1.27–1.89)	0.0001	68
	≤34 wk	22	1266	4649	3320	16,532	1.47 (1.27–1.69)	0.00001	60
	<37 wk	26	2455	3917	6437	12,080	1.66 (1.43–1.93)	0.00001	65
Asymptomatic women									
Monochorionicity versus dichorionicity	≤28 wk	2	22	698	49	2830	1.63 (0.97–2.72)	0.06	0
	≤32 wk	4	84	826	257	3264	1.29 (0.99–1.68)	0.06	0
	≤34 wk	5	197	854	435	3450	1.85 (1.42–2.40)	0.00001	25
	<37 wk	4	318	518	590	1230	1.75 (1.22–2.53)	0.003	61

Table 2. Pooled odds ratios (OR) for spontaneous preterm birth (SPTB) in the systematic review of association between chorionicity and preterm birth in twin pregnancies

Predictor	Outcome: SPTB	No of studies	Monochorionicity		Dichorionicity		OR (95% CI)	*P*-value	I^2 (%)
			No. of SPTB	No. of women	No. of SPTB	No. of women			
Symptomatic and asymptomatic women									
Monochorionicity versus dichorionicity	≤28 wk	3	31	392	67	1249	1.90 (0.79–4.60)	0.15	65
	≤32 wk	5	54	677	144	1788	1.05 (0.65–1.70)	0.83	43
	≤34 wk	8	162	748	420	2300	1.25 (1.01–1.55)	0.04	0
	<37 wk	5	272	469	718	1530	1.41 (1.13–1.78)	0.003	0

a significantly higher risk of any preterm birth at gestation ≤28 weeks (OR 2.05, 95% CI 1.42–2.95, I^2 = 37%) and ≤34 weeks (OR 1.58, 95% CI 1.10–2.27, I^2 = 0%). As for spontaneous preterm birth among twin pregnancies excluding twin-twin transfusion syndrome, a significantly increased odds of preterm birth was seen only at ≤34 weeks' gestation (OR 1.26, 95% CI 1.02–1.54, I^2 = 61%) as evaluated in three studies.[38,45,51] The odds of spontaneous preterm birth was not significantly increased among monochorionic twin pregnancies at gestations ≤32 weeks,[37,38,45] and <37 weeks.[38,51] The risk of spontaneous preterm birth at gestation ≤28 weeks was not evaluated due to the limited number of studies (Table S2 and Figure S3).

Small-study effects

Egger's method was used to assess funnel plot asymmetry. Small-study effect was not evident for any of the outcomes and chorionicity in the symptomatic and asymptomatic group (Figure S1).

Discussion

Main findings

This systematic review has provided us with precise quantitative estimates of the association between monochorionicity and preterm birth among women with twin pregnancies. Monochorionicity was significantly associated with preterm birth at ≤28, ≤32, ≤34 and <37 weeks both in women who were asymptomatic for preterm labour and in those symptomatic for preterm labour. Among women asymptomatic for preterm labour, monochorionicity was significantly associated with preterm birth at ≤34 and <37 weeks' gestation. A high risk of spontaneous preterm birth was seen in monochorionic twin pregnancies at

gestations ≤34 and <37 weeks. In studies that excluded twin-twin transfusion syndrome, monochorionicity was significantly associated with any preterm birth at gestations ≤28 and ≤34 weeks and spontaneous preterm birth at gestations ≤34 weeks.

Strengths and limitations

Our systematic review is the first comprehensive assessment between chorionicity and preterm birth in twin pregnancies. Due to the large sample size, we were able to provide precise information regarding the association between chorionicity and preterm birth. We used a prospective protocol for our review and also performed a thorough literature search without any language restrictions, thereby increasing the chance of capturing all relevant studies. We explored the sources of heterogeneity. A comprehensive study quality assessment was performed, and we assessed the effect of study quality on the results. We undertook a robust methodology, and we were able to show a positive association between monochorionicity and preterm birth.

Limitations in our review are mainly due to the disparities in the inclusion and exclusion criteria among different studies. Some studies included only spontaneous preterm birth, whereas most studies included data on both spontaneous and iatrogenic preterm delivery. Exclusion criteria varied, with some studies excluding complications specific to monochorionic twin pregnancies such as twin-twin transfusion syndrome, monoamnionicity, twin anaemia-polycythaemia sequence, twin reversed arterial perfusion sequence, and others also excluding non-specific complications such as major structural fetal anomalies, fetal chromosomal abnormalities, selective fetal reduction and selective intrauterine growth restriction. Only a few studies reported on treatment or prophylaxis for preterm labour. Such treatment could have led to the underestimation of the actual number of preterm births. A majority of the studies were conducted in high-income countries, with only seven being conducted in upper-middle or middle-income countries.

The results of our review did not show a significantly high odds of preterm birth at gestations ≤28 and ≤32 weeks among twin pregnancies asymptomatic for preterm labour and women with spontaneous preterm birth. The limited number of studies at these gestations may have possibly contributed to this result. Also, a sensitivity analysis was not possible for twin pregnancies excluding all complications specific to monochorionicity, as only one such study was identified. Although we evaluated the effect of chorionicity on preterm birth by limiting the number of studies to those that excluded twin-twin transfusion syndrome, we were unable to demonstrate a statistically significant difference at ≤32 and <37 weeks' gestations, which may have been contributed by the limited number of studies. Furthermore, due to the paucity of studies, we were unable to perform a meta-analysis for spontaneous preterm birth at ≤28 weeks' gestation among this group.

Ideally, if the studies presented a strict follow-up protocol for twin-twin transfusion syndrome, the robustness of diagnosis would be high. However, no study provided such detail; hence, the primary author's diagnosis of twin-twin transfusion syndrome was accepted, limiting the potential for diagnosis in some studies where it may have gone unrecognised. Also, due to the paucity of information in the published studies, we were unable to undertake a meta-analysis for adjusted prognostic effect estimates.

Interpretation

Although it is assumed that monochorionicity is associated with an inherently higher risk of preterm delivery, this is the first systematic review evaluating the association between chorionicity and preterm birth in twin pregnancies. Our review demonstrated a significant association between monochorionicity and preterm birth in twin pregnancies at all gestations for any preterm birth among women both asymptomatic and symptomatic for preterm labour.

Experts recommend delivery of monochorionic twins, even among those uncomplicated, as early as 34 weeks and indeed less than 37 weeks.[52,53] Planned delivery is recommended for uncomplicated monochorionic diamniotic twin pregnancies from 36^{+0} weeks' gestation, as per NICE guidelines.[8] These recommendations may have led to the observed increase in overall preterm birth among monochorionic twin pregnancies contributed by iatrogenic prematurity; however, from our review we were able to demonstrate a high risk of spontaneous preterm birth for monochorionicity at gestations ≤34 and <37 weeks.

Even after exclusion of twin-twin transfusion syndrome, we were able to observe a high risk of spontaneous preterm birth among monochorionic twin pregnancies at ≤34 weeks' gestation, suggesting that monochorionicity by itself has a high association with spontaneous preterm birth. Therefore, even among those with apparently uncomplicated monochorionic twin pregnancies, there appears to be an increased risk of preterm birth which must be considered when counselling and managing women with monochorionic twin pregnancies.

Conclusion

Monochorionicity is significantly associated with preterm birth at all gestations in women both symptomatic and asymptomatic for preterm labour. Among twin pregnancies asymptomatic for preterm labour and women with spontaneous preterm birth, monochorionicity is significantly associated with preterm birth at gestations ≤34 and <37 weeks.

The absence of robust evidence in predicting preterm birth among twin pregnancies has been consistently emphasised across all guidelines. The focus on predicting preterm birth in twin gestations has been mainly on cervical length assessment and fetal fibronectin. Current evidence for predicting preterm birth supports the use of cervical length screening at 18–24 weeks for asymptomatic twin pregnancies;[54–56] the routine use of fetal fibronectin is not recommended due to its limited predictive accuracy.[57]

The early diagnosis of monochorionicity by sonography enables us to identify and counsel women regarding their inherently high risk of preterm birth. Necessary measures can then be taken for early referral, close follow up and initiation of preventive measures to minimise complications associated with preterm birth.

Our systematic review was able to provide an association between chorionicity and preterm birth using aggregate data meta-analysis. Ideally, with access to individual participant data meta-analysis, other factors that might affect preterm birth could be explored; therefore, further research utilising such methodology is recommended.

Disclosure of interests

All authors have no financial, personal, political, intellectual or religious interests. Completed disclosure of interests forms are available to view online as supporting information. All authors declare no support from any organisation for the submitted work; no financial relations with any organisations that might have an interest in the submitted work; no other relations or activities that could appear to have influenced the submitted work.

Contribution to authorship

SM was fully involved in the conception, planning, literature search, study selection, data extraction, data analysis and writing up of the review. CD was involved in the literature search, study selection, data extraction, analysis, and writing up of the review. RN was involved in data analysis and writing up during revisions. RM was involved in the literature search and study selection. John Allotey was involved in data analysis and writing up. Joseph Aquilina was involved in writing up the review and supervision. AK was involved with writing up of the review and supervision. ST was involved in the conception, planning, data extraction, data analysis, writing up and overall supervision.

Details of ethics approval

Not required.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Assessment of small-study effects.

Figure S2. Pooled odds ratios (OR) for spontaneous preterm birth (SPTB).

Figure S3. Pooled odds ratios (OR) for spontaneous preterm birth (SPTB) in studies excluding twin-twin transfusion syndrome.

Table S1. Study characteristics in the systematic review of association between chorionicity and preterm birth in twin pregnancies

Table S2. Pooled odds ratios (OR) for preterm birth (PTB) in studies excluding TTTS in the systematic review of association between chorionicity and preterm birth in twin pregnancies

Appendix S1. Search strategy used in the systematic review of association between chorionicity and preterm birth in twin pregnancies. ■

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