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Antenatal Corticosteroids in Preterm Small-for-Gestational Age Infants: A Systematic Review and Meta-Analysis

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Abstract

Objective: To estimate the effect of antenatal corticosteroid (ACS) administration on neonatal mortality and morbidity in preterm small-for-gestational age (SGA) infants through a systematic review and meta-analysis.

Data sources: A predefined, systematic search was conducted through Ovid Medline, Embase, Scopus, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trial Registry Portal, and ClinicalTrials.gov yielding 5,324 articles from 1970–2019.

Study eligibility criteria: Eligible studies compared neonatal morbidity and/or mortality among SGA infants delivered preterm who received ACS to those who did not.

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Authors Contributions: SAB and MGT made substantial contributions to study conception and design. LES performed the initial literature search. SAB and KEB performed all data extraction. MGT and SAB performed data analysis and interpretation of data. SAB drafted the manuscript. All authors critically revised the manuscript for important intellectual context. All authors gave final approval of the version to be published and agree to be accountable for accuracy and integrity of this work.

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Study appraisal and synthesis methods: The primary outcome was neonatal mortality. Secondary outcomes were respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage and/or periventricular leukomalacia (IVH and/or PVL), bronchopulmonary dysplasia or chronic lung disease of prematurity (BPD or CLD), or neonatal sepsis. We assessed heterogeneity via Higgins I^2 and Cochrane's Q test, and calculated pooled odds ratios (OR) with 95% confidence intervals (CI) using random effects models.

Results: Sixteen observational cohort and case-control studies published from 1995–2018 met selection criteria for the systematic review and included 8,989 preterm SGA infants. ACS administration was explicitly reported among 8,376 SGA infants; 4,631 (55.3%) received ACS and 3,741 (44.7%) did not. Thirteen studies including 6,387 preterm SGA infants were then included in the meta-analysis. Neonatal mortality was significantly lower among infants who received ACS compared to those who did not (12 studies: 12.8% vs. 15.1%, pooled odds ratio [OR] 0.63 [95% CI 0.46–0.86]), with significant heterogeneity between studies (I^2=55.1%, p=0.011). There was no significant difference in RDS (12 studies: OR 0.89 [95% CI 0.69–1.15]), NEC (7 studies: OR 0.93 [95% CI 0.70–1.22]), IVH and/or PVL (10 studies: OR 0.82 [95% CI 0.56–1.20]), BPD or CLD (8 studies: OR 1.11 [95% CI 0.88–1.41]), or neonatal sepsis (6 studies: OR 1.13 [95% CI 0.86–1.49]).

Conclusions: These data show that ACS reduces neonatal mortality in SGA infants delivered preterm, with no apparent effect on neonatal morbidity. This supports the use of ACS to reduce neonatal mortality in pregnancies with SGA infants at risk for preterm birth.

Condensation

Antenatal corticosteroids reduce neonatal mortality in SGA infants delivered preterm, with no apparent effect on neonatal morbidity.

Keywords

small-for-gestational age; fetal growth restriction; antenatal corticosteroids; neonatal morbidity; neonatal mortality

Introduction

Small-for-gestational age (SGA) is commonly defined as birthweight less than the tenth percentile. SGA infants can be either constitutionally small or pathologically growth-restricted antenatally.[1–2] Clinically, it can be difficult to differentiate the etiology of FGR (fetal growth restriction). Approximately 3 to 7% of newborns are affected by pathologic FGR, a major risk factor for preterm birth, and the incidence of FGR increases with increasing prematurity.[3–5] FGR in a preterm neonate specifically carries an increased risk of perinatal morbidity and mortality.[5,6]

Administration of antenatal corticosteroids (ACS) has become the standard of care in the setting of anticipated preterm delivery in order to prevent neonatal morbidity and mortality. ACS has been shown to reduce neonatal mortality by 31% in appropriate-for-gestational age (AGA) infants, with efficacy demonstrated specifically in reducing rates of respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis, among other

neonatal outcomes.[7–9] However, large-scale prospective studies evaluating the effect of ACS on preterm birth outcomes have not made small-for-gestational age (SGA) infants a primary population of focus, with data for this population limited to mostly retrospective studies. Furthermore, clinical management related to ACS administration in pregnancies with SGA infants has wide variation largely guided by expert opinion without an evidence-based consensus.

Due to pathologic intrauterine stress, SGA infants may be exposed to higher levels of endogenous corticosteroids at baseline as a result of multiple mechanisms. These mechanisms include increased fetal adrenal cortisol production, compromised ability to remove corticosteroids through the blood brain barrier or placenta, and reduced ability to block the passage of maternal cortisol across the placenta.[10–18] As SGA infants are already exposed to higher levels of endogenous steroids, the additional administration of exogenous ACS prior to impending preterm delivery may not offer additional benefit. In fact, exposure to single or repeated courses of corticosteroids in utero has been associated with reduced fetal growth; impaired cardiovascular and brain development; and impaired gas exchange and physiologic adaptive mechanisms in the growth-restricted neonate.[10–18] Administration of exogenous ACS may ultimately alter the ability of an SGA infant to compensate for intrauterine stress caused by placental insufficiency.[18] As a result, some researchers have postulated that administration of exogenous steroids may even be detrimental to SGA infants[2].

Objective

Given limited and conflicting evidence guiding the use of ACS in SGA infants, the present study aims to summarize the totality of evidence on ACS administration in SGA infants at risk for preterm delivery. We performed a systematic literature review and meta-analysis to estimate the effect of ACS on neonatal mortality and morbidity in preterm SGA infants. We hypothesized that administration of ACS in preterm SGA infants would have limited benefit given adaptive physiologic mechanisms in SGA infants.

Methods

We used a predesigned methodology according to guidelines for Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-analyses of Observational Studies in Epidemiology (MOOSE).[19,20] The study protocol was registered with PROSPERO (#156264).

Information Sources and Search Strategy

A medical librarian searched published literature for records discussing ACS (i.e. betamethasone, dexamethasone, alternate drug names and suggested synonyms for dexamethasone and betamethasone), and preterm SGA infants. The librarian created search strategies using a combination of keywords and controlled vocabulary in Ovid Medline (1946- present), Embase.com (1947-present), Scopus (1823-present), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization International Clinical Trial Registry Portal (WHO ICTRP), and

Clinicaltrials.gov (1997-present). Animals were excluded using the OVID human filter recommended in *Cochrane Handbook for Systematic Reviews of Interventions.*[21] The filter was translated to exclude animals in Embase and Scopus. All search strategies were completed initially in June 2019, and a total of 10,139 results were exported to EndNote. 5,204 records were deleted after using the deduplication processes described by Bramer et al.[22] A total of 4,935 unique records remained in the project library. In addition to these, 35 records were identified in ClinicalTrials.gov, and 24 in World Health Organization International Clinical Trials Registry Portal (WHO ICTRP). A manual search of bibliographies of relevant articles was also performed.

The search was updated in all databases again in May 2020. A total of 10,151 search results were exported from the databases without any date limits and were added to the project Endnote project library (15086). A total of 9,824 duplicates were removed and deleted revealing 330 new citations. Due to the search and site no longer being available, the World Health Organization International Clinical Trials Registry Portal (WHO ICTRP) was not searched in May 2020. All references were exported to an excel workbook for review. Fully reproducible search strategies for each database can be found in the appendix.

Eligibility Criteria and Study Selection

Two investigators (SAB and KEB) independently screened abstracts and articles pertaining to ACS administration that reported on neonatal mortality and/or other perinatal outcomes that contribute to overall neonatal morbidity or mortality in SGA infants, and extracted data from each study. Study corresponding authors were contacted via email in attempt to obtain missing data for outcomes of interest. Discrepancies in coding required agreement between authors (SAB, KEB and MT) to be considered resolved.

Studies were included if they reported on SGA infants delivered preterm that received ACS, either betamethasone or dexamethasone, prior to delivery. Included studies reported on neonatal mortality and/or any of the following adverse perinatal outcomes: respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD) or chronic lung disease of prematurity (CLD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) and/or periventricular leukomalacia (PVL), or neonatal sepsis after delivery.

Studies were excluded if they were a review article; included non-human, animal fetuses; did not report on outcomes distinctly for SGA infants according to ACS administration; analyzed combined effect of surfactant and steroids on perinatal outcomes or compared steroids to an alternative intervention; reported on the effect of repeated or “rescue” doses of steroids; included duplicate data previously reported in another publication by the same author; or included multiple gestations. Additionally, studies were excluded from the meta-analysis if they did not report raw data for the included aforementioned neonatal outcomes.

Data Extraction

The primary outcome was neonatal mortality. Secondary outcomes of interest were RDS, BPD or CLD, IVH and/or PVL, NEC and neonatal sepsis, as defined in Supplementary Table 1. Long term childhood neurodevelopmental outcomes were also extracted when available.

For each study, when data were available, we extracted mean maternal age, maternal parity, mean gestational age at delivery, mean birth weight, number of infants delivered via Cesarean section, infant sex, number of infants who received surfactant, number of infants affected by chorioamnionitis, and use of surfactant or mechanical ventilation postnatally. Maternal risk factors and co-morbidities were also extracted, including gestational or pregestational diabetes mellitus and maternal hypertensive disorders (chronic hypertension, pregnancy-induced hypertension, pre-eclampsia, eclampsia or HELLP syndrome). Each of the aforementioned variables was stratified by the number of SGA infants who did or did not receive ACS.

Data Synthesis

Meta-analysis was performed using the metan add-on program in Stata (Stata 2015 Release 12, StataCorp, Texas, USA). Two-by-two contingency tables were created to compare the presence or absence of neonatal mortality or adverse neonatal outcome stratified by ACS administration. Although the majority of studies were cohort studies, we calculated pooled odds ratios (OR) as one case control study was included. Random effects models were used to account for clinical heterogeneity between studies even when statistical heterogeneity was not evident. To further account for heterogeneity related to varied time periods among included studies, we also performed a subgroup analysis for neonatal mortality among studies that evaluated patients up to the year 2010 analyzed separately from those that evaluated patients beyond the year 2010. Forest plots were created to visually assess both effect size and identify outliers.

We estimated heterogeneity across studies and tested its significance using the Higgins I^2 statistic and Cochrane's Q test. I^2 of 50% was considered evidence of significant heterogeneity. Publication bias was evaluated visually using funnel plots and asymmetry was tested statistically using Egger's test.

Assessment of Risk of Bias

Quality assessment to determine risk of bias of included studies was also performed using the Downs and Black assessment tool.[23] The checklist is composed of 27 questions, with a total possible score of 28 for randomized and 25 for non-randomized studies. Downs and Black score ranges are given corresponding quality levels: excellent (26–28); good (20–25); fair (15–19); and poor (≤14). Only randomized studies can achieve a quality level of excellent according to the scoring methodology of the Downs and Black checklist. As all studies were observational and not randomized, the maximum quality level of included studies is "good."

Results

Study Selection

The search yielded 5,324 articles published from 1970–2019. Sixteen observational cohort and case-control studies published from 1995–2018 met inclusion and exclusion criteria and were selected for the systematic review. [24–39] In aggregate, the 16 studies included in the systematic review included 8,989 preterm SGA infants.

Study Characteristics

All studies were observational, with fourteen retrospective cohort studies, one prospective cohort study, and one case-control study included (Table 1). ACS administration was explicitly reported among 8,376 SGA infants; 4,631 (55.3%) received ACS and 3,741 (44.7%) did not. Nine studies reported on type of ACS administered, with betamethasone the most commonly used in 8 studies; two studies included infants who received either betamethasone or dexamethasone. Ten studies specified birth weight less than the tenth percentile in their definition for SGA. Additional maternal and neonatal characteristics in the included studies are detailed in Tables 2 and 3, respectively.

Table 4 contains weighted-averages for the primary and all secondary outcomes among SGA infants stratified by ACS administration. Fourteen studies reported on overall neonatal mortality, 14 studies reported on RDS, 8 studies reported on BPD or CLD, 7 studies reported on NEC and 6 studies reported on neonatal sepsis. Among 11 studies that reported on IVH and/or PVL, seven studies reported on IVH alone; 4 studies included grade 3 or 4 IVH and/or PVL as a combined outcome.[26,32,37,38]

Long-term neurodevelopmental outcomes were reported among three studies[30,31,35] Two studies reported on severe global delay up to three years of age as determined by a development quotient (DQ) less than 70, or more than two standard deviations below the mean DQ of 100, as defined by the Kyoto Scale of Psychological Development test or the Griffiths test for mental developmental scales[40,41] Among infants with long term follow up data, 16.8% (54/321) of infants that received ACS had severe global delay, while 13.5% (71/525) infants that did not receive ACS had severe global delay. Schaap et al. reported abnormal behavior in long-term follow-up at school age of surviving infants, with 43% (21/62) of children who received ACS and 45% (19/45) of children who did not receive ACS exhibiting abnormal behavior.[34] However, this study did not report how it classified abnormal behavior.

Meta-analysis and Synthesis of Results

Three studies did not provide raw data for neonatal outcomes according to ACS administration and thus were unable to be included in the meta-analysis. Among these three studies, Griffin et al. reported odds ratios for neonatal mortality; Bernstein et al. reported odds ratios for RDS; and Ley et al. reported odds ratios for neonatal mortality, RDS and IVH and/or PVL (Table 4).[29,36,38] The remaining thirteen studies reported raw data for neonatal outcomes among 6,387 preterm SGA infants and were quantitatively synthesized in the meta-analysis.[24–28,30–35,37,39]

ACS administration was associated with a significant reduction in neonatal mortality (12 studies: 12.8% vs. 15.1%, OR 0.63 [95% confidence interval (CI) 0.46–0.86]). There was significant heterogeneity between studies (I^2 =55.1% [p=0.011]) (Figure 2). There was no evidence of publication bias (Figure 3, Egger's p=0.87). In the subgroup analysis by study year, no significant difference in mortality was detected among studies that followed patients up to 2010 (OR 0.93 [95% CI 0.71, 1.21], I^2=0.0% [p=0.452], 7 studies), but a significant reduction in mortality was found among infants who received ACS among studies that

followed patients after 2010 (OR 0.48 [95% CI 0.38, 0.60], I^2=5.0% [p=0.378]; 5 studies, Figure 4).

Among the secondary outcomes, there was no significant difference in RDS (12 studies: OR 0.89 [95% CI 0.69–1.15], I=66.7% [p=0.001], Supplementary Figure 1), NEC (7 studies: OR 0.93 [95% CI 0.70–1.22], I^2=0.0% [p=0.447], Supplementary Figure 2), or IVH and/or PVL (10 studies: OR 0.82 [95% CI 0.56–1.20], I^2=53.1% [p=0.024], Supplementary Figure 3). Among the 3 studies that reported on individual values for IVH and PVL, only the values for IVH were included in the forest plot for IVH and/or PVL as IVH was more common in these studies.[30–32] Significant heterogeneity was seen in studies reporting RDS and IVH and/or PVL, as reflected by the I^2 statistic. There was no significant difference in risk of BPD or CLD (8 studies: OR 1.11 [95% CI 0.88–1.41], I^2=40.2% [p=0.111], Supplementary Figure 4) and neonatal sepsis (6 studies: OR 1.13 [95% CI 0.86–1.49], I^2=0.0% [p=0.583], Supplementary Figure 5).

Risk of Bias of Included Studies

In the quality assessment of included studies, the majority of studies were assessed to be “fair” quality, with two studies determined to be of “good” quality and two studies of “poor” quality (Table 5). Only two studies performed a power calculation and external validity was unable to be determined in most studies. While lack of randomization decreased the quality of all included studies, all studies achieved at least average (e.g. score of 3 or higher) internal validity in both the bias and confounding assessments by using appropriate statistical regression to adjust for potential confounders in the provided analyses.

Comment

Main Findings and Comparison with with Existing Literature

We found that ACS reduces neonatal mortality in SGA infants delivered preterm, with no apparent effect on individual neonatal morbidities. Our results are similar to those of a 2016 systematic review and meta-analysis of 2,846 SGA infants in eight studies conducted up until 2010 that found that administration of ACS to growth-restricted preterm infants did not improve neonatal morbidity.[42] However, in contrast to our findings, the 2016 meta-analysis was unable to detect a reduction in neonatal mortality with ACS. Our meta-analysis includes five studies with 2,982 SGA infants (46.7% of the study population included in the meta-analysis) followed after 2010, 2,124 (71.2%) of whom received ACS. Our meta-analysis provides a more current and comprehensive update to prior available data and supports ACS administration to SGA infants to reduce neonatal mortality.

Of note, studies in our analysis that followed patients beyond 2010 include data predominately from the 2000s to 2010s, whereas studies that followed patients up to 2010 included patient data also from the 1980s and 1990s. Multiple aspects of medical care and technology have evolved over the past few decades in an effort to reduce infant mortality with improved antenatal interventions, neonatal resuscitation, and other postnatal management among preterm infants. While our subgroup analysis seeks to account for these differences according to study period, it is plausible the reduction in mortality seen in

studies that followed patients beyond 2010 could be attributed to other advancements in medical care for SGA infants delivered preterm, not solely due to ACS administration.

Strengths and Limitations

Our study offers several strengths. We included a large representative sample of 8,989 preterm SGA infants, most with birthweight less than the tenth percentile. We used a predefined protocol and comprehensive search strategy to limit selection bias. The SGA population as the specific target in our analysis represents a major strength of our study as SGA infants, albeit an important population of clinical interest, have been either excluded from prior large-scale trials evaluating ACS administration and neonatal outcomes or not specifically a population of focused analysis in these trials.

As with all meta-analyses, the limitations of the primary studies must be considered. Eleven of the thirteen included studies included in the meta-analysis were retrospective cohort studies, inherently limited in their study design compared to prospective or randomized controlled trials studies. Most studies did not distinguish etiology of SGA infants, whether constitutional versus pathologic, but the benefits and risks of ACS likely vary according to their physiology. As a result of variable definitions for SGA, we were unable to perform a subgroup analysis based on etiology of SGA or to evaluate for differences in the primary or secondary outcomes for more or less severely growth-restricted infants (for example, less than the fifth percentile versus less than the tenth percentile). Missing data for secondary outcomes, and variable ways in which data were reported or outcomes were defined, also limited data synthesis. Gestational age at delivery was highly variable and individual studies included neonates over a broad range of gestational ages, thus limiting our ability to perform subgroup analysis comparing outcomes among very early preterm (less than 28 or 32 weeks' gestation, for example) versus preterm infants at more advanced gestational ages (32 to 34 weeks' gestation). Similarly, heterogeneity in type of steroid used, betamethasone versus dexamethasone, limited subgroup analysis to determine which may be preferential in SGA infants. Few studies reported on what percentage of infants, if any, received a rescue course of ACS, nor did they report on the average time interval from ACS administration to infant delivery, specifically how close the timing of ACS administration was within the optimal window of 48 hours to within seven days of delivery. However, five of the sixteen included studies did exclude infants with suboptimal or partial ACS administration less than 24 hours before birth or greater than 7 days before delivery.

Future studies should further evaluate the effect of ACS administration on SGA infants in the late preterm period from 34 to 37 weeks and in non-singleton pregnancies, as data on ACS use in late preterm and multiple gestations is limited. In fact, the majority of studies excluded multiple gestations. More expansive investigation is also needed to further identify the effect of ACS on long term neurodevelopmental childhood outcomes in SGA infants, outcomes among constitutionally versus pathologically growth-restricted infants who receive ACS, and the benefit or harm of repeated or rescue doses of steroids in SGA infants delivered preterm.

Conclusions and Implications

Despite these limitations, our findings suggest ACS administration among preterm SGA infants could be beneficial in reducing neonatal mortality. Our study provides evidence-based support for the continued clinical use of ACS as the standard of care for reduction of neonatal mortality among infants at risk of preterm birth in the next seven days, including the SGA population, in accordance with current guidance set for by the American College of Obstetricians and Gynecologists.[43] Although a large randomized-controlled trial (RCT) would provide a higher level of evidence and reduce the effect of bias and heterogeneity on study outcomes, an RCT is likely not feasible to evaluate the effect of ACS administration in SGA infants due to both ethical reasons and patient preference for an intervention that is likely to be beneficial. Our meta-analysis of thirteen observational studies provides the highest level of evidence currently available demonstrating benefit of ACS administration for reducing neonatal mortality in SGA infants at risk of preterm delivery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AJOG at a Glance

Why was the study conducted?

Prior literature offers conflicting evidence guiding antenatal corticosteroid (ACS) administration in small-for-gestational age (SGA) infants given their increased endogenous steroid exposure due to pathologic intrauterine stress. The present study estimates the effect of ACS on neonatal mortality and morbidity in preterm SGA infants through a systematic literature review and meta-analysis.

What are the key findings?

ACS administration in preterm SGA infants significantly reduces neonatal mortality, with no apparent effect on neonatal morbidity.

What does the study add to what is already known?

The SGA population is one of clinical interest that has not been a population of focus in large-scale randomized trials evaluating ACS administration and neonatal outcomes. Our focused analysis on ACS administration in SGA infants provides the highest level of evidence currently available demonstrating benefit of ACS administration for reducing neonatal mortality in SGA infants delivered preterm.

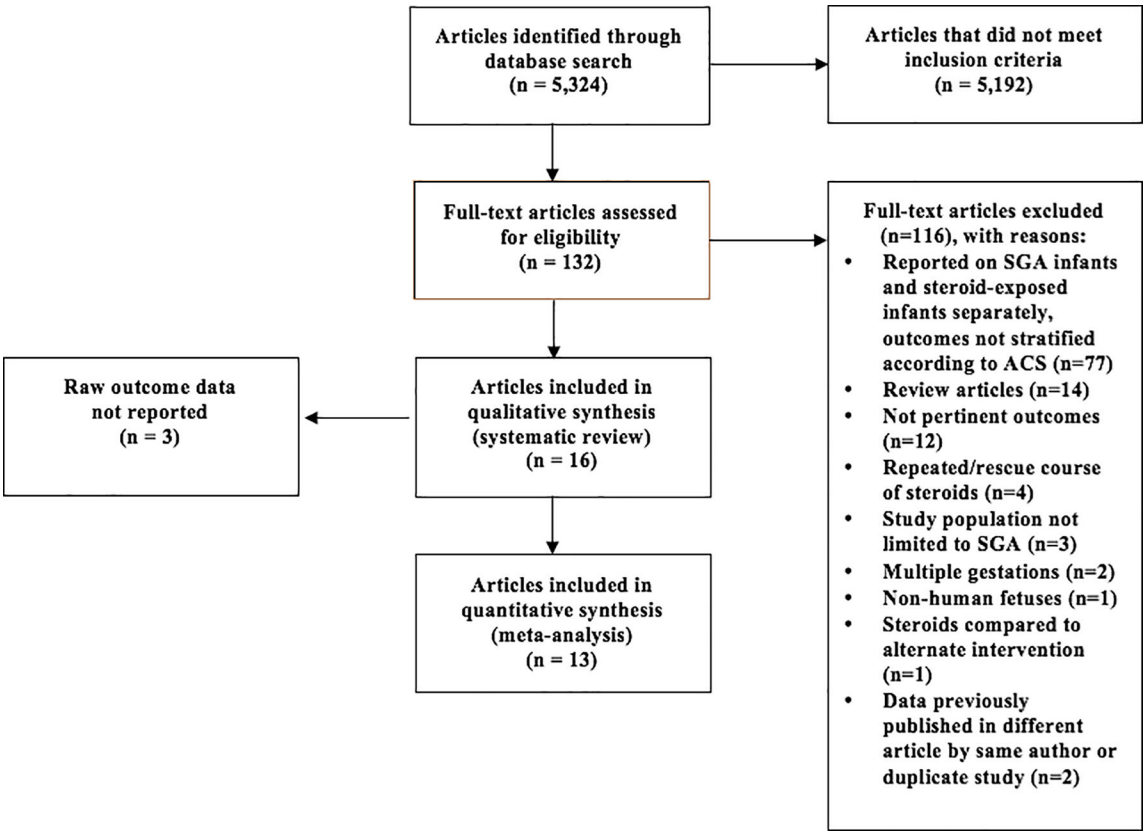

Figure 1. Flow Chart of the Literature Review

Flow chart demonstrates the literature search, including inclusion and exclusion of selected studies.

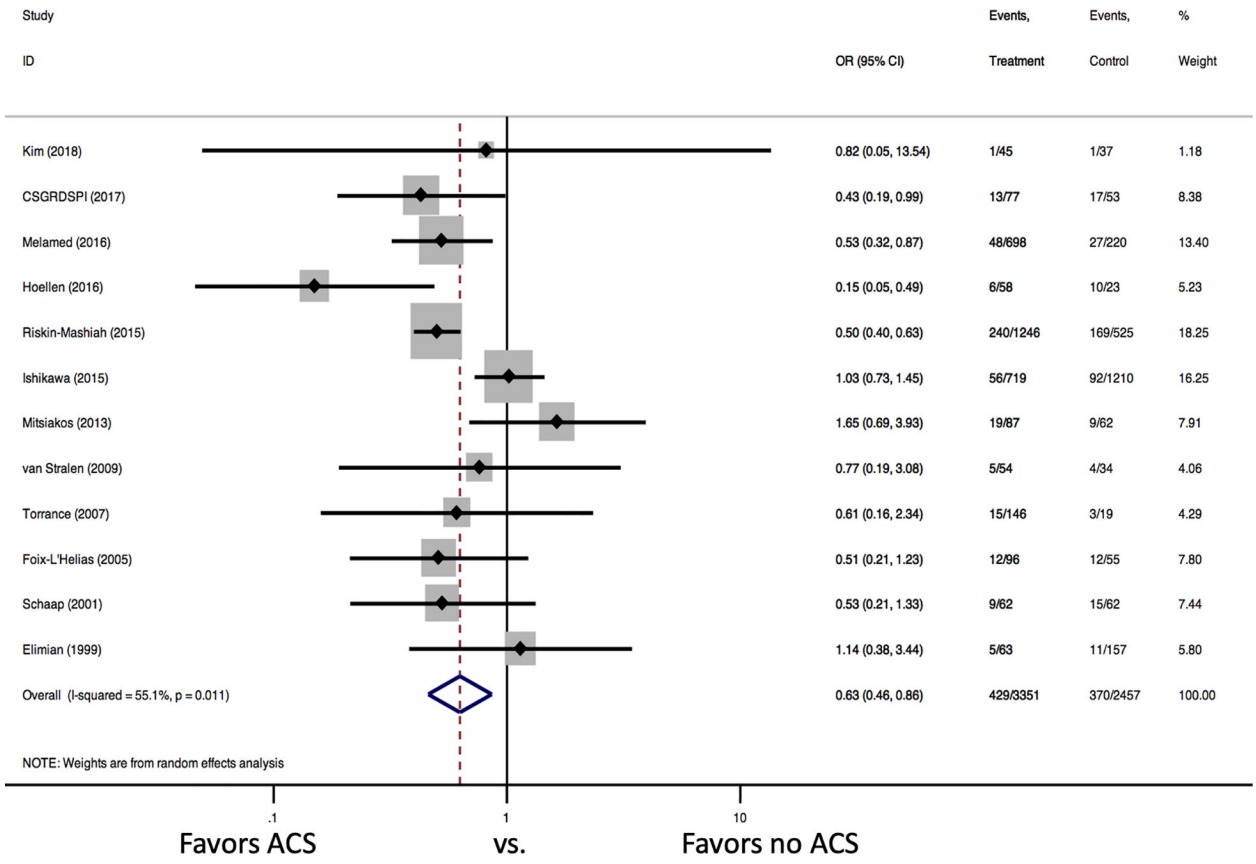

Figure 2. Forest Plots for Neonatal Mortality

Forest plot demonstrates a significant reduction in neonatal mortality for SGA infants that received ACS.

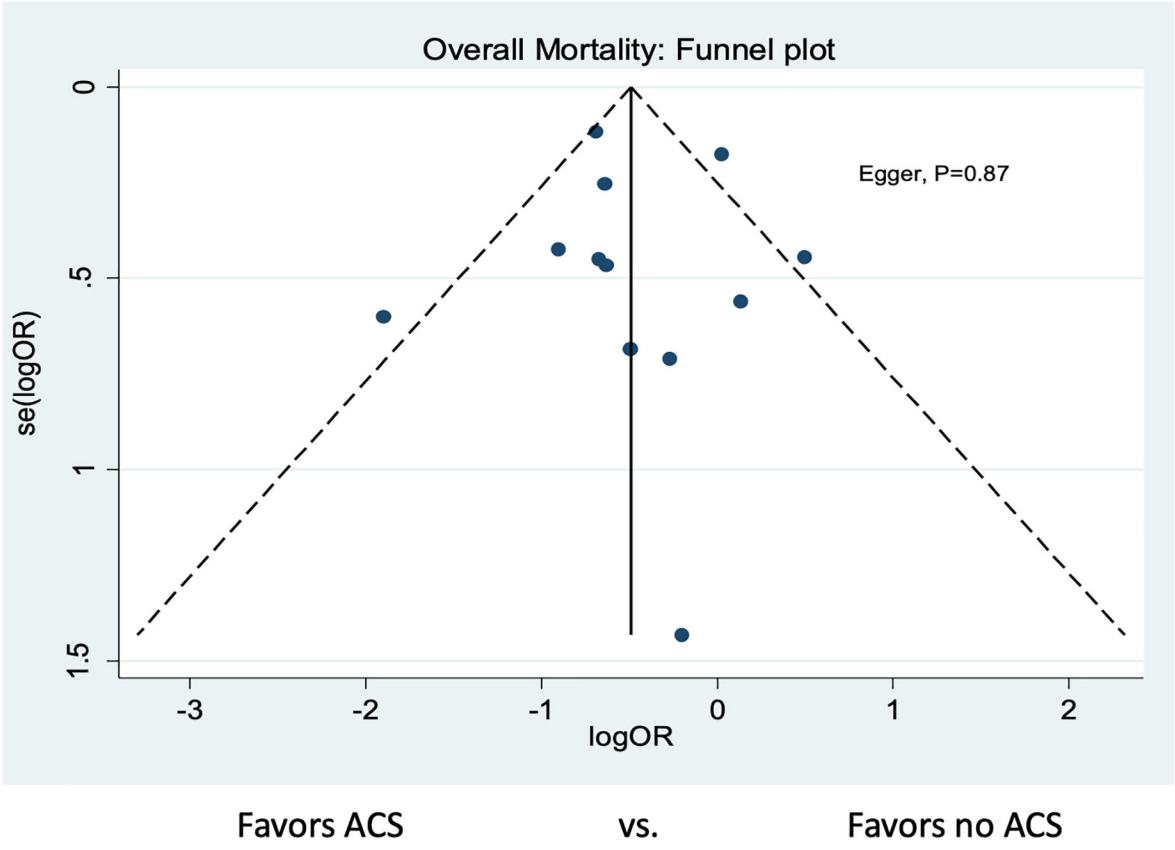

Figure 3. Funnel Plot for Publication Bias for Overall Mortality

Funnel plot demonstrates symmetry for studies that reported overall mortality, suggesting a lack of publication bias.

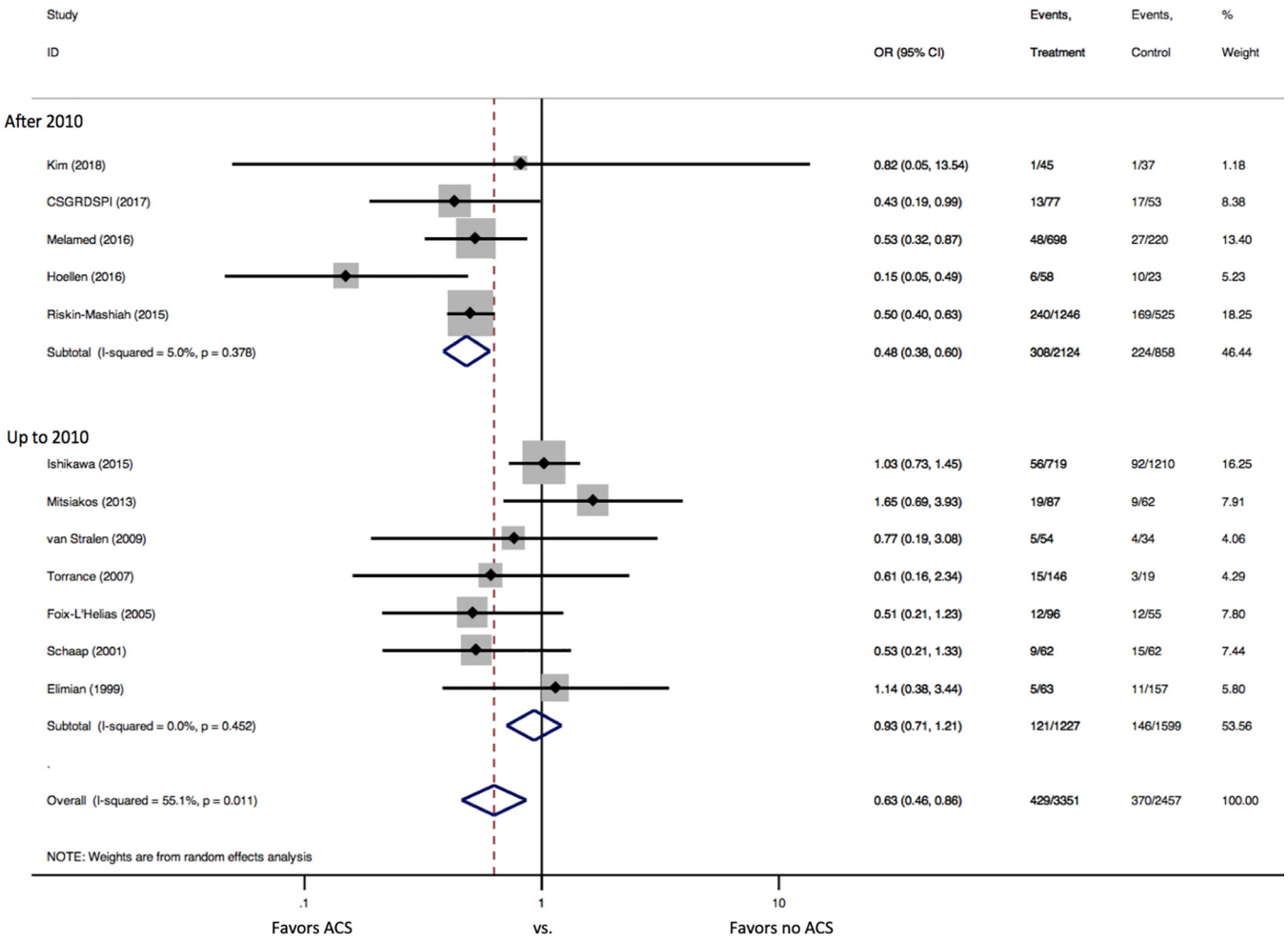

Figure 4. Forest Plots for Neonatal Mortality by Study Year

Forest plot demonstrates a significant reduction in neonatal mortality for SGA infants that received ACS among studies that followed patients after 2010, but no significant difference in mortality among studies that followed patients up to 2010.

Table 1.

Baseline Study Characteristics

Author	Publication year (study years)	Country	Study design	Gestational age at delivery (weeks)	Type of steroid	SGA defined	Number of SGA infants (n)	Number of SGA infants receiving ACS (n)	Number of SGA infants not receiving ACS (n)
Kim	2018 (2009–2016)	Korea	Retrospective cohort	29–34	D	BW <10%ile	82	45	37
Collaborative Study Group for Respiratory Distress in Preterm Infants (CSGRDSPI)	2017 (2013–2014)	China	Retrospective cohort	24–34	-	-	602	-	-
Melamed	2016 (2010–2014)	Canada	Retrospective cohort	24–33w6d	B or D	BW <10%ile	918	698	220
Hoellen	2016 (2000–2011)	Germany	Retrospective cohort	22w5d-29w6d	-	early onset FGR <32weeks and BW <10%ile	92	58	23
Riskin-Mashiah	2015 (1995–2012)	Israel	Retrospective cohort	24–31	-	BW <10%ile	1771	1246	525
Griffin	2015 (2005–2012)	United States	Retrospective cohort	22–29w6d	-	BW < 1 %ile	648	271	377
Ishikawa	2015 (2003–2007)	Japan	Retrospective cohort	22–33w6d	B	BW <10%ile	1929	719	1210
Mitsiakos	2013 (-)	Canada	Retrospective cohort	24–31w6d	B	BW <10%ile	149	87	62
van Stralen	2009 (2001–2005)	Netherlands	Retrospective cohort	<34	B	BW <3%ile	88	54	34
Torrance	2007 (1999–2003)	Netherlands	Retrospective cohort	<34	B	Abnormal PI, UA or MCA dopplers	165	146	19
Foix-L'Helias	2005 (1993–1996)	France	Retrospective cohort	24–31	-	FGR antenatally suspected and BW <10%ile	151	96	55
Schaap	2001 (1984–1991)	Netherlands	Case-control	26–31	B	fundal height and biometry less than dates; placental dysfunction confirmed on histopathology	124	62	62
Bernstein	1999 (1991–1996)	Canada/United States	Retrospective cohort	25–30	-	BW <10%ile	1720	937	783
Elimian	1999 (1990–1997)	United States	Retrospective cohort	-	B	BW <10%ile	220	63	157

Author	Publication year (study years)	Country	Study design	Gestational age at delivery (weeks)	Type of steroid	SGA defined	Number of SGA infants (n)	Number of SGA infants receiving ACS (n)	Number of SGA infants not receiving ACS (n)
Ley	1997 (1985–94)	Sweden	Retrospective cohort	25–32	-	Use of growth curve based on longitudinal EFW on US	234	117	117
Spinillo	1995 (1988–1993)	Italy	Prospective cohort	<35	B or D	BW<10% and AC or HC <10%ile on US	96	32	64

*SGA=small-for-gestational age, ACS=antenatal corticosteroids, B=betamethasone, D=dexamethasone, BW=birth weight, PI=pulsatility index, UA=umbilical artery, MCA=middle cerebral artery, FGR=fetal growth restriction, EFW=estimated fetal weight, US= ultrasound, AC=abdominal circumference, HC=head circumference

†Blank cells represent missing data

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Table 2.

Maternal Characteristicstab

Author (publication year)	Number of SGA infants receiving ACS (n)	Number of SGA infants not receiving ACS (n)	Mean maternal age (years ± SD)		Nulliparity (n, %)		Maternal diabetes (n, %)		Maternal hypertensive disorder (n, %)		Chorioamnionitis† (n, %)	
			+ACS	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*
Kim (2018)	45	37	34	33	29 (64.6)	26 (70.3)	2 (4.4)	2 (5.4)	25 (55.6)	18 (48.6)	0 (0.0)	1 (2.7)
CSGRDSPI (2017)	-	-	-	-	-	-	-	-	-	-	-	-
Melamed (2016)	698	220	32.4 ± 6.1	30.8 ± 5.3	395 (56.6)	110 (50.0)	71 (10.2)	16 (7.3)	489 (70)	94 (44)	0 (excluded)	0 (excluded)
Hoellen (2016)	58	23	-	-	-	-	-	-	-	-	-	-
Riskin-Mashiah (2015)	1246	525	-	-	-	-	64 (5.1)	23 (4.4)	753 (76.8)	227 (23.2)	-	-
Griffin (2015)	271	377	-	-	-	-	-	-	-	-	-	-
Ishikawa (2015)	719	1210	32.0 ± 4.9	32.1 ± 5.0	437 (60.8)	746 (61.7)	8 (1.1)	25 (2.1)	318 (44.2)	605 (50.0)	clinical: 43 (6.0) histologic: 46 (9.1)	clinical: 75 (6.3) histologic: 46 (5.5)
Mitsiakos (2013)	87	62	30.9 ± 6.3	29.5 ± 6.0	-	-	-	-	41 (47.1)	35 (56.4)	6 (6.9)	2 (3.2)
van Stralen (2009)	54	34	30.0 ± 5.9	32.8 ±5.5	22 (40.7)	8 (23.5)	-	-	46 (85.2)	24 (70.5)	-	-
Torrance (2007)	146	19	-	-	-	-	-	-	99 (67.8)	7 (36.8)	-	-
Foix-L'Helias (2005)	96	55	-	-	-	-	-	-	-	-	-	-
Schaap (2001)	62	62	29.0 ± 5.0	29.0 ± 5.0	37 (59.6)	40 (64.5)	-	-	37 (59.7)	51 (82.3)	-	-
Bernstein (1999)	937	783	-	-	-	-	-	-	-	-	-	-
Elimian (1999)	63	157	-	-	-	-	-	-	-	-	clinical: 2 (3.2) histologic: 11 (17.5)	clinical: 6 (3.8) histologic: 34 (21.6)
Ley (1997)	117	117	-	-	-	-	-	-	-	-	-	-
Spinillo (1995)	32	64	-	-	-	-	-	-	-	-	-	-
Weighted-average	-	-	**32.0**	**31.7**	**58.3%**	**59.5%**	**5.4%**	**3.3%**	**59.1%**	**48.9%**	**clinical: 5.6% histologic: 7.3%**	**clinical: 5.7% histologic: 5.9%**

*SGA=small-for-gestational age, ACS=antenatal corticosteroids, SD=standard deviation, CSGRDSPI=Collaborative Study Group for Respiratory Distress in Preterm Infants, +ACS=infants received antenatal corticosteroids, −ACS=infants did not receive antenatal corticosteroids

†Chorioamnionitis is clinically diagnosed unless otherwise specified

‡Blank cells represent missing data

Table 3.

Neonatal Characteristics

Author (publication year)	Number of SGA infants receiving ACS (n)	Number of SGA infants not receiving ACS (n)	Mean gestational age (weeks ± SD)		Mean birthweight (g)		Cesarean delivery (n, %)		Male sex (n, %)		Post-natal surfactant (n, %)		Mechanical ventilation (n, %)	
			+ACS	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*
Kim (2018)	45	37	32.7 (-)	34.1 (-)	1190	1450	40 (88.9)	34 (91.9)	24 (53.3)	11 (29.7)	-	-	23 (51.1)	14 (37.8)
CSGRDSPI (2017)	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Melamed (2016)	698	220	29.8 ± 2.6	30.7 ± 2.5	959	1061	636 (91.1)	178 (80.9)	369 (52.8)	114 (51.8)	-	-	312 (44.7%)	106 (48%)
Hoellen (2016)	58	23	-	-	-	-	-	-	-	-	-	-	-	-
Riskin-Mashiah (2015)	1246	525	-	-	-	-	1169 (72.8)	436 (27.2)	657 (69.7)	286 (30.3)	-	-	-	-
Griffin (2015)	271	377	-	-	-	-	-	-	-	-	-	-	-	-
Ishikawa (2015)	719	1210	29.1 ± 2.6	29.7 ± 2.7	886	959	661 (91.9)	1058 (87.4)	386 (53.8)	615 (50.9)	-	-	-	-
Mitsiakos (2013)	87	62	27.5 ± 2.5	27.8 ± 2.5	779	787	73 (83.9)	53 (85.5)	34 (39.1)	615 (50.9)	-	-	-	-
van Stralen (2009)	54	34	30.0 ± 1.7	30.4 ± 1.7	-	-	50 (92.6)	33 (97.1)	21 (38.9)	15 (44.1)	19 (35.2)	13 (38.2)	30 (55.6%)	18 (52.9%)
Torrance (2007)	146	19	30.3 ± 1.9	31.0 ± 1.6	899	903	13 (95.2)	19 (100.0)	79 (54.1)	9 (47.4)	45 (30.8)	3 (15.8)	66 (45.2%)	11 (57.9%)
Foix-L'Helias (2005)	96	55	-	-	-	-	-	-	-	-	-	-	-	-
S chaap (2001)	62	62	29.9 ± 1.3	30.3 ± 1.0	943	987	62 (100.0)	62 (100.0)	39 (62.9)	39 (62.9)	4 (6.5)	9 (14.5)	31 (50.0%)	27 (43.5%)
Bernstein (1999)	937	783	-	-	-	-	-	-	-	-	-	-	-	-
Elimian (1999)	63	157	-	-	-	-	-	-	-	-	17 (27.0)	31 (19.7)	-	-
Ley (1997)	117	117	-	-	-	-	-	-	-	-	-	-	-	-
Spinillo (1995)	32	64	-	-	-	-	-	-	-	-	-	-	-	-
Weighted-average	-	-	**29.5**	**29.9**	**921**	**978**	**92.6%**	**86.4%**	**52.6%**	**51.2%**	**26.2%**	**20.6%**	**46.0% (mean 0.8 days)**	**47.3% (mean 2.2 days)**

*SGA=small-for-gestational age, ACS=antenatal corticosteroids, SD=standard deviation, CSGRDSPI=Collaborative Study Group for Respiratory Distress in Preterm Infants, +ACS=inJants received antenatal corticosteroids, −ACS=infants did not receive antenatal corticosteroids

† Blank cells represent missing data

Table 4.

Neonatal Outcomes

Author (Publication Year)	Number of SGA infants receiving (n)	Number of SGA infants not ACS (n)	Neonatal mortality (n, %)		RDS (n, %)		BPD or CLD of Prematurity (n, %)		IVH and/or PVL (n, %)		NEC (n, %)		Neonatal sepsis (n, %)	
			+ACS	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*
Kim (2018)	45	37	1 (2.2)	1 (2.7)	22 (48.9)	11 (29.7)	-	-	4 (8.7)	1 (2.7)	5 (11.1)	2 (5.4)	9 (20.0)	3 (8.1)
CSGRDSPI (2017)	-	-	13/77 (16.9)	17/53 (32.1)	37/77 (48.1)	42/53 (79.2)	-	-	27/248 (10.9)	13/224 (5.8)	-	-	-	-
Melamed (2016)	698	220	48 (6.9)	27 (12.3)	364 (52.1)	98 (44.5)	134 (19.2)	30 (14.5)	35 (5.0)	20 (9.1)	30 (4.3)	7 (1.4)	-	-
Hoellen (2016)	58	23	6 (10.3)	10 (43.5)	-	-	-	-	-	-	-	-	-	-
Riskin-Mashiah (2015)	1246	525	240 (19.3)	169 (32.2)	840/1236 (68.0)	365/505 (72.3)	225/1009 (22.3)	68/363 (18.7)	IVH: 77/1180 (6.5) PVL: 41/992 (4.1)	IVH: 49/446 (11.0) PVL: 30/347 (8.6)	101/1235 (8.2)	55/505 (10.9)	-	-
GrifRn[†] (2015)	271	377	OR 0.16 (0.07–0.34)		-	-	-	-	-	-	-	-	-	-
Ishikawa (2015)	719	1210	56 (7.8)	92 (7.6)	341 (47.4)	510 (42.1)	194 (27)	250 (21)	IVH: 54 (7.5) PVL: 11 (1.5)	IVH: 99 (8.2) PVL: 28 (2.3)	13 (1.8)	15 (1.2)	51 (7.1)	75 (6.2)
Mitsiakos (2013)	87	62	19 (21.8)	9 (14.5)	45 (51.7)	36 (58.1)	16 (23.5)	15 (28.3)	IVH: 3 (3.4) PVL: 1 (1.4)	IVH: 3 (4.8) PVL: 1 (1.8)	10 (11.5)	5 (8.0)	29 (33.3)	20 (32.3)
van Stralen (2009)	54	34	5 (9.3)	4 (11.8)	22 (40.7)	17 (50.0)	6 (11.1)	4 (11.8)	4 (7.4)	1 (2.9)	3 (5.6)	2 (5.9)	33 (61.1)	24 (70.6)
Torrance (2007)	146	19	15 (10.3)	3 (15.8)	64 (43.8)	8 (42.1)	34 (23.3)	6 (31.6)	-	-	-	-	-	-
Foix- L'Helias (2005)	96	55	12 (12.5)	12 (21.8)	49 (51.0)	35 (63.6)	25 (26.4)	21 (37.8)	-	-	-	-	-	-
Schaap (2001)	62	62	9 (14.5)	15 (24.2)	23 (37.1)	25 (40.3)	16 (25.8)	19 (30.6)	8 (12.9)	9 (14.5)	-	-	12 (19.4)	12 (19.4)
Bernstein[†] (1999)	937	783	-	-	OR 0.70		-	-	-	-	-	-	-	-
Elimian (1999)	63	157	5 (7.9)	11 (7.0)	17 (26.9)	38 (24.2)	-	-	3 (4.8)	8 (5.1)	1 (1.6)	3 (1.9)	6 (9.5)	9 (5.7)
Ley[†] (1997)	117	117	OR 0.53 (95% CI 0.21–1.32)		OR 1.20 (95% CI 0.62–2.34)		-	-	OR 0.72 (95% CI 0.28–1.84)		-	-	-	-

Author (Publication Year)	Number of SGA infants receiving (n)	Number of SGA infants not ACS (n)	Neonatal mortality (n, %)		RDS (n, %)		BPD or CLD of Prematurity (n, %)		IVH and/or PVL (n, %)		NEC (n, %)		Neonatal sepsis (n, %)	
			+ACS	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*	*+ACS*	*−ACS*
Spinillo (1995)	32	64	-	-	10 (31.3)	30 (46.9)	-	-	2/28 (7.1)	18/58 (31.0)	-	-	-	-
Weighted-Average	-	-	**12.8%**	**15.1%**	**55.3%**	**49.0%**	**22.6%**	**20.4%**	**6.8%**	**8.8%**	**5.6%**	**4.0%**	**13.6%**	**9.2%**

*SGA=small-for-gestational age, ACS=antenatal corticosteroids, RDS=respiratory distress syndrome, BPD=bronchopulmonary dysplasia, CLD=chronic lung disease, IVH=intraventricular hemorrhage, PVL=periventricular leukomalacia, NEC=necrotizing enterocolitis, CSGRDSPI=Collaborative Study Group for Respiratory Distress in Preterm Infants, +ACS=infants received antenatal corticosteroids, −ACS=infants did not receive antenatal corticosteroids, OR=odds ratios, CI=confidence interval

†Raw data for neonatal outcomes according to ACS administration was not reported for 3 studies; only odds ratios with 95% confidence intervals were reported in these studies comparing SGA infants that received ACS to those that did not receive ACS

‡Blank cells represent missing data Blank cells represent missing data

Table 5.

Results of the Risk of Bias Assessment using the Downs and Black Assessment Tool

Author (Publication Year)	Reporting (11)*	External validity (3)*	Bias (7)*	Confounding (6)*	Power (1)*	Total (28)*
Kim (2018)	10	0	5	3	0	18
CSGRDSPI (2017)	5	0	5	2	0	12
Melamed (2016)	10	2	5	3	0	20
Hoellen (2016)	6	0	4	2	0	12
Riskin- Mashiah (2015)	9	2	5	3	0	19
Griffin (2015)	7	1	5	3	0	16
Ishikawa (2015)	10	2	5	3	0	20
Mitsiakos (2013)	10	0	5	3	0	18
van Stralen (2009)	10	0	5	3	0	18
Torrance (2007)	9	0	4	3	0	16
Foix-L'Helias (2005)	8	0	5	3	0	16
Schaap (2001)	10	0	5	2	1	18
Bernstein (1999)	8	1	4	3	0	16
Elimian (1999)	10	0	5	3	1	19
Ley (1997)	8	2	4	3	0	17
Spinillo (1995)	10	0	5	3	0	18

*Maximum number can be scored in that criterion.