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REVIEW ARTICLE

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Neurological implications of antenatal corticosteroids on late preterm and term infants: a scoping review

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The objective of this study was to synthesize the body of knowledge on the association between ACS exposure for risk of preterm birth and brain development in infants ultimately born late preterm and term. Three databases and eight conference proceedings were systematically searched (1972–2021). Selection criteria included ACS administration for risk of preterm delivery, cohort of late preterm and term infants, and assessment of brain development. Data on study characteristics, ACS administration, and neurological outcomes were extracted and qualitatively synthesized according to themes. Neurological outcomes of the included studies ($n = 27$) were grouped into four themes. The most common adverse outcomes were reduced neonatal head circumference, structural cortical differences on MRI, increased prevalence of psychiatric problems, and increased risk of neurodevelopmental delays in ACS-exposed late preterm and term infants. Our scoping review demonstrated that ACS exposure for risk of preterm delivery may have important neurological implications in infants ultimately born late preterm and term. Given that the existing research is at serious risk for bias, further research that accounts for confounders such as preterm labor, maternal stress, and the number of ACS courses is needed to better establish the long-term neurological effects of ACS on late preterm and term infants.

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IMPACT:

- Due to the difficulty in predicting preterm birth, approximately 40% of fetuses exposed to antenatal corticosteroids (ACS) are born at term (≥37 weeks' gestation).
- This scoping review summarizes the knowledge on the association between ACS exposure for risk of preterm birth and brain development in late preterm and term infants.
- The majority of studies reported that ACS exposure was associated with adverse brain development outcomes across various domains, such as reduced neonatal head circumference, cortical differences on MRI, and increased prevalence of psychiatric problems and neurodevelopmental delays in late preterm and term infants.

INTRODUCTION

Antenatal corticosteroids (ACS) are commonly given to women at risk of preterm delivery.[1] ACS accelerate fetal lung maturation and reduce morbidity and mortality, including the incidence of respiratory distress syndrome and severe brain injuries in preterm infants.[1,2] The neurological benefits of ACS in preterm infants <34 weeks' gestation are undeniable.[3–5] However, due to the significant challenge of accurately predicting preterm delivery, as many as 40% of infants exposed to ACS are born at term (≥37 weeks' gestation).[2] The short-term benefits of ACS in late preterm and term infants are much attenuated relative to those in more preterm infants (<34 weeks' gestation);[2] as such, any long-term neurological adverse effects of ACS may take on an outsized importance in late preterm and term infants.

ACS have been shown to be a life- and brain-saving treatment for preterm infants; however, several lines of evidence suggest that ACS may also have important effects on brain development.[1,3] Exposure to ACS was recently demonstrated to induce lasting changes in DNA methylation in vitro in a human fetal hippocampal progenitor cell line. In theory, these epigenetic changes could contribute to a heightened stress response and modify risk of later psychiatric disorders.[6] In addition, glucocorticoids inhibit hormones critical for fetal growth.[7] In animal models, exposure to ACS has been shown to result in detrimental long-term neurocognitive and neurobehavioral effects,[8] including anxiety-like behavior,[9–12] delayed motor development,[13,14] and impaired spatial memory.[15,16] In a systematic review of animal fetuses, ACS exposure most commonly altered glucocorticoid receptors in the hippocampus and hypothalamus with coincident neurocognitive sequelae.[8]

Several studies have assessed the long-term neurological implications of ACS on preterm infants.[4,5] However, the available data around the neurological implications of ACS on late preterm and term infants is heterogenous and has not been systematically synthesized. As such, this scoping review aims to evaluate the association between ACS exposure for risk of preterm birth and brain development in infants ultimately born late preterm and

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term and thereby expose gaps in our knowledge around the clinical care of women at risk for preterm delivery.

METHODOLOGY

Protocol design

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[17] our scoping review protocol was registered with the Open Science Framework (OSF), on December 5, 2020 (https://osf.io/vxrs2). A scoping review methodology was selected as it serves to effectively map the available research and provides a mechanism for summarizing and disseminating research findings.[18] The review adhered to the checklist provided by the PRISMA extension for scoping reviews.[17] Methods for this study were derived from Colquhoun et al.'s[19] refinement of the original Arksey and O'Malley's scoping review methodology.[18] According to this framework, the following five stages guided this scoping review: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results.

Stage 1: identifying the research question. The main research question was: "What is the association between ACS exposure for risk of preterm birth and brain development in infants ultimately born late preterm and term?"

Stage 2: identifying relevant studies. Identification of studies relevant to this review was achieved by searching published literature in the following three electronic databases: MEDLINE, EMBASE, and the Cochrane Library. The search was last executed on November 1, 2021. Terms were searched as both keywords in the title/abstract (MeSH, EMTREE) and subject headings. Details of the search strategy are provided in Appendix S1. The methodology and search strategy were reviewed by a research librarian. The reference lists of studies included in the second phase of screening were hand-searched in order to ensure that all relevant studies had been captured in this review. The search was limited to studies published after 1972 as this was the first paper that focused on the effect of glucocorticoids on fetal lung maturation by Graham Liggins.[20] The proceedings of the following major conferences were searched from 2015 to 2021: Journal of Obstetrics and Gynaecology Canada, American College of Obstetricians and Gynecologists, Australian and New Zealand Journal of Obstetricians and Gynaecology, European Journal of Obstetrics & Gynecology and Reproductive Biology, Society for Maternal-Fetal Medicine, Pediatric American Societies, Organization for Human Brain Mapping and the International Society for Magnetic Resonance in Medicine.

Stage 3: selecting eligible studies. The screening process consisted of two stages: (1) a title and abstract review and (2) full-text review. For the first stage, two independent reviewers (E.B.S. and M.L.S.) screened the title and abstract of all retrieved citations. Inter-rater reliability demonstrated strong agreement of selected studies (Cohen's kappa = 0.92). At this stage, if there was uncertainty about the inclusion of a study, the full text was retrieved and included in the second stage. In the second stage, disagreements regarding study eligibility were discussed between the two reviewers until consensus was reached or by mediation of a third senior reviewer (J.G.), when required.

For a study to be included, its study design must have met all of the following criteria:

1. ACS exposure for risk of preterm birth
2. Term-born infants with or without late preterm-born infants (≥34 weeks' gestation)
3. Assessment of prenatal or postnatal brain development via either:
   a. Neurodevelopmental or neuropsychological evaluation
   b. Neurological evaluation
   c. Measurement of head size
   d. Brain imaging
4. English or French language.

Our original protocol included *only* term infants. However, many studies included a combination of term *and* late preterm infants rather than exclusively term infants (see below). In line with the iterative process of a scoping review, we amended our original inclusion criteria to include studies that evaluated term (≥37 weeks' gestation) with or without late preterm infants (≥34 weeks' gestation) so as to not exclude these studies.[21]

Any study without a comparison group of ACS-unexposed infants was excluded.

Both original studies and review studies were initially included. Once the full-text reviews were retrieved and reference screened for new studies, these reviews were excluded from further thematic analysis as they did not provide additional findings beyond those of the original studies.

All eligible studies were first uploaded into the Endnote X9 software in order to identify and remove duplicates. The de-duplicated library was then uploaded into Rayyan (https://rayyan.qcri.org/) to carry out the blinded screening process by the two independent reviewers.

Stage 4: charting the data. A standardized data extraction form was used by two independent reviewers (E.B.S. and M.L.S.) to electronically capture relevant information from each included study. The following information was extracted from each study: author(s), year of publication, aim of study, study participants and sample size, methodology, intervention and comparator, outcome, most relevant findings, limitations, and additional comments. Additionally, two review authors (E.B.S. and M.L.S.) independently assessed the risk of bias of each included study against seven key criteria: confounding, selection of study participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported result in accordance with the Cochrane Risk of Bias for Non-Randomised Studies (ROBINS-1).[22] The following judgments were used: low, moderate, serious, or unclear risk (lack of information). Authors resolved disagreements by consensus, and the authors (J. G. and A.-M.M.) were consulted to resolve disagreements if necessary.

Stage 5: synthesis and presentation of results. The main characteristics of the studies included were listed (Table S1). The outcomes relevant to our study were then identified and grouped into a thematic analysis of neurological outcomes with risk of bias assessment (Table 1). Simplified results are presented in Table 2.

RESULTS

Our systematic search yielded 9736 citations, 25 of which were included in this study following the screening process (Fig. 1). Two of these studies were conference abstracts. Reference and hand-searching identified 2 additional studies for a total of 27 included studies. Only a single included study was published before 2000.

Study characteristics and ACS administration

All 27 studies were observational and comprised 12 retrospective cohort studies,[2,23–33] 11 prospective cohort studies,[7,34–43] and 4 cross-sectional studies.[44–47]

Table 1. Main findings of studies comparing neurological outcomes of late preterm and term infants exposed to antenatal corticosteroids for risk of preterm birth against ACS-unexposed infants ($n = 27$).

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Biometric head measurement							
Braun et al.[7]	Head circumference (cm)	Newborn	27.19 ± 0.68 $n = 13$	31.83 ± 0.44 $n = 3$	0.004	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
							Overall bias: serious
Chen et al.[25]	Head circumference (cm)	6-10 years	52.63 ± 2.02 $n = 29$	54.05 ± 1.85 $n = 87$	0.017	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Piazze et al.[41]	Head circumference (cm)	Newborn	33 [32–34] $n = 63$	34 [33–35] $n = 189$	<0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Rizzo et al.[31]	Head circumference growth velocity before and after ACS exposure (*Z*-score)	36 weeks GA (intrauterine)	−0.61 $n = 262$	0.12 $n = 270$	<0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Rodriguez et al.[2]	Head circumference point estimate	Newborn	ACS-exposed vs. unexposed: −0.21 ± 0.04 (0.21 cm smaller) $n = 1279$ $n = 6326$		<0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious

Table 1. continued

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Eriksson et al.[27]	Rate of head circumference <2 SD below the mean sex-specific fetal growth curve	Newborn	1.61% *n/N* = 94/6020	3.90% *n/N* = 88/2303	<0.05	Favorable outcome	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: moderate Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Braun et al.[24]	Head circumference	Newborn	34 ± 0.1 *n* = 91	34 ± 0.0 *n* = 658	0.546	No association	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Davis et al.[36,a]	Head circumference (cm)	Newborn	33.3 ± 1.8 *n* = 18	33.8 ± 2.2 *n* = 15	0.5	No association	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Diguisto et al.[26,a]	Rate of head circumference below the 5th percentile sex-specific fetal growth curve	Newborn	5.8% *n/N* = 196/3388	4.3% *n/N* = 304/7077	>0.05	No association	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: moderate Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Kang et al.[45]	Head circumference	Newborn	34.93 ± 1.71 34.69 ± 1.29	34.38 ± 1.34 34.82 ± 1.30	0.61 0.79	No association	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: moderate Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Stafford et al.[32]	Head circumference	Newborn	32.18 ± 0.38 *n* = 60	32.36 ± 0.10 *n* = 367	0.892	No association	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious

Table 1. continued

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Verder et al.[43]	Head circumference	Newborn	N/A $n = 98$	N/A $n = 1012$	>0.05	No association	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Structural brain imaging							
Davis et al.[35]	Structural MRI for cortical thickness	6–10 years	Left rostral anterior cingulate cortex: 8% thinner in ACS-exposed children ($n = 18$) Right rostral anterior cingulate cortex: 9% thinner in ACS-exposed children ($n = 18$)		<0.05 <0.05	Adverse outcome Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Modi et al.[39]	Structural MRI for surface area (cm^2) Brain volume (cm^3) Whole cortex convolution index	Newborn	Surface area: 563 cm^2 Volume: 457 cm^3 Mean 15.7 $n = 10$	Surface area: 649 cm^2 Volume: 477 cm^3 Mean 20.0 $n = 6$	0.02 0.5 0.001	Adverse outcome No association Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Psychiatric symptoms							
Behavioral control							
Ilg et al.[47]	Event-related potentials recorded during a modified version of the Cued Continuous Performance Task	14–18 years	N2 NoGo amplitude: 267 ± 10 ms $n = 28$	N2 NoGo amplitude: 271 ± 10 ms $n = 24$	0.01	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Ligges et al.[38]	Strengths and difficulties questionnaire (SDQ)	7–9 years	N/A	N/A	0.004	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: no information
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious

Table 1. continued

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Raikkonen et al.[30]	Disorder diagnoses coded using International Statistical Classification of Diseases (ICD-10)	3.1–8.7 years (median age 5.8 years)	8.89% *n*/*N* = 598/6730	6.31% *n*/*N* = 40,051/634,757	<0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Attention							
Ilg et al.[47]	Intraindividual reaction time variability at the end of a task	14–18 years	122 ms *n* = 28	94 ms *n* = 24	0.03	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Khalife et al.[37]	Rutter B2 inattention score by teachers	8 years	1.01 *n* = 37	0.22 *n* = 6069	0.02	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: moderate
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Ligges et al.[38]	Attention deficit hyperactivity disorder rating scale by parents	7–9 years	N/A *n* = 39	N/A *n* = 39	0.01	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: no information
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Psychiatric disturbance							
Ghosn et al.[34]	Modified checklist for autism in toddlers (M-CHAT-R)	30 months	~1.0	~0.2	0.031	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious

Table 1. continued

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Khalife et al.[37]	Rutter B2 neurotic score by teachers	8 years	3.13 $n = 37$	0.65 $n = 6076$	<0.01	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: moderate
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Raikkonen et al.[30]	Psychological development disorders coded using International Statistical Classification of Diseases (ICD-10)	3.1–8.7 years (median age 5.8 years)	4.00% $n/N = 269/6730$	2.83% $n/N = 17{,}994/634{,}757$	<0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Wolford et al.[33]	Any mental and behavioral disorder coded using International Classification of Diseases-10 (ICD-10)	3.5 years	17.9% $n/N = 10/56$	8.4% $n/N = 373/4465$	<0.05	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: moderate
							Bias in classification of interventions: low
	Mother-reported child psychiatric problems using the Child Behavior Checklist	3.5 years	N/A	N/A	N/A	Adverse outcome	Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Psychological stress response							
Erni et al.[46,a]	Anticipatory stress appraisal before the Trier Social Stress Test for Children	10 years	4.280 ± 0.170 $n = 43$	4.810 ± 0.190 $n = 35$	<0.05	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: moderate
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Ilg et al.[47]	Cortical activation in specified brain regions in response to specific tasks	14–18 years	ACC: $r = -0.55$ Precuneus: $r = 0.61$ $n = 28$	ACC: N/A Precuneus: N/A $n = 24$	0.002 0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious

Table 1. continued

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Neurocognitive and neuromotor functions							
Neurodevelopment							
Melamed et al.[29]	Suspected neurocognitive disorders	>5 years	25.8% *n/N* = 1397/5423	21.6% *n/N* = 113,181/523,782	<0.001	Adverse outcome	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low
	Diagnostic or billing code for visual and audiometry testing	>5 years	Vision: 45.4% 2461/5423 Hearing: 15.3% *n/N* = 827/5423	Vision: 43.5% *n/N* = 227,948/523,782 Hearing: 12.7% *n/N* = 66,555/523,782	0.006 0.001	Adverse outcome	Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Paules et al.[40]	Risk of mild neurodevelopmental delay using Merrill-Palmer-Revised Scales of Development	24–29 months	47.8% *n/N* = 11/23	14.6% *n/N* = 6/42	0.004	Adverse outcome	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Schneider et al.[42]	Cortical auditory-evoked responses (CAER)	<34 weeks GA (intrauterine)	P2pm: 187 ms P3pm: 484 ms *n* = 10	P2pm: 178 ms P3pm: 466 ms *n* = 10	0.042 0.043	Adverse outcome	Bias due to confounding: serious Bias in selection of study participants: low Bias in classification of interventions: low Bias due to deviations from intended interventions: no information Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Kang et al.[45]	Identical Pictures Task Reaction Time (IPT RT)	8 years	3368.84 ± 762.22	3447.77 ± 665.01	0.56	No association	Bias due to confounding: serious
		16 years	2064.21 ± 295.59	2064.21 ± 295.59	0.64	No association	Bias in selection of study participants: low Bias in classification of interventions: low
	Spot-a-Word-Task (SaW)	8 years	2.70 ± 3.63	3.50 ± 2.98	0.15	No association	Bias due to deviations from intended interventions: no information
		16 years	13.21 ± 4.70	13.21 ± 4.70	0.48	No association	Bias due to missing data: low Bias in measurement of outcomes: low Bias in selection of the reported result: moderate Overall bias: serious
Wolford et al.[33]	Ages and Stages Questionnaire-3: Communication skills						Bias due to confounding: serious Bias in selection of study participants: moderate Bias in classification of interventions: low
			9.8%	4.1%	0.38	No association	Bias due to deviations from intended interventions: no information
	Fine motor skills	3.5 years	5.9%	4.9%	0.99	No association	Bias due to missing data: low
	Gross motor skills		7.8%	5.0%	0.54	No association	Bias in measurement of outcomes: low
	Problem solving skills		13.7%	4.6%	0.07	No association	
	Personal social skills		11.8%	3.9%	0.01	Adverse outcome	Bias in selection of the reported result: moderate
							Overall bias: serious

Table 1. continued

Themes	Outcome	Age at assessment	ACS-exposed infants	ACS-unexposed infants	*P* value	Association	Risk of potential source of bias
Intelligence							
Ligges et al.[38]	Raven's Colored Progressive Matrices (CPM) test	7–9 years	N/A $n = 39$	N/A $n = 39$	0.001	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: no information
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Alexander et al.[44,a]	Cattell's Culture Fair Test	6–11 years	107.14 ± 12.8 $n = 97$	107.6 ± 11.7 $n = 36$	0.018	No association	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Grant et al.[28]	Wechsler Intelligence Scale for Children	6–10 years	101.2 ± 13.5 $n = 26$	98.1 ± 13.6 $n = 85$	0.05	No association	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Memory							
Paules et al.[40]	Memory abnormalities using Merrill–Palmer-Revised Scales of Development	24–29 months	56.5% $n/N = 13/23$	26.8% $n/N = 11/42$	0.019	Adverse outcome	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious
Grant et al.[28]	Wide Range Assessment of Memory and Learning	6–10 years	9.1 ± 2.2 $n = 26$	9.5 ± 2.1 $n = 85$	>0.05	No association	Bias due to confounding: serious
							Bias in selection of study participants: low
							Bias in classification of interventions: low
							Bias due to deviations from intended interventions: no information
							Bias due to missing data: low
							Bias in measurement of outcomes: low
							Bias in selection of the reported result: moderate
							Overall bias: serious

ACS antenatal corticosteroids, *N/A* not applicable, *MRI* magnetic resonance imaging.

[a]The comparison group for these four studies is infants unexposed to ACS but exposed to preterm labor rather than unexposed to ACS and unexposed to preterm labor.

Table 2. Synthesis of neurological outcomes of late preterm and term infants exposed to antenatal corticosteroids for risk of preterm birth ($n = 27$).

Themes and outcomes	Association with adverse outcome	Association with favorable outcome	No association
Biometric head measurement	✓✓✓✓✓[2,7,23,25,31,41]	✓[27]	✓✓✓✓✓[24,26,32,36,43,45]
Structural brain imaging	✓✓[35,39]		
Psychiatric problems			
Behavioral control	✓✓✓[30,38,47]		
Attention	✓✓✓[37,38,47]		
Psychiatric disturbance	✓✓✓✓[30,33,34,37]		
Psychological stress response	✓✓[46,47]		
Neurocognitive and neuromotor functions			
Neurodevelopment	✓✓✓[29,40,42]		✓✓[33,45]
Intelligence	✓[38]		✓✓[28,44]
Memory	✓[40]		✓[28]

✓Represents the number of studies reporting the respective association.

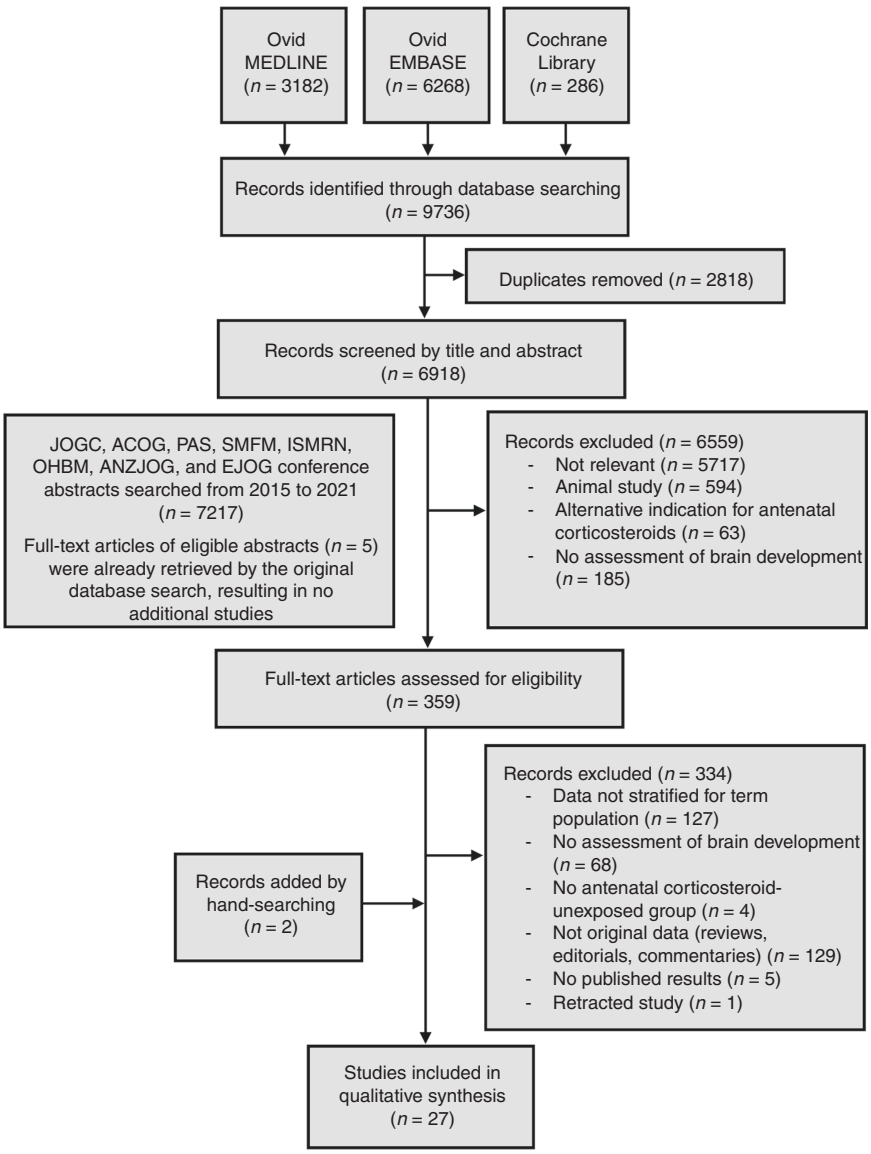

Fig. 1 PRISMA flow diagram. Flow diagram detailing the study identification and selection process.

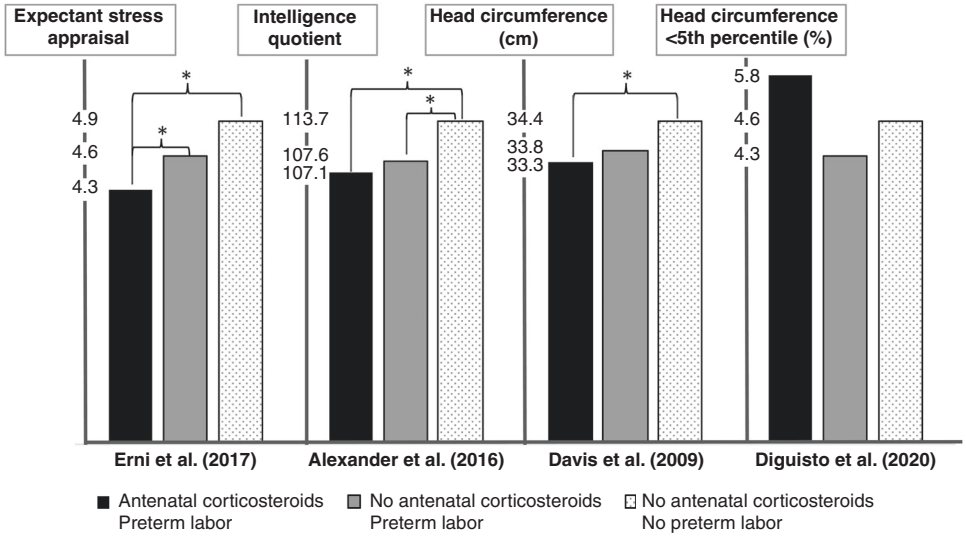

Fig. 2 Neurological outcomes from four different studies evaluating three groups born late preterm or term: exposed to preterm labor and exposed to antenatal corticosteroids, exposed to preterm labor but unexposed to antenatal corticosteroids, and a control group of unexposed to preterm labor and unexposed to antenatal corticosteroids. *$P < 0.05$.

There was variability in the dosing regimen and number of courses of ACS administered across studies. Betamethasone was administered in 19 studies,[2,7,23,24,26,28,30–33,35,36,38–43,46] and either betamethasone or dexamethasone was administered in 8 studies.[25,27,29,34,37,44,45,47] In 14 studies, a single course of ACS was administered (12 mg intramuscular (IM) of betamethasone q24h × two doses or 6 mg IM of dexamethasone q12h × four doses);[7,24,26,28,31,32,34–36,42–45,47] in two studies, two or more courses of ACS were administered;[25,39] in seven studies, the number of courses of ACS varied among study participants;[2,23,29,33,37,38,41] and in four studies, the regimen was not specified.[27,30,40,46] Almost all studies restricted ACS administration between 23 and 33 + 6 weeks' gestation; one study extended the period of administration to 34 + 6 weeks' gestation;[30] one study was restricted to administration of ACS to ≥34 weeks' gestation[32] and eight studies did not specify the gestational age at the time of ACS administration.[2,33,37,39,40,43,45,46] Only three studies registered the time interval between ACS administration and birth, recording mean intervals ranging between 52 and 65 days.[7,28,35]

The included studies represented a total of 26,816 ACS-exposed infants born at ≥34 weeks, and each group ranged from 10 to 6730 infants. Nineteen studies included infants born at ≥37 weeks' gestation, one included infants born at ≥36 weeks',[31] two included infants born at ≥35 weeks,[25,39] and five included infants born at ≥34 weeks' gestation.[32,38,42,43,46] Four studies did not specify whether they controlled for gestational age at birth in comparing ACS-exposed and ACS-unexposed infants, as outlined in Table 1.[34,40,41,43]

OUTCOMES' ASSESSMENT

All studies included in this review were primarily designed to assess at least one neurological outcome and 11 studies included both neurological and non-neurological assessments as the primary outcomes. Thirteen studies evaluated biometric head measurements, two evaluated magnetic resonance imaging (MRI) findings, five included psychiatric assessments, six included neurocognitive and neuromotor assessments, and two studies included both psychiatric and neurocognitive or neuromotor assessments. Two studies evaluated fetuses ultimately born late preterm or term,[31,42] 11 evaluated newborns,[7,23,24,26,27,32,34,36,39,41,43] 3 evaluated children 2–6 years of age,[2,40,45] and 12 evaluated children >6 years of age.[25,28–30,32,35,37,38,44–47] The main findings of these studies are presented in Table 1 and their results are synthesized in Table 2.

Biometric head measurement

Biometric head measurement was the most commonly reported outcome of brain development ($n = 13$ studies). Six studies reported a statistically significant decrease in head circumference in the ACS-exposed group compared to the ACS-unexposed group, with mean differences ranging from 0.21 to 4.64 cm.[2,7,23,25,31,41] Six studies reported no significant difference between the ACS-exposed and unexposed groups.[24,26,32,36,43,45] In one study, ACS exposure in term infants was associated with a reduced risk of head circumference ≤2 standard deviations below the mean as compared to ACS-unexposed infants.[27]

Structural brain imaging

Brain imaging was performed in two prospective cohort studies to evaluate the consequences of fetal exposure to ACS on brain development. In one study, 6–10-year-old children exposed to a single course of ACS had thinner cortices on MRI, with limbic regions, such as the rostral anterior cingulate cortex, most affected.[35] A second study showed reduced cortical maturation in infants exposed to multiple courses of ACS, manifested by lower whole cortex convolution indices and a smaller cortical surface area compared to ACS-unexposed infants.[39]

Psychiatric problems

Three studies evaluated the effect of ACS exposure on mental health and behavior of term children and reported an increased prevalence of psychiatric and behavioral problems as compared to ACS-unexposed children.[30,33,37] Failure to meet the age-appropriate development in personal–social skills was also higher in mother reports of term children exposed to ACS.[33] Additionally, term infants exposed to ACS for preterm labor showed higher autistic symptom load at 30 months than term infants not exposed to ACS or threatened preterm labor.[34]

In response to a self-reported psychosocial stress test (TSST-C), ACS-exposed children showed higher stress appraisal and had less positive emotionality in comparison to unexposed children.[46] The ACS-exposed children also had reduced behavioral response consistency[47] and showed more difficulties with sustained attention.[37,38,47]

Neurocognitive and neuromotor development

Various modalities were used to assess the associations between ACS exposure and neurocognitive and neuromotor development and showed different results. Children who were born at term after being exposed to ACS for threatened preterm birth had an increased risk of mild neurodevelopmental delay, demonstrated by the Merill–Palmer Revised Scales of Development (ACS-exposed: 47.8% vs. ACS-unexposed: 14.6%).[40] In another study, ACS-exposed and ACS-unexposed infants scored similarly on the Ages and Stages Questionnaire assessment of neurodevelopmental milestones.[33]

ACS exposure in fetuses ultimately born late preterm and term was associated with latent cortical auditory-evoked responses, reflecting an acute change in cerebral information processing.[42] One study evaluated the behavioral and brain indicators of error and novelty monitoring and found no difference between term infants exposed and unexposed to ACS.[45] At 5 years of age, term infants exposed to ACS were significantly more likely to undergo assessment for a suspected neurocognitive disorder than their unexposed counterparts (ACS-exposed: 25.8% vs. ACS-unexposed: 21.6%). This study also reported higher rates of vision and hearing testing outside the routine provincial screening program in ACS-exposed infants compared to ACS-unexposed infants.[29]

With regard to cognition, three studies assessed Intelligence Quotient (IQ) scores of ACS-exposed infants born late preterm and term. Two studies reported significantly lower IQ score in the ACS-exposed group compared to an ACS-unexposed group.[38,44] In Alexander et al., the IQ scores of the ACS-exposed group was similar to a second group exposed to preterm labor but unexposed to ACS.[44] Grant et al. reported no significant effect of ACS exposure on intelligence independent of sociodemographic adversity risk.[28]

Summary of results

In summary, of the 27 studies included, 17 studies (63%) reported an association with an adverse outcome between ACS exposure and brain development across various domains, 1 study (4%) reported an association with a favorable neurological outcome, 1 study (4%) identified an association with an adverse outcome and otherwise statistically nonsignificant associations, and 8 studies (30%) did not identify any statistically significant associations.

In the 19 studies that exclusively studied term infants exposed to ACS, 12 studies (63%) reported an association with an adverse neurological outcome, 1 study (5%) reported an association with a favorable neurodevelopmental outcome, and 6 studies (32%) did not identify any statistically significant associations. The results of these studies are stratified and summarized in Supplemental Table S2.

When stratifying the neurological outcomes according to the number of courses of ACS administered, an association with an adverse outcome was demonstrated in 6/14 studies that administered a single course of ACS, 7/7 studies that administered either single or multiple courses of ACS, 2/2 of the studies that administered multiple courses of ACS, and 3/4 of the studies that did not specify the number of courses of ACS administered. These proportions were similar when limited to studies of term infants only: associations with adverse outcomes were demonstrated in 4/10 studies that administered a single course of ACS, 6/6 studies that administered either single or multiple courses of ACS, and 2/3 studies that did not specify the number of courses of ACS administered (Supplemental Table S2).

ACS confounders

Of the 27 included studies, 4 studies attempted to disentangle the effects of ACS from those of preterm labor on neurological outcomes.[26,36,44,46] These studies divided their cohort into three groups: exposed to preterm labor and ACS, exposed to preterm labor but unexposed to ACS, and a control group unexposed to preterm labor and unexposed to ACS, with each group ultimately born late preterm and term. Each study reported different outcomes and attributed their findings to the effects of ACS,[46] preterm labor,[44] or the cumulative effect of both ACS and preterm labor (Fig. 2).[36] For example, in Erni et al., the group exposed to preterm labor and ACS demonstrated a greater psychological stress response relative to both the group exposed to preterm labor but unexposed to ACS and the control group.[46] Conversely, in Alexander et al., both groups exposed to preterm labor, irrespective of ACS exposure, had a significantly reduced IQ relative to the control group.[44] This study therefore attributed the reduced IQ to preterm labor rather than ACS. In the study by Davis et al., only the group exposed to *both* ACS and preterm labor showed significantly reduced head circumference compared to the control group.[36] Lastly, in the study by Diguisto et al., there was no statistically significant difference in the frequency of microcephaly between the three groups.[26]

Risk of bias

All studies were at serious risk of overall bias due to confounding by indication (Table 2). Even in the four studies with a second control group of infants exposed to preterm labor but unexposed to ACS, there is likely serious residual confounding as the reasons for administering or not administering ACS were not specified.

DISCUSSION

Main findings

Our scoping review focused on the association between ACS exposure for risk of preterm birth and brain development in infants ultimately born late preterm and term. The review included 27 original studies and assigned the findings to four thematic categories: biometric head measurement, structural brain imaging, psychiatric problems (e.g., behavioral disorders, increased difficulties with sustained attention, and higher stress appraisal), and neurocognitive and neuromotor function. The most common adverse outcomes were reduced head circumference, structural cortical differences on MRI, and increased prevalence of psychiatric problems and neurodevelopment delays in ACS-exposed late preterm and term infants. Importantly, all studies were at serious risk of overall bias due to confounding by indication.

Strengths and limitations

Although this scoping review followed the PRISMA guidelines and included a comprehensive search strategy with two independent reviewers, our study has limitations, many of which are inherent to scoping reviews. A scoping review approach, however, aligned with our objective of mapping out the literature on an inconsistently studied group of patients. One limitation is that the individual studies were heterogenous in that data collection and outcome measures varied significantly. The age at assessment of neurological outcome was variable and earlier neurological assessments, such as head circumference at birth, may not translate into long-term neurological adversities. Second, the included studies were primarily observational and thus carry a serious risk of bias due to confounding. Third, there may be publication bias within the literature given the challenge of publishing "negative" studies and this bias may magnify the associations we found. Fourth, studies with small sample sizes were not excluded. As such, with many small studies, our scoping review may overestimate the magnitude of the associations between ACS and adverse neurological outcomes. Fifth, two of the abstracts did not have a full-text manuscript and thus provided only limited information. Lastly, eight studies included both late preterm and term infants in their ACS-exposed and ACS-unexposed groups and did not perform a subgroup analysis of term infants only. Rather than excluding these eight studies, we decided to broaden our inclusion criteria in line with the iterative process of a scoping review.[21] As such, the initial term-only

definition was widened to include term *and* late preterm infants, thereby decreasing the precision of the associations on term children. To enable comparisons across studies, the overall literature would benefit from more congruency in the reporting of neurological outcomes associated with ACS in term infants.

Interpretation

To our knowledge, this is the first scoping review to address the possible neurological effects of ACS in late preterm and term infants. Biometric head measurement was the most commonly reported neurological outcome ($n = 13$) and six studies reported a reduced head circumference in ACS-exposed fetuses and infants born late preterm and term.[2,7,23,25,31,36,41] This short-term finding may carry long-term neurodevelopmental implications: for instance, in preterm infants, small head circumference at birth is associated with suboptimal neurodevelopmental outcome at 2 years of age.[48] However, included studies used various measurements for head circumference such as *Z*-scores and rates of microcephaly, and none of them investigated the association between head circumference and later development, thus making clinical interpretation difficult.

Our review included four studies that attempted to isolate the direct effects of ACS on brain development from the confounding influence of preterm labor and maternal stress. Each of the four studies resulted in different interactions among the three groups, thus making it difficult to know whether exposure to ACS, preterm labor, or both, is responsible for the adverse neurological outcomes. Preterm labor may impact brain development via several pathways, including inflammation (e.g., preterm premature rupture of membranes) and maternal stress.[49,50] For example, children exposed to elevated prenatal maternal cortisol and pregnancy-specific anxiety are at an increased risk for developing anxiety problems[51] and negative temperament as a child.[52] In the study by Ghosn et al., maternal state anxiety at the time of preterm labor diagnosis was evaluated through linear regression to be a predictor of higher autism symptom load at 30 months in infants who were exposed to preterm labor and ACS.[34] Further research is thus required to better distinguish the neurological effects of preterm labor and maternal stress from those of ACS.

Two studies evaluated structural brain imaging and reported changes in cortical development in late preterm and term infants exposed to ACS. The effects of ACS on brain development are supported physiologically. Placental 11-β hydroxysteroid dehydrogenase type 2 (11βHS2) inactivates maternal cortisol, thereby reducing early fetal exposure to cortisol. However, the synthetic ACS used in threatened preterm labor, betamethasone and dexamethasone, are poorly catalyzed by placental 11βHS2, resulting in their unrestricted transfer to the fetus.[53] Endogenous steroids serve as a critical trigger in fetal development. Thus, fetal exposure to premature steroid signals may result in early differentiation and maturation of the developing brain and may thereby lead to alterations in physiologic function throughout life.[53] Specific regions within the brain have an increased susceptibility to these changes due to their high density of glucocorticoid receptors. One study in our review reported that cortical regions most affected by ACS exposure in term infants were part of the limbic system,[35] which is functionally associated with cognition, behavior, memory, and regulation of multiple endocrine systems.[54]

Most studies in our review that assessed psychiatric problems found an increased prevalence of psychiatric and behavioral disorders. ACS exposure may have programming effects on the hypothalamic–pituitary–adrenal (HPA) axis, and this effect on the HPA axis may mediate the interaction between ACS exposure and the higher prevalence of later psychiatric morbidities. Several studies have documented increased cortisol levels in response to standardized laboratory stress tests in late preterm and term children exposed to ACS.[46,55,56] Glucocorticoids play a pivotal role in regulating the cortisol stress response by inhibiting the release of corticotrophin-releasing hormone by the hypothalamus. Thus, early exposure to ACS may result in increased feedback sensitivity and impact neuroendocrine set points, which may confer increased vulnerability for developing stress-related disorders.[6]

Future large-scale studies with well-aligned and congruent outcome measures are necessary to provide sufficient evidence and guide clinical practice. The Consortium for the study Of Pregnancy Treatments (Co-OPT) is a collaborative project that plans to address the knowledge gaps by determining short- and long-term outcomes of ACS in term infants, with a focus on childhood neurodevelopment. The recruitment for this study is expected to be completed in 2023 (https://www.ed.ac.uk/usher/research/projects/co-opt). Given the variability in reported outcomes among the studies, the development of a Core Outcome Set would benefit future research by prioritizing and standardizing the selection and reporting of outcomes. The Core Outcome Set would ideally be developed with input from parents to guide trial developers and allow for future meta-analyses.

CONCLUSION

Overall, our scoping review demonstrated that ACS exposure for risk of preterm birth may have important neurological implications in infants ultimately born late preterm and term. Nonetheless, ACS is life saving and significantly improves the neurological outcomes of very preterm infants and our results should not detract from the obvious benefits of ACS in infants born at <34 weeks' gestation.[1,3] The administration of ACS is challenging in that the clinician strives to accurately predict which fetuses will benefit by determining which pregnancies will result in preterm birth. Importantly, the studies identified in this review were all at serious risk of bias. As such, high-quality, population-based studies with longitudinal follow-up that consider confounders such as preterm labor, maternal stress, and the number of ACS courses will be required to better isolate the effect of ACS on brain development in infants ultimately born late preterm and term. In addition, future trials of ACS should evaluate the long-term outcomes of both infants born very preterm, who stand to benefit, and infants born late preterm and term. A proper assessment of the risks and benefits of ACS can only be completed by analyzing both groups of patients. In anticipation of more robust evidence, the findings of this scoping review may be considered in the clinician's complex decision-making algorithm around the administration of ACS for risk of preterm birth.

DATA AVAILABILITY

All data analyzed during this study are included in this review and its Supplemental Information file.

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Each author has met the *Pediatric Research* authorship requirements. J.G. conceived the review. E.B.S., M.L.S., and J.G. participated in the development of the design of the

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not required.

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