Association of antenatal steroid and risk of retinopathy of prematurity: a systematic review and meta-analysis

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ABSTRACT

Background Retinopathy of prematurity (ROP) is one of the leading causes of childhood blindness. Use of antenatal steroid can reduce neonatal morbidity and mortality in preterm births, but its effect on ROP remained controversial. We aim to determine the association between antenatal steroid and risk of ROP by a systematic review and meta-analysis.

Methods Reported studies on the association between antenatal steroid and risk of ROP or severe ROP were identified from MEDLINE and Embase databases from their inception to November 2016. Outcome measures were ORs with 95% CIs. Extracted data were pooled using a random-effect model or fixed-effect model where appropriate. Heterogeneity was assessed, and sensitivity analysis was performed.

Results A total of 434 relevant studies were identified, and 28 studies were eligible for the meta-analysis, involving 20 731 neonates with 4202 cases of ROP. Among the 28 studies included, 13 studies provided data evaluating the association between antenatal steroid use and severe ROP, involving 4999 neonates with 792 cases of severe ROP. Antenatal steroid administration was associated with a reduced risk of ROP development ($OR_{unadjusted}$=0.82, 95% CI 0.68 to 0.98; $OR_{adjusted}$=0.67, 95% CI 0.47 to 0.94) and progression to severe ROP ($OR_{unadjusted}$=0.58, 95% CI 0.40 to 0.86).

Conclusion Antenatal steroid administration is associated with a reduced risk of ROP development and progression to severe ROP. Our results strengthened the indications of antenatal steroid therapy to high-risk mothers giving preterm births, especially in low-income and middle-income countries where antenatal steroid are not yet widely used.

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading causes of blindness in prematurely born children.[1] It is a retino-proliferative disease in preterm infants consisting of initial hyperoxia-induced vascular obliteration, followed by hypoxia-induced aberrant vasoproliferation in an increasingly metabolically activated yet poorly vascularised retina.[2 3] Low birth weight and low gestational age are the two main risk factors for ROP development.[4] Other risk factors include prolonged oxygen therapy, artificial ventilation, blood transfusion and surfactant therapy.[4–7] Severe ROP may progress to total retinal detachment and blindness.[8] Inadequate ROP screening programme and treatment access in some localities increases the chances of unfavourable visual outcomes in these children,[9–11] thus making the prevention of ROP onset and progression to the severe form of the disease important. Potential protective factors for ROP have been reported, including aggressive parental nutrition, supplementation of omega-3, vitamin A, E or inositol and breast milk feeding.[12 13]

Antenatal steroids are currently administered to prevent neonatal mortality, respiratory distress syndrome (RDS), intraventricular haemorrhage and necrotising enterocolitis associated with preterm delivery without increasing maternal infections or neonatal morbidities.[14 15] However, its effect on ROP development remains controversial. In 1997, Console *et al*[16] reported a 65% and 93% reduction in respective risk of developing ROP and progression to severe ROP after antenatal steroid administration in a cohort of 380 neonates. Higgins *et al*[17] showed an 82% reduction in risk of developing ROP stage 2 or above after antenatal steroid administration in a small cohort of 62 infants. Yu-Shu Liu *et al*[18] also found a decrease of incidence of severe ROP with the antenatal steroid use, from 81.9% of infants whose mother did not receive antenatal steroid to 60% with antenatal steroid. This protective effect was also supported by other subsequent studies.[19] Conversely, Eriksson *et al*[20] demonstrated an increased risk of 1.57 times on ROP development after antenatal steroid administration in a cohort of 7200 neonates in Sweden. Other studies could not find a relationship between antenatal steroid administration and ROP development.[5 21–26] We therefore conducted this systematic review and meta-analysis to determine the relationship between antenatal steroid and risk of ROP and more importantly the risk of severe ROP development.

METHODS

Searching strategy

Embase and MEDLINE (Medical Literature Analysis and Retrieval System Online, via Ovid platform) databases were our sources for electronic search from their starting date to November 2016. Both controlled vocabularies and free words including ["Retinopathy of Prematurity" or "ROP" or "Retrolental Fibroplasia" or "Prematurity Retinopathy" or

"Prematurity Retinopathies"] AND ["Steroid*" or "Cortico*" or "Dexamethasone" or "Betamethasone"] AND ["Prenatal Care" or "Risk Factors" or "Antenatal" or "Prenatal Exposure Delayed Effects" or "Prenatal"] were used. The searching strategies were summarised in online supplementary file 1. All articles in English were identified. Citation lists of included articles were screened for additional eligible studies that might have been omitted in the electronic search.

Study selection

The inclusion criteria included: (1) studies about antenatal steroid administration and risk of ROP, including randomised controlled trials, prospective cohort, retrospective studies, case–control and observational studies; (2) studies that reported the outcomes, in the form of ORs for ROP and their CIs, or numerical counts that allow the calculation of the aforementioned outcomes; and (3) studies that reported any type of antenatal steroid administration regimens, including partial, complete, single and multiple courses. Animal studies, reviews, abstracts, conference proceedings, editorials and studies with insufficient data for meta-analysis were excluded. Abstracts were screened by three independent reviewers (C-LY, MT and H-LC). ROP status was based on the highest stage observed with the international classification.[27] We included studies that defined severe ROP as stage 3 or above, with threshold or plus disease, or ROP requiring treatment.

Data extraction

According to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines for reporting meta-analysis of observational studies,[28] all retrieved records were screened and reviewed by two independent reviewers (C-LY and MT). Discrepancies were resolved by discussion with a third reviewer (S-MT). Data were recorded into predetermined data sheets.

The data extracted included: first author, year of publication, country of study, sample size, mean gestational age and mean birth weight in both the ROP and non-ROP group, type of steroid administered, regimens of steroid administration, definition of ROP, the number of subjects with and without steroid exposure in the ROP and non-ROP group, respectively and, if any, the adjusted OR with 95% CI and confounding factors that were adjusted.

Quality assessment

The methodological quality was assessed by using the Newcastle-Ottawa Scale (NOS; http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) for case–control or cohort studies as appropriate.[29] The NOS contained three domains: potential selection bias, comparability and the ascertainment of exposure or outcome, with a total of nine items. For cohort studies, there are four items in the selection domain (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and demonstration that outcome of interest was not present at start of study); two items in the comparability domain (gestational age and birth weight); and three items in the outcome domain (assessment of outcome, follow-up time and adequacy of follow-up). For case–control studies, there are four items in the selection domain (case definition, representativeness of cases, selection of controls and definition of controls); two items in the comparability domain (gestational age and birth weight); and three items in the exposure domain (ascertainment of exposure, method of ascertainment for cases and controls and non-response rate). One star is awarded for each item, with a maximum total score of nine stars. A score of 5 or above out of 9 was considered satisfactory for inclusion. The quality of each article was assessed by two independent reviewers (MT and H-LC). Discrepancies were resolved by discussion with the third reviewer (S-MT).

Statistical analysis

The main outcomes were evaluated for: (1) association between antenatal steroid administration and any stages of ROP; and (2) association between antenatal steroid administration and severe ROP.

The unadjusted ORs and CIs were calculated from the number of subjects with and without antenatal steroid administration in the ROP and non-ROP group. The adjusted ORs were extracted from the studies and were subsequently combined to further evaluate the association after adjusting for possible confounding factors. For studies that provided adjusted ORs for subgroups receiving different number of steroid courses, adjusted OR for one course of steroid was selected since the majority of the included studies used one course of steroid. In studies that provided separate adjusted ORs for subgroups receiving betamethasone and dexamethasone individually, we selected the adjusted OR of the group with larger sample size.

Heterogeneity across the studies were evaluated by Cochran Q Statistic testing and I^2 statistic. I^2 was the amount of total variation that is due to variation between studies. I^2 values of approximately 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively. If p value for Cochran Q Statistic <0.1 or $I^2 > 50\%$, a random-effect model (DerSimonian and Laird method) was used,[30] otherwise, a fixed-effects model (Mantel-Haenszel method) was used.[31]

Sensitivity analyses were conducted by removing one study at a time to assess its influence to the summary outcomes. The Modified Egger's regression test was used to assess for publication bias. P value <0.05 was considered statistically significant. The unadjusted and adjusted ORs were synthesised using the fixed-effect and random-effect models in the Review Manager 5 software (http://community.cochrane.org/tools/review-production-tools/revman-5).

RESULTS

Description of included studies

We identified 434 relevant studies in the initial literature search. Finally, 28 studies were eligible for the meta-analysis, including a total of 20 731 neonates with 4202 cases of ROP (figure 1). The studies were conducted in different parts of the world: 7 from Europe,[16 19 20 32–35] 8 from Asia Pacific countries,[5 18 22–26 36] 2 from Middle East,[37 38] 10 from North America[17 21 39–46] and 1 from South America.[47] The majority, 26 of them, were cohort studies.[5 16–24 26 32–37 39–47] One study was an interventional case series[25] and one case-control study.[38] All studies attained an assessment score >5 on the methodological quality by NOS. Characteristics of the studies were summarised in online supplementary file 2.

Overall association between antenatal steroid exposure and ROP

Twenty-seven out of 28 studies provided primary data on the counts of neonates with and without antenatal steroid exposure in the ROP and non-ROP groups.[5 16–18 20–26 32–47] Unadjusted OR was calculated as 0.82 (95% CI 0.68 to 0.98, P=0.03, I^2=58%), indicating that antenatal steroid was associated with a lower risk of ROP development (figure 2A; table 1).

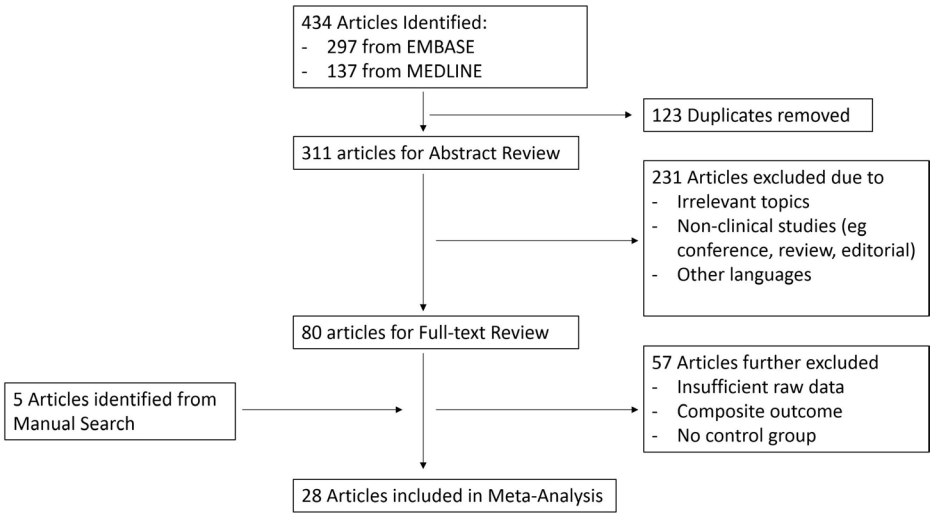

Figure 1 Flow chart of study inclusion.

Eight studies provided adjusted ORs of the association between antenatal steroid exposure and ROP, after adjustment for different possible confounding factors.[16 19–21 32 34 44 47] Pooled adjusted OR was 0.67 (95% CI 0.47 to 0.94, P=0.02, I^2=58%), indicating that antenatal steroid was associated with a lower risk of ROP development after adjusting for possible confounders (figure 2B; table 1).

Association between antenatal steroid exposure and severe ROP

Thirteen studies[5 16–18 21 23 24 26 32 37 44 45 47] provided separate data on the counts of neonates with and without exposure to antenatal steroid for the severe ROP subgroup. Among these 13 studies, four provided the counts for neonates that developed ROP requiring treatment. The unadjusted OR 0.58 (95% CI 0.40 to 0.86, P=0.006, I^2=55%) indicated that antenatal steroid was associated with a lower risk of severe ROP development, including ROP requiring treatment (figure 2C; table 1). Adjusted ORs for these subgroups were not available for analysis.

Subgroup analysis: adjustment for RDS/oxygen therapy

We have conducted further subgroup analysis for studies adjusted for RDS or oxygen therapy. Four studies were included, and the pooled adjusted OR was 0.52 (95% CI 0.35 to 0.76, P=0.0009, I^2=23%). The results remained significant, suggesting that antenatal steroid use was associated with lower risk of ROP

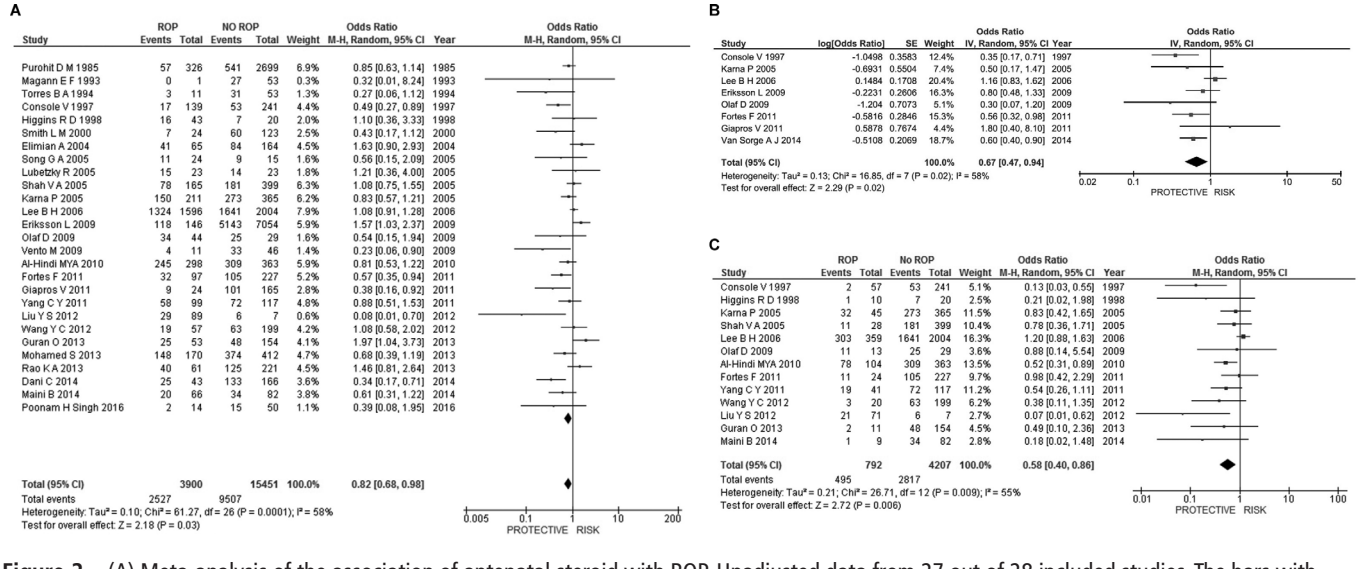

Figure 2 (A) Meta-analysis of the association of antenatal steroid with ROP. Unadjusted data from 27 out of 28 included studies. The bars with squares in the middle represent 95% CIs and ORs. The central vertical solid line indicates the ORs for the null hypothesis. Diamond indicates summary OR with its corresponding 95% CI. Events represent antenatal steroid use. (B) Meta-analysis of the association of antenatal steroid with ROP. Adjusted data from 8 out of 28 included studies. The bars with squares in the middle represent 95% CIs and ORs. The central vertical solid line indicates the ORs for the null hypothesis. Diamond indicates summary OR with its corresponding 95% CI. (C) Meta-analysis of the association of antenatal steroid with severe ROP. Unadjusted data from 13 out of 28 included studies. The bars with squares in the middle represent 95% CIs and ORs. The central vertical solid line indicates the ORs for the null hypothesis. Diamond indicates summary OR with its corresponding 95% CI. Events represent antenatal steroid use. ROP, retinopathy of prematurity.

Table 1 Meta-analysis of association of antenatal steroid with ROP

Type of comparison	No of studies	Sample size	Cases with ROP (%)	Overall effect			Heterogeneity		
				OR (95% CI)	z Score	P values	I^2%	Q (p values)	Egger's test
Unadjusted OR for any types of ROP	27	19 351	20.2	0.82 (0.68 to 0.98)	2.18	0.03	58	0.0001	0.121
Adjusted OR for any types of ROP	8	13 722	18.6	0.67 (0.47 to 0.94)	2.29	0.02	58	0.02	0.572
Unadjusted OR for severe ROP	13	4999	15.8*	0.58 (0.40 to 0.86)	2.72	0.006	55	0.009	0.005
Adjusted OR for any types of ROP (studies that has include adjustment for RDS/oxygen therapy)	4	1469	32.1	0.52 (0.35 to 0.76)	3.32	0.0009	23	0.27	0.302
Unadjusted OR for any types of ROP (Asia subgroup)	8	1665	34.5	0.94 (0.75 to 1.17)	0.55	0.58	37	0.13	0.025
Unadjusted OR for any types of ROP (Europe subgroup)	6	8108	5	0.52 (0.26 to 1.03)	1.87	0.06	79	0.0002	0.078
Unadjusted OR for any types of ROP (North America subgroup)	10	9001	30.5	0.95 (0.84 to 1.07)	0.85	0.4	37	0.11	0.097

*Percentage of cases with severe ROP.
RDS, Respiratory distress syndrome; ROP, retinopathy of prematurity.

development independent of the use of oxygen therapy and the RDS status (online supplementary file 3; table 1).

Subgroup analysis in different localities

Subgroup analysis was also conducted for studies in different localities, namely Asia (8 studies), Europe (6 studies) and North America (10 studies). In the Asia subgroup, the OR is 0.94 (95% CI 0.75 to 1.17, P=0.58, I^2=37%) (online supplementary file 4; table 1). In the Europe subgroup, the OR is 0.52 (95% CI 0.26 to 1.03, P=0.06, I^2=79%) (online supplementary file 5; table 1). In the North America subgroup, the OR is 0.95 (95% CI 0.84 to 1.07, P=0.40, I^2=37%) (online supplementary file 6; table 1).

Sensitivity analysis

The overall association between antenatal steroid exposure and ROP became marginally insignificant, (p value ranging from 0.05 to 0.07, ORs remained positive) when we excluded the following studies individually: Console *et al*,[16] Dani *et al*,[35] Fortes *et al*,[47] Giapros *et al*,[34] Smith *et al*[42] and Vento *et al*[33] (table 2). There was no significant change in heterogeneity on removal of individual papers. In the analysis of the combined adjusted OR, the removal of Lee *et al*[44] significantly reduced the heterogeneity from 58% to 10%. When van Sorge *et al*'s[19] study was removed the association became non-significant with an adjusted OR 0.67 (95% CI 0.44 to 1.03, P=0.07, I^2=61%). After excluding Console *et al*'s[16] study the adjusted OR became 0.74 (95% CI 0.53 to 1.03, P=0.07, I^2=50%). In the subgroup analysis between antenatal steroid and severe ROP, the removal of Lee *et al*[44] also substantially reduced the heterogeneity from 55% to 22%. In the analysis of combined unadjusted OR in the Europe subgroup, after the removal of Eriksson *et al*'s[20] study the result became significant with OR 0.41 (95% CI 0.28 to 0.59, P<0.00001, I^2=0%). In the combined unadjusted OR analysis in the North America subgroup, after the removal of Lee *et al*'s study,[44] the result became significant with OR 0.83 (95% CI 0.70 to 0.99, P=0.04, I^2=22%).

Publication bias

No evidence of publication bias was found in the analysis of pooled unadjusted OR, pooled adjusted OR for risk of ROP at any stage, pool adjusted OR for studies adjusted for oxygen therapy or RDS, pooled unadjusted OR for Europe and North America subgroup (Egger's test, P=0.121, 0.572, 0.302, 0.078 and 0.097, respectively). However, publication bias was present in the pooled unadjusted OR for severe ROP and pooled unadjusted OR for Asia subgroup (Egger's test, P=0.005 and 0.025, respectively).

DISCUSSION

This is the first meta-analysis evaluating the association between antenatal steroid and risk of ROP. Meta-analysis of 28 studies involving 20 731 infants has revealed antenatal steroid is associated with a reduced risk of development of any stage of ROP and, in particular, progression to severe ROP. Since ROP is a leading cause of treatable childhood blindness in prematurely born infants, identification of this potential protective factor ROP confers clinical benefits.

Among 28 studies, a protective effect between antenatal steroid use and ROP development was demonstrated in eight studies.[16 18 19 33–35 45 47] One of the included studies, Eriksson *et al*[20] demonstrated a risk rather than protective effect between antenatal steroid and ROP development in their unadjusted

Table 2 Meta-analyses with statistically significant changes in sensitivity analysis

Omitted paper	Sample size	OR	95% CI	P values	I^2 (%)
Meta-analysis of overall unadjusted outcomes					
Console *et al*[16]	380	0.84	0.70 to 1.01	0.06	56
Dani *et al*[35]	209	0.85	0.71 to 1.02	0.07	54
Fortes *et al*[47]	324	0.84	0.69 to 1.00	0.06	57
Giapros *et al*[34]	189	0.84	0.70 to 1.00	0.06	56
Smith *et al*[42]	147	0.84	0.69 to 1.00	0.05	57
Vento *et al*[33]	57	0.84	0.70-.1.00	0.05	56
Meta-analysis of overall adjusted outcomes					
Console *et al*[16]	380	0.74	0.53 to 1.03	0.07	50
Fortes *et al*[47]	324	0.68	0.46 to 1.02	0.06	62
van Sorge *et al*[19]	1380	0.67	0.44 to 1.03	0.07	61
Meta-analysis of severe ROP					
No change in statistical significance					
Meta-analysis of adjusted outcomes adjusted for RDS/oxygen therapy					
No change in statistical significance					
Meta-analysis of unadjusted outcomes in Asia subgroup analysis					
No change in statistical significance					
Meta-analysis of unadjusted outcomes in Europe subgroup analysis					
Eriksson *et al*[20]	7200	0.41	0.28 to 0.59	<0.00001	0
Meta-analysis of unadjusted outcomes in North America subgroup analysis					
Lee *et al*[44]	3600	0.83	0.70 to 0.99	0.04	22

RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

analyses. In their cohort of 7200 neonates, Eriksson *et al*[20] reported a change of direction from a risk (unadjusted OR 1.57) to a protective factor (adjusted OR 0.8) after adjustment of potential confounding factors including gestational age. We conducted adjusted analysis in our meta-analysis to minimise the influence of confounders. The result remained significant after pooling adjusted data from the available studies, with an adjusted OR 0.67 (95% CI 0.47 to 0.94, P=0.02, I^2=58%).

RDS is another major confounder that should be addressed. Antenatal steroid improves lung maturation and therefore resulting in a lower demand for supplementary oxygen and mechanical ventilation.[48] Nevertheless, our subgroup analysis for studies that had adjusted for RDS/oxygen therapy also revealed a significant protective association between antenatal steroid use and ROP development, with an adjusted OR 0.52 (95% CI 0.35 to 0.76, P=0.0009, I^2=23%). This supported the protective effect of antenatal steroid on ROP development, independent of RDS/oxygen therapy status.

Different mechanisms have been postulated for the protective effect of antenatal steroid. First, steroids could reduce the expression of tumour necrosis factor alpha, which has an angiogenic and inflammatory role in the pathogenesis of proliferative retinopathy, and hence reducing ROP development.[49] Second, steroids may reduce the oxidative stress.[50] Premature infants had lower antioxidant level that increases the vulnerability to reactive oxygen species-induced damage leading to the development of ROP.[50] Vento *et al*[33] found that infants who received antenatal steroid had increased antioxidant enzymes activity and reduced oxidative stress markers in umbilical cord blood at birth.

In this meta-analysis, we used risk of bias assessment tools for observational studies referring to MOOSE guidelines and the Cochrane Handbook for Systematic Reviews. Including only studies published in English language could be a potential source of bias. However, the studies included in our review do represent wide geographical distribution, including Europe, Asia Pacific region, Middle East, America and South America. Inclusion of diverse ethnic groups increased the generalisability of our results. Subgroup analysis according to localities (Asia, Europe and North America) was conducted, but the results were statistically non-significant. A potential reason for this could be the smaller sample size after dividing the subjects into subgroups. Moreover, prenatal and postnatal care vary substantially across various countries and therefore may contribute to confounding factors in respective studies. Nevertheless, we collected adjusted data in our analysis to minimise the influence of potential confounders. The overall combined adjusted OR remained statistically significant.

However, this meta-analysis has certain limitations. First, majority of the studies were cohort studies. Randomised controlled trials were not available. Second, heterogeneity of the studies made comparison difficult. One source of heterogeneity is the variation in definitions of adjusted ORs among studies. Different factors were adjusted in each study, which might potentially introduce heterogeneity into this meta-analysis. Nevertheless, gestational age and birth weight were two crucial factors that have been adjusted for in the majority of the data we collected. Other sources of heterogeneity included the differences in the type of steroid, timing of steroid administration or duration of course of steroid.[20 21 24 26 42] Studies using either dexamethasone or betamethasone were included in this study for the purpose of comprehensive analysis.

CONCLUSION AND CLINICAL SIGNIFICANCE

We confirmed that antenatal steroid administration is associated with a reduced risk of development of ROP and progression to severe ROP. Antenatal steroid has been recommended to all women at high risk for delivery between 24 and 34 weeks of gestation since 1994.[51] There are proven benefits to reduce neonatal mortality and morbidity, including RDS, cerebroventricular haemorrhage, necrotising enterocolitis, intensive care admission and systemic infections in the first 48 hours of life.[52] However, a recent WHO study reported that in low-income to middle-income countries, only about 50% of women giving birth to preterm infant have received antenatal steroids despite its beneficial effects.[53] Notably, these countries tended to have higher incidence of ROP and ROP-associated blindness, due to higher rate of premature births, lack of ROP awareness, screening and treatment.[54–60] Our study suggested an additional benefit of antenatal steroid on reducing the risk of ROP development and progression into severe ROP. This would further strengthen the indications of antenatal steroid therapy to those women at high risk, especially those in low-income countries.

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Contributors JCSY conceptualised and directed the work. C-LY, MT and H-LC did the literature search; C-LY and MT did the data extraction and analysis; MT and H-LC did the quality assessment, while discrepancies were resolved by discussion with S-MT. C-LY, MT and H-LC drafted the article, and contributed equally. JCSY, SCLA, SSR and S-MT provided critical revision of the article. All authors revised and approved the final manuscript.

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