BMJ Open

Association of antenatal corticosteroids with morbidity and mortality among preterm multiple gestations: meta-analysis of observational studies

Dongxin Lin,[1,2] Dazhi Fan,[1,2] Gengdong Chen,[1,2] Caihong Luo ,[2] Xiaoling Guo,[1,2] Zhengping Liu [1,2]

To cite: Lin D, Fan D, Chen G, *et al*. Association of antenatal corticosteroids with morbidity and mortality among preterm multiple gestations: meta-analysis of observational studies. *BMJ Open* 2021;**11**:e047651. doi:10.1136/bmjopen-2020-047651

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-047651).

Received 07 December 2020
Accepted 07 September 2021

[1]Foshan Institute of Fetal Medicine, Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, Guangdong, China
[2]Department of Obsterics, Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, Guangdong, China

Correspondence to
Dr Caihong Luo;
lawcaihong@outlook.com

ABSTRACT

Objective This meta-analysis aimed to assess the efficacy of antenatal corticosteroids (ACS) on morbidity and mortality among preterm multiple pregnancies.

Methods The PubMed, Embase, Web of Science and Cochrane Library databases were searched for studies investigating the outcomes among preterm multiple gestations following to ACS, from their inception to 1 November 2020. Two authors independently performed the study selection, risk of bias assessment and data extraction. The primary outcomes were respiratory distress syndrome (RDS) and mortality and secondary outcomes included intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), necrotising enterocolitis, retinopathy of prematurity and bronchopulmonary dysplasia. Pooled ORs were obtained using random effects models. Subgroup analyses were performed to explain heterogeneity by ACS completeness, administration-to-delivery intervals (≤7 days) and single or multicentre.

Results A total of 16 observational studies with 36 973 newborns were included in the meta-analysis. ACS treatment was associated with a reduction in RDS (OR 0.66; 95% CI 0.54 to 0.82; I^2=91.4%; p<0.001), mortality (OR 0.64; 95% CI 0.50 to 0.81; I^2=85.9%; p<0.001), IVH (OR 0.67; 95% CI 0.54 to 0.83; I^2=77.4%; p<0.001) and PVL (OR 0.65; 95% CI 0.47 to 0.92; I^2=75.5%; p<0.001). Subgroup analyses showed ACS completeness, administration-to-delivery interval and multicentre study affected these associations.

Discussion ACS may be beneficial for reducing the risks of RDS, mortality, IVH and PVL among preterm multiple gestations. The efficacy of ACS could be affected by ACS completeness and administration-to-delivery. More robust evidence on the efficacy of ACS treatment among multiple gestations is warranted.

Strengths and limitations of this study

- ► This is a meta-analysis investigating the benefits of antenatal corticosteroids (ACS) in preterm multiple gestations since this group is not addressed separately in previous systematic reviews.
- ► We aimed to generate pooled estimates of effect of ACS on important outcomes of newborns in multiple pregnancies.
- ► No evidence of randomised controlled trials was available; thus, we focused on observational studies and synthesised the evidence in real world.
- ► The high heterogeneity remained in some subgroups, which suggested the presence of unexplained heterogeneity.

INTRODUCTION

Preterm birth (PTB) is one of the most common complications and the leading cause of perinatal morbidity and mortality among multiple gestations.[1–3] In the USA, the rates of PTB (<37 weeks, 60.32%) and early PTB (<34 weeks, 19.52%) among twin pregnancies were substantially higher than those among singletons (10.02% for PTB <37 weeks and 2.75% for PTB <34 weeks) in 2018.[4] The rate of PTB among multiple gestations remains at a high level in many countries.[5–8]

Improving the prognosis of premature newborns has become an important issue in clinical practice. Liggins and Howie first demonstrated the advantage of treatment with antenatal corticosteroids (ACS) to promote lung maturation and reduce respiratory distress syndrome (RDS) among premature infants.[9] The effect of a single course of ACS prior to PTB on reduction not only in RDS but also in other complications related to prematurity have been ascertained by the latest Cochrane review.[10] Although this prophylactic treatment is recommended for potential premature births by the American College of Obstetricians and Gynecologists[11] and the Royal College of Obstetricians and Gynecologists,[12] there remains a controversy regarding multiple gestations.[13 14] While the efficacy of ACS treatment in singletons is supported by abundant evidence, the current evidence in multiple gestations is limited and less consistent.[15–25]

Therefore, we aimed to perform a meta-analysis of observational studies investigating the efficacy of ACS treatment on neonatal mortality and morbidity among multiple PTB.

METHODS

The meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (available in online supplemental table S1)[26] and Meta-analysis of Observational Studies in Epidemiology Guidelines.[27]

Patients and public involvement statement

No individual patient was involved in the study design, conduct, reporting or dissemination.

Literature search and study selection

We conducted a systematic literature search in the PubMed, Embase, Web of Science and Cochrane Library databases using a search strategy that combined the following keywords/MeSH terms: (1) steroids, corticosteroids, betamethasone, dexamethasone, hydrocortisone, (2) preterm, premature, (3) prenatal, antenatal, antepartum and (4) twins, multiple gestation, twin pregnancy. Articles in English were searched from their inception to 1 November 2020. Search strategies for each database are shown in online supplemental table S2. All records retrieved from literature search were imported into Endnote and duplicate records were first removed. Then, the titles and abstracts of the remaining studies were screened for potential eligibility based on the search strategies. Third, full texts were reviewed based on the inclusion criteria. In addition, the references were manually searched in the procedure of full-text review.

Eligible criteria

Studies that met the following inclusion criteria were eligible for the current meta-analysis: (1) the study evaluated the association of ACS treatment with morbidity and/or mortality (comparison between ACS and non-ACS users); (2) the outcomes assessed in individual studies were within the scope of outcomes of interest in the current meta-analysis and (3) the study provided results in subgroups of multiples if it enrolled both singleton and multiple pregnancies. Studies were excluded if they did not provide relevant data on the incidence or ORs of outcomes of interest between ACS and non-ACS users. Articles published as conference abstracts, letters to the editor or systematic reviews were also excluded due to insufficient information. We imposed no restriction on the study design in current meta-analysis in the procedure of study selection.

Risk of bias and evidence quality assessment

The risk of bias of the included studies was assessed based on the Newcastle-Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), which consists of eight items for three subscales (four items for selection, one item for comparability and three items for outcome). The maximum score is 9 (2 for the comparability item and 1 for each of the other items). A score of 5 or below indicated a high risk of bias, 6–7 points indicated an intermediate risk of bias and 8–9 points indicated a low risk of bias. We applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to assess the overall quality of evidence for each outcome across studies.[28] According to the guidelines, observational studies started as low-quality evidence. The evidence quality could be downgraded based on study limitations, imprecision, inconsistency, indirectness and publication bias, whereas it could be upgraded based on a larger magnitude of effect, a dose-response gradient and all plausible confounding which would reduce a demonstrated effect.

Data extraction

The following information regarding study characteristics and primary results was extracted by using a predesigned form: the first author, year of publication, country, study design, sample size, population characteristics, exclusion criteria, gestational age at delivery, details of ACS administration (type of drug, dose, ACS completeness and administration-to-delivery interval), outcomes reported, incidence or adjusted ORs of each outcome. The results of the subgroup analysis based on complete ACS and administration-to-delivery were also extracted if available. Complete ACS was defined as four 6 mg doses of intramuscular dexamethasone at 12-hour intervals or two 12 mg doses of intramuscular betamethasone at a 24-hour intervals. Studies were categorised as 'complete ACS' when they only included cases with complete ACS or reported results in 'complete ACS' subgroups. Studies that only included cases with administration-to-delivery intervals ≤7 days or provided results in such subgroups were categorised as 'administration-to-delivery intervals ≤7 days'. Those without information on ACS completeness or the timing of therapy were categorised as 'unclear'. Two authors (GC and FD) independently performed study selection, risk of bias assessment and data extraction and any disagreements were resolved by the discussion.

Outcomes of interest

The primary outcomes in the current meta-analysis were RDS and mortality while secondary outcomes included intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), necrotising enterocolitis (NEC), retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD). These outcomes were defined by the authors of individual studies and were evaluated before hospital discharge. Overall, RDS was diagnosed based on clinical manifestations (cyanosis, grunting, retractions and tachypnoea), blood gas and radiographic chest findings, need for oxygen or lung surfactant administration; IVH (graded by Papile *et al* criteria[29]) and PVL were diagnosed based on cranial ultrasonography, MRI or autopsy; NEC (graded by Bell's criteria[30]) was diagnosed based on the clinical and radiological manifestations; ROP

(graded by the International Classification of ROP[31]) was diagnosed based on ophthalmological examination; and BPD was diagnosed based on duration of supplementary oxygen, radiographic or histological findings.

Statistical analysis

The meta-analysis was performed by using Stata V.15.1 software (StataCrop). A fixed effects model was used to calculate a pooled OR if a study only provided results on subgroups and this pooled OR was used for meta-analysis.[32] A random effects models with the Mantel-Haenszel method was used to calculate the pooled ORs and 95% CIs since we cannot discount a small study by giving it a very small weight (the way in a fixed effect model) and want to be sure that all the effect sizes are represented in the summary estimate.[33] The heterogeneity across the included studies was assessed by Cochran Q test and I^2 statistics. The heterogeneity with a $p<0.1$ for Cochran Q test or a I^2 statistics >50% was considered statistically significant. To explore the potential sources of heterogeneity, we performed subgroup analyses based on ACS completeness, administration-to-delivery interval and study design (multicentre vs single centre). Publication bias was evaluated by using Begg's and Egger's tests. A $p<0.05$ indicated potential bias. A trim-and-fill procedure was also performed to further assess the possibility of publication bias when a significant p value was found for Begg's and/or Egger's tests. To evaluate the stability of the pooled results, sensitivity analyses were carried out by omitting individual studies at a time.

RESULTS

Study selection

The process of study selection is outlined in figure 1. A total of 590 records were obtained in the literature search. Duplicate (n=161) and irrelevant records (n=373) were removed after title and abstract screening, leaving 56 studies for full-text review. Additionally, one study was regarded as potentially eligible after manually reference lists. Finally, a total of 16 studies, involving 36 973 multiple gestation infants, were included in the meta-analysis.[15–25 34–38]

Characteristics of included studies

The characteristics are presented in online supplemental table S3. There were 10 retrospective cohort studies,[16 19–23 25 34 37 38] 3 population-based studies,[17 18 24]

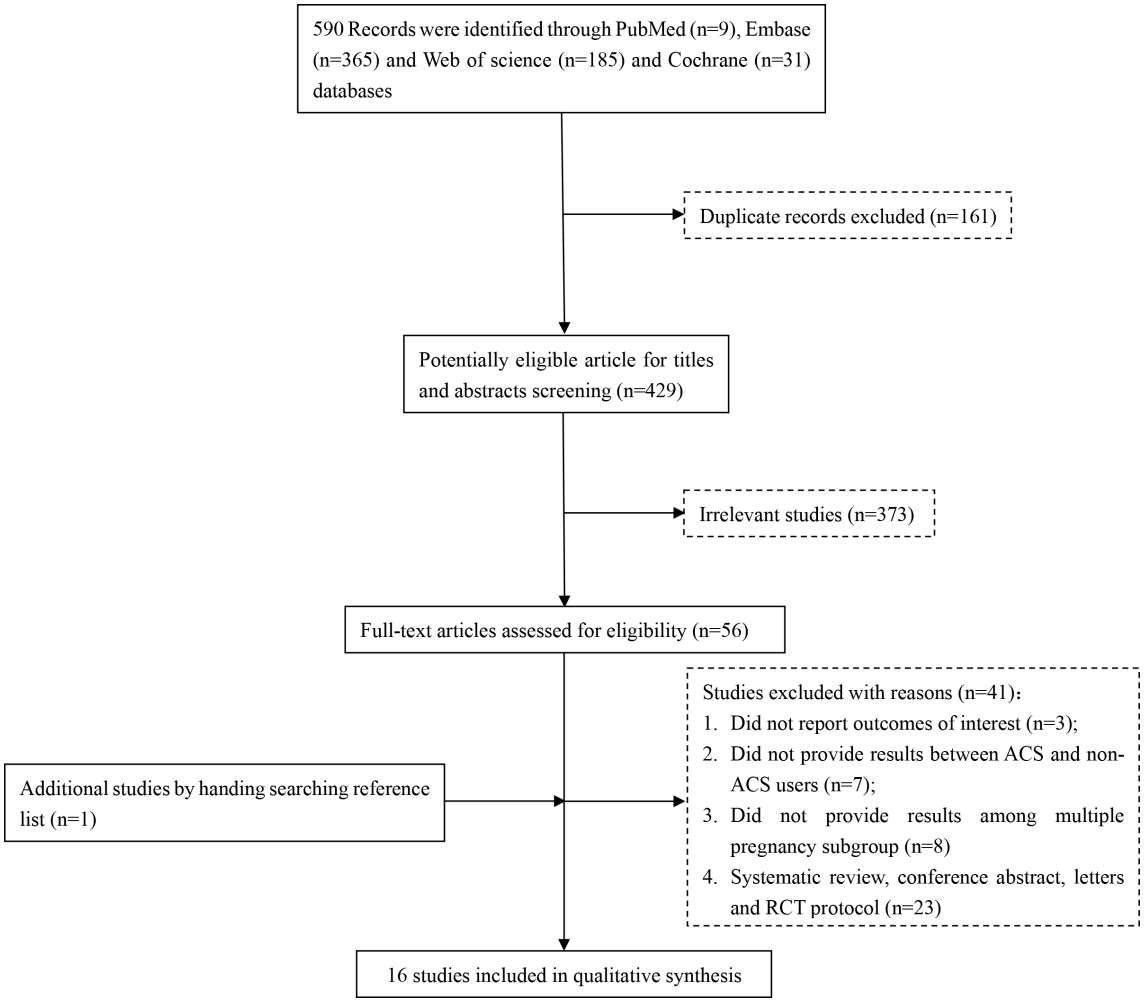

Figure 1 Flow chart of study selection. ACS, antenatal corticosteroids; RCT, randomised controlled trial.

2 prospective cohort studies[35 36] and 1 secondary analysis of randomised controlled trial (RCT).[15] Seven studies had information on the ACS administration-to-delivery interval.[16 19 20 25 34–36] Nine studies provided results on the 'complete ACS' subgroup or only enrolled patients with complete ACS treatments.[16 19–21 23 25 34–36] The range of gestational age at delivery of the included participants differed across the included studies. Four studies included triplets or higher order pregnancies.[21 22 24 25] The definition or grading of outcomes (IVH, NEC, ROP and BPD) was not all the same across included studies. Most studies included IVH ≥grade III, NEC ≥grade II and ROP ≥grade III.

Quality assessment of included studies

Overall, the quality of the included studies was good, with a score ranging from 7 to 9, based on the NOS (online supplemental table S4). All included studies were derived from non-randomised samples. Seven studies[16 20 23 34 35 38] had a risk of bias on representativeness of the exposed cohort mainly due single-centre sample or small study size. The representativeness of the non-exposed group was considered good in all 16 studies regarding the same origin as the exposed groups. Eight studies[15 17 18 22 24 37 38] had a risk of bias on ascertainment of exposure since these studies did not have specific information on the ACS course. All the studies had no bias with respect to the 'demonstration that outcome of interest was not present at start of study' since these outcomes did not occur before birth. All studies except one[16] show good comparability with controlling important confounders such as gestational age, chorionicity, birth weight and maternal age. All included studies acquired one star in 'assessment of outcome' since the data on outcomes were extracted from medical records or by database linkage. The length of follow-up was acceptable in all studies, as the outcomes were assessed before hospital discharge. Seven studies[17 20 21 25 34–36] scored no star in the 'adequacy of follow-up' item due to a lost to follow-up rate >10% or due to lacking description.

Meta-analysis of the association between ACS treatment and neonatal outcomes of preterm multiples

Respiratory distress syndrome

Fourteen studies reported results on RDS between ACS and non-ACS groups. The pooled OR was 0.66 (95% CI 0.54 to 0.82; I^2=91.4%; p<0.001), indicating that preterm twins with ACS exposure were associated with a lower risk of RDS development (table 1, online supplemental figure S1). In the subgroup analysis, we found that a lower pooled OR of RDS (OR 0.42; 95% CI 0.26 to 0.68) was obtained among participants exposed to complete ACS. A non-significant pooled OR, however, was obtained among those studies that had no information on ACS completeness (OR 0.88; 95% CI 0.71 to 1.10). In the subgroup analysis by ACS administration-to-delivery interval, preterm multiples with ACS treatment with an administration-to-delivery interval of ≤7 days had a lower pooled OR (0.34; 95% CI 0.17 to 0.70) for RDS. In contrast, those studies including pregnancies with ACS treatment with an administration-to-delivery interval of >7 days or having no information on the administration-to-delivery interval obtained a non-significant pooled OR (0.84; 95% CI 0.69 to 1.02). Single-centre studies obtained a significantly decreased pooled OR (0.47; 95% CI 0.19 to 0.90), however, multicentre studies did not (0.82; 95% CI 0.67 to 1.00) (online supplemental table S5). The GRADE assessment indicated that the overall quality of evidence for the risk of RDS was very low due to the very serious inconsistency (online supplemental table S6).

Mortality

Among 11 studies reporting neonatal mortality, a pooled OR of 0.64 (95% CI 0.50 to 0.81; I^2=85.9%; p<0.001) was obtained (table 1, online supplemental figure S2). In the subgroup analysis, the mortality was lower among preterm multiples following to a complete ACS compared with non-ACS multiples (pooled OR 0.41; 95% CI 0.32 to 0.53), but not different when the completeness of treatment was not reported (pooled OR 0.76; 95% CI 0.56 to 1.01). The mortality was lower among twins with ACS exposure, irrespective of ACS administration-to-delivery intervals. The

Table 1 Meta-analyses of the associations of ACS treatment and neonatal outcomes

			Heterogeneity		Bias	
Outcomes	No of studies	Pooled OR (95% CI)	I^2 (%)	P value	Begg's test	Egger's test
RDS	14	0.66 (0.54 to 0.82)	91.4	<0.001	0.743	0.015
Mortality	11	0.64 (0.50 to 0.81)	85.9	<0.001	0.876	0.464
IVH	11*	0.67 (0.54 to 0.83)	77.4	<0.001	0.640	0.818
PVL	8*	0.65 (0.47 to 0.92)	75.5	<0.001	0.711	0.639
NEC	7	1.02 (0.76 to 1.36)	67.2	0.006	1.000	0.403
ROP	7	0.97 (0.85 to 1.11)	38.7	0.134	0.548	0.917
BPD	8	1.00 (0.81 to 1.23)	53.3	0.036	0.536	0.747

*Two studies assessed IVH and PVL as a composite measure.
ACS, antenatal corticosteroids; BPD, bronchopulmonary dysplasia; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, periventricular leukomalacia; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

pooled OR of mortality was significantly lower among multicentre studies (pooled OR 0.64; 95% CI 0.50 to 0.82) but not among single-centre studies (pooled OR 0.59; 95% CI 0.24 to 1.43) (online supplemental table S5). The GRADE assessment indicated that the overall quality of evidence for the risk of mortality was very low due to the very serious inconsistency (online supplemental table S6).

IVH and PVL

There were nine and six studies reporting results on IVH and PVL, respectively. Another two reported results on IVH and PVL as a composite measure. We yielded a decreased pooled OR for IVH (pooled OR 0.67; 95% CI 0.54 to 0.83; I^2=77.4%; p<0.001) and PVL (pooled OR 0.65; 95% CI 0.47 to 0.92; I^2=75.5%; p<0.001) (table 1, online supplemental figure S3–S4). Subgroup analyses revealed that the odds of IVH were lower among multiples exposed to ACS, irrespective of treatment completeness or administration-to-delivery interval. The pooled OR was significant among multicentre studies (pooled OR 0.68; 95% CI 0.55 to 0.85) but not among single-centre studies (pooled OR 0.47; 95% CI 0.09 to 2.41). For PVL, the OR was lower only when mothers received complete ACS (pooled OR 0.41; 95% CI 0.21 to 0.81), delivered within 7 days after the first ACS dose (pooled OR 0.40; 95% CI 0.18 to 0.89) and among multicentre studies (pooled OR 0.66; 95% CI 0.46 to 0.93) (online supplemental table S5). The GRADE assessment indicated that the overall quality of evidence for the risk of IVH and PVL was very low due to the very serious inconsistency (online supplemental table S6).

NEC, ROP and BPD

We detected no difference in NEC (pooled OR 1.02; 95% CI 0.76 to 1.36; I^2=67.2%; p=0.006), ROP (pooled OR 1.01; 95% CI 0.94 to 1.08; I^2=38.7%; p=0.134) or BPD (pooled OR 1.00; 95% CI 0.81 to 1.23; I^2=53.3%; p=0.036) between multiple newborns with and those without ACS (table 1, online supplemental figure S5–S7). We did not find any significantly decreased pooled ORs between subgroups, based on ACS completeness, administration-to-delivery intervals and multicentre or single-centre studies (online supplemental table S5). The GRADE assessment indicated that the overall quality of evidence for the risk of NEC was very low due to the very serious inconsistency and that for the risk of ROP and BPD was low due to the serious inconsistency (online supplemental table S6).

Sensitivity and publication bias analyses

To assess the robustness of the current findings, sensitivity analyses were performed by omitting individual studies. The results confirmed that the pooled estimates of each outcome were reliable (available in online supplemental figure S8–S14).

The Begg's and Egger's tests showed no any evidence of publication bias on any outcomes (p>0.05), except RDS (Egger's test, p=0.015) (table 1). The Egger's publication bias plots for neonatal outcomes were shown in online supplemental figure S15–S21). Then we performed sensitivity analysis using the trim and fill method to assess the possibility of publication bias. No trimming was performed, and the data were unchanged throughout the analysis, suggesting the absence of publication bias for the association between ACS and RDS.

DISCUSSION

In the current meta-analysis, based on the very low-quality evidence, we found that ACS treatment may be associated with a reduction in RDS, neonatal mortality, IVH and PVL among multiple PTB, despite the substantial heterogeneity. There was no difference in NEC, ROP or BPD between preterm multiples with and without ACS treatment. Different associations of ACS treatment and RDS, mortality and PVL were found between subgroups in terms of ACS completeness, administration-to-delivery interval as well as multicentre or single-centre study. The sensitivity analyses confirmed the robustness of the current results and no publication bias was found.

The prior evidence of the efficacy of ACS among singletons has been abundant, but evidence among multiple births has been sparse and limited to small observational studies. No evidence of randomised trials on the efficacy of ACS in multiple pregnancies is currently available. We retrieved only one RCT protocol by Hong *et al*,[39] despite no restriction on study design in the literature search. Among these observational studies, the quality of evidence for outcomes of interest was categorised as very low or low, mainly due to huge inconsistency across studies, according to the GRADE criteria. In this regard, it is necessary to investigate the impact of ACS on the outcomes among multiple gestations.

ACS has been confirmed to be effective to prepare fetal lung for air breathing through multiple mechanisms, including the induction of protein and enzymes, the acceleration of antioxidant production and induction of beta-receptor expression in alveolar cells as well as the acceleration of parenchymal change.[40] Though ACS has been internationally recommended in clinical practice, there is no difference in the guidelines for administration of ACS between multiple gestations and singletons.[11 41] From the view of pharmacokinetics, however, shorter half-life and faster clearance of corticosteroids in multiple pregnancies might raise some doubts in the effectiveness of ACS among multiple pregnancies when using the regime as same as for singletons.[42] Overall, we found benefits of ACS to reduce RDS, IVH, PVL and mortality based on the combined results, but no difference in NEC, ROP and BPD. These results were similar to previous ones obtained from singletons regarding RDS, IVH, PVL and neonatal death but not regarding NEC, ROP and BPD.[10 43–45] It was not surprising to detect substantial heterogeneity since there was variation in the exclusion criteria as well as the definition of outcomes. In the subgroup analysis, a complete ACS course was found to be attributed to a reduction in RDS, mortality and PVL. In contrast, no benefit was found in these outcomes when

those studies had no information on ACS completeness. Based on the assumption that these studies could include both populations with and without a complete ACS, we thought that ACS completeness could play a role in heterogeneity. Although the efficacy of incomplete ACS was shown by a previous study conducted in singletons,[46] it remained challenged by gestational age at delivery.[47] Herrera *et al*[21] did not show a significant reduction in the risks of death and RDS among multiple gestations exposed to incomplete ACS. The ACS administration-to-delivery interval was also regarded as a source of heterogeneity, since a significant reduction of RDS and PVL was found among preterm twins delivered within 7 days after administration but not among those without information on administration timing. To date, it has been recommended that the corticosteroids should be administered within 7 days prior to PTB, respective of plurality.[41 48–51] Kuk *et al*[20] compared RDS between twins without treatments and those with ACS-to-delivery intervals of <2, 2–7 and >7 days. The reduction in RDS was only observed in the group with an ACS-to-delivery interval of 2–7 days but not in the other groups. A retrospective cohort of 106 twin pregnancies with suspected PTB found that newborns born beyond 7 days after the ACS course experienced increased composite respiratory complications in comparison to those born within 7 days after ACS treatment.[52] We still found a reduction of other adverse outcomes even though the studies were thought to include populations with administration-to-delivery intervals of >7 days. A retrospective study by Rottenstreich *et al*[53] demonstrated that the rate of optimal initial ACS (ACS administration-to-delivery interval ≥24 hour and ≤7 days) was significantly lower in twin pregnancies than in singletons (19.7% vs 33.2%, p=0.001). It was a challenge to predict PTB among multiple gestations, which hampers the healthcare providers from achieving optimal ACS administration. In this regard, a more robust model of prediction for PTB among multiple gestations is expected to provide evidence for ACS administration.

There were several limitations that should be considered in the present meta-analysis. First, the majority of included studies were retrospective in design, suggesting that some bias in retrospective nature cannot be avoided and the overall quality of evidence was low, which may impede the interpretation of the current results. Higher levels of evidence on the efficacy of ACS among preterm twins are of great need.[39] Second, the high heterogeneity may weaken the validity of current results. Even though subgroup analyses were performed, the high heterogeneity remained in some subgroups, suggesting the presence of unexplained heterogeneity. Third, we were unable to perform subgroup analysis on gestational age at delivery because of the substantial variation in this information. Overall, the studies included preterm pregnancies before 35 weeks of gestational age except two,[15 38] and the sensitivity analysis confirmed the robustness of pooled results after omitting these studies, however.

CONCLUSIONS

Our meta-analysis of observational studies suggests that a complete course of ACS treatment within 7 days of delivery is beneficial to reduce neonatal complications in terms of RDS, mortality, IVH and PVL among preterm multiple births. ACS is not associated with a reduction in NEC, ROP or BPD. ACS completeness, administration-to-delivery interval and multicentre study could play a role in the heterogeneity. More robust evidence on the efficacy of ACS treatment among multiple gestations is warranted.

Acknowledgements The authors thank the researchers of included studies for sharing their knowledge.

Contributors DL and CL contributed to the study conception and drafted the protocol. GC and DF contributed to study selection and data collection; DL performed data analysis and drafted the manuscript. CL and XG contributed to interpretation. ZL contributed to manuscript revision. All authors have read and approved the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iDs
Caihong Luo http://orcid.org/0000-0002-1289-0325
Zhengping Liu http://orcid.org/0000-0002-4964-0258

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