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Strategies for optimising antenatal corticosteroid administration for women with anticipated preterm birth (Review)

Rohwer AC, Oladapo OT, Hofmeyr GJ

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[Intervention Review]

Strategies for optimising antenatal corticosteroid administration for women with anticipated preterm birth

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ABSTRACT

Background

Preterm birth is a serious and common pregnancy complication. The burden is particularly high in low- and middle-income countries where available care is often inadequate to ensure preterm newborn survival. Administration of antenatal corticosteroids (ACS) is recommended as the standard care for the management of women at risk of imminent preterm birth but its coverage varies globally. Efforts to improve preterm newborn survival have largely been focused on optimising the coverage of ACS use. However, the benefits and harms of such strategies are unclear.

Objectives

To determine the relative benefits and risks of individual patient protocols, health service policies, educational interventions or other strategies which aim to optimise the use of ACS for anticipated preterm birth.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (26 September 2019), and reference lists of retrieved studies.

Selection criteria

We planned to include randomised controlled trials (RCTs), randomised at individual or cluster level, and quasi-randomised trials that assessed strategies to optimise (either by increasing or restricting) the administration of ACS compared with usual care amongst women at risk of preterm birth. Our primary outcomes were perinatal death and a composite outcome of offspring mortality and early or late neurodevelopmental morbidity.

Data collection and analysis

Two review authors independently assessed studies for inclusion. All three review authors independently extracted data and assessed risk of bias. We used narrative synthesis to analyse results, as we were unable to pool data from the included studies. We assessed the certainty of evidence using the GRADE approach.

Main results

We included three cluster-RCTs, all assessing the effects of a multifaceted strategy aiming to promote the use of ACS among women at risk of preterm birth. We did not identify any trials assessing strategies to restrict the use of ACS versus usual care. Two of the included trials assessed use of ACS in high-resource hospital settings. The third trial, the Antenatal Corticosteroid Trial (ACT) was a multi-site trial conducted in rural and semi-urban settings of six low- and middle-income countries in South Asia, sub-Saharan Africa and Central and South America. In two trials, promoting the use of ACS resulted in increased use of ACS, whereas one trial did not find a difference in the rate of ACS administration compared to usual care.

Whilst we included three studies, we were unable to pool the data in meta-analysis due to outcomes not being reported across all studies, or outcome results being reported in different ways. The main source of data in this review is from the ACT trial. We assessed the ACT trial as high risk for performance and selective reporting bias. In the protocol for this review, we planned to report all settings and subgroup by low-middle versus high-income countries; these planned analyses were not possible in this version of the review, although adding further studies in future updates may allow us to carry out planned subgroup analyses.

The ACT trial was conducted in low-resource settings and reported data on appropriate ACS treatment and inappropriate ACS treatment. Although a strategy of promoting the administration of ACS compared to routine care may increase appropriate ACS treatment (RR 4.34, 95%CI 3.59 to 5.25; 1 study; n = 4389; low-certainty evidence), it may also increase inappropriate ACS treatment (RR 9.11 95%CI 8.04 to 10.33, 1 study, n = 89,237; low-certainty evidence).

In low-resource settings, a strategy of promoting the administration of ACS probably increases population level perinatal death by 3 per 1000 infants (risk ratio (RR) 1.11, 95% confidence interval (CI) 1.04 to 1.19; 1 study; n = 100,705; moderate-certainty evidence); stillbirth by 2 per 1000 infants (RR 1.11, 95% CI 1.02 to 1.21; 1 study; n = 100,705; moderate-certainty evidence); and neonatal death before 28 days by 2 per 1000 infants (RR 1.12, 95% CI 1.02 to 1.23; 1 study; n = 100,705; moderate-certainty evidence); may increase the risk for 'suspected' maternal infection or inflammation (RR 1.49, 95% CI 1.32 to 1.68; 1 study; n = 99,742; low-certainty evidence); and make little or no difference to the risk of maternal mortality (RR 1.11, 95% CI 0.64 to 1.92; 1 study; n = 99,742; low-certainty evidence) compared to routine care.

Included trials did not report on the composite outcomes offspring mortality, early neurodevelopmental morbidity or late neurodevelopmental morbidity; and offspring mortality or severe neonatal morbidity.

Authors' conclusions

In low-resource settings, a strategy of actively promoting the use of ACS in women at risk of preterm birth may increase ACS use in the target population, but may also carry a substantial risk of unnecessary exposure of ACS to women in whom ACS is not indicated. At the population level, these effects are probably associated with increased risks of stillbirth, perinatal death, neonatal death before 28 days, and maternal infection.

The findings of this review support a more conservative approach to clinical protocols and clinical decision-making particularly in low-resource settings, along the lines of the World Health Organization's ACS 2015 recommendations, which take into account both the established clinical efficacy of ACS when used in the correct situation and context, and the possibility of important adverse effects when certain conditions are not met.

Given the unanticipated results of the ACT trial, further research on strategies to optimise the use of ACS in low-resource settings is justified.

PLAIN LANGUAGE SUMMARY

Strategies for optimising antenatal corticosteroid administration for women with anticipated preterm birth

What is the issue?

A pregnancy normally lasts between 37 and 40 completed weeks. If the birth takes place earlier than that and the baby is born prematurely, there is a high risk that the baby will have breathing problems and might suffer from other complications. There is also a risk that the premature baby dies, especially if it is born in a facility that does not have advanced care for newborns. Mothers with signs of premature labour or planned for elective preterm birth are commonly injected with steroids, which can help mature the baby's lungs and prevent severe breathing problems once the baby is born.

Why is this important?

In high-income countries and in hospital settings with advanced care facilities, administration of steroids for mothers who are at risk of giving birth prematurely is standard care. As this is not always the case in low-income countries, where premature birth is more common compared to other countries, there have been worldwide efforts to increase the use of steroids in these settings. However, as there is usually also a lack of other supportive newborn care and accurate assessment of gestational age in these settings, the benefits and harms of increasing the use of steroids, compared to usual approach of care, need to be evaluated.

What evidence did we find?

We searched for evidence in September 2019 and identified three studies that met our inclusion criteria. All three studies assessed interventions that aimed to promote the use of steroids for mothers at risk of giving birth prematurely, while we did not find any study that assessed interventions that aimed to restrict the use of steroids. Two studies were conducted in hospital settings of mostly high-income countries, while one study was conducted in low-resource settings in six low-and middle-income countries. Two studies found that the interventions led to an increase in the use of steroids, while one study found no difference in the use of steroids. One large study in low-resource settings found that among women who delivered preterm infants, more women in the intervention group (45%) received steroids compared to women the control group (10%) (low-certainty evidence). However, in the group of women who did not deliver preterm infants more women in the intervention group (10%) compared to the control group (1%) received steroids although they did not need them (low-certainty evidence).

Only the one large study that was conducted in low-resource settings assessed important outcomes. The study found that perinatal death (death of the baby before birth or within the first seven days of life), stillbirth (death of the baby before birth), and neonatal death before 28 days (death of the baby during the first 28 days of life) probably occurs more often among all babies (not just those that are born prematurely) when the use of steroids is actively promoted compared to usual care (moderate-certainty evidence). It also found that infection in the mother may be more common when strategies to increase the use of steroids are in place. However, there may be little or no difference between groups in the mothers' risk of dying (low-certainty evidence).

What does this mean?

In low-resource settings, a strategy of actively promoting the use of steroids in mothers at risk of giving birth prematurely could be harmful to infants and their mothers at population level. Policy makers need to carefully weigh the benefits against the potential risks when considering scaling up of this intervention in low-resource settings. There is a need to do more research on the effectiveness of approaches to scale up the use of steroids for mothers at risk of premature delivery in low-resource countries.

Summary of findings 1. Strategies to increase use of antenatal corticosteroids versus routine (usual) care for optimising antenatal corticosteroid administration for anticipated preterm birth

Strategies to increase use of antenatal corticosteroids versus routine (usual) care for optimising antenatal corticosteroid administration for anticipated preterm birth

Patient or population: women at risk of preterm birth
Settings: rural and semi-urban settings in low- and middle-income countries (Argentina, Guatemala, India, Kenya, Pakistan, and Zambia)
Intervention: promotion of increased use of antenatal corticosteroids by means of a multifaceted intervention that consisted of health-provider training, posters, pregnancy disc, and uterine height tape to facilitate identification of women at risk of preterm birth, and kits for provision of antenatal corticosteroids; plus training in essential newborn care
Comparison: training in essential newborn care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Routine care	Promotion of increased use of antenatal corticosteroids				
Perinatal death (at population level)	**32 per 1000**	**35 per 1000** (33 to 38)	**RR 1.11** (1.04 to 1.19)	100,705 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
Offspring mortality, early neurodevelopmental morbidity or late neurodevelopmental morbidity	-	-	-	-	-	not reported
Offspring mortality or severe neonatal morbidity	-	-	-	-	-	not reported
Neonatal death before 28 days (at population level)	**16 per 1000**	**18 per 1000** (17 to 20)	**RR 1.12** (1.02 to 1.23)	100,705 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
Stillbirth (at population level)	**20 per 1000**	**22 per 1000** (20 to 24)	**RR 1.11** (1.02 to 1.21)	100,705 (1 study)	⊕⊕⊕⊖ **moderate** [1]	
Appropriate ACS treatment (women)	**104 per 1000**	**452 per 1000** (374 to 546)	**RR 4.34** (3.59 to 5.25)	4389 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Inappropriate ACS treatment (women)	**12 per 1000**	**105 per 1000**	**RR 9.11**	89,237	⊕⊕⊖⊖	

		(92 to 119)	(8.04 to 10.33)	(1 study)	**low** [1,2]
Maternal infection or inflammation (at population level)	**17 per 1000**	**25 per 1000** (22 to 28)	**RR 1.49** (1.32 to 1.68)	99,742 (1 study)	⊕⊕⊖⊖ **low** [1,3]
Maternal mortality (at population level)	**1 per 1000**	**1 per 1000** (1 to 2)	**RR 1.11** (0.64 to 1.92)	99,742 (1 study)	⊕⊕⊖⊖ **low** [1,4]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

Specified outcomes with no data: offspring mortality, early neurodevelopmental morbidity, or late neurodevelopmental morbidity; perinatal death or severe neonatal morbidity.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded -1 for serious limitations in study design. The study was at high risk of performance and selective reporting bias (in trial protocol, the proxy for preterm infant was defined < 10th percentile birthweight while it was < 5th percentile birthweight in the trial report).
[2] Downgraded -1 for serious concerns about indirectness for the measured outcomes: authors used birthweight (less-than-5th percentile birthweight) as a proxy for preterm infants.
[3]Downgraded -1 for serious concerns about indirectness. Indirect outcome reported for maternal infection. "Suspected maternal infection" was defined as a composite process outcome measure that included admission to the hospital, antibiotic use, intravenous fluid use, and surgery related to infection.
[4]Downgraded -1 for serious concerns about imprecision due to the wide confidence interval
Note: whilst three studies are included in the review only one study (Althabe 2015) reported data that were able to be analysed (i.e. no meta-analysis conducted)

BACKGROUND

The protocol for this review was published in PROSPERO, and not the Cochrane Library.

Description of the condition

Preterm birth (birth before 37 weeks' gestation) is a common complication of pregnancy. The global preterm birth rate was estimated to be 10.6% (uncertainty interval (UI) 9.0 to 12.0) of all live births in 2014 (Chawanpaiboon 2019). The highest rates were observed in North Africa (13.4%; UI 6.3 to 30.9), sub-Saharan Africa (12.0%; UI 8.6 to 16.7) and North America (11.2%; UI 9.5 to 13.2). Sub-Saharan Africa accounted for 28.2% of global preterm births (Chawanpaiboon 2019). The societal economic cost associated with preterm birth in 2005 was USD 26.2 billion (Institute of Medicine (US) 2007). The causes of preterm birth are complex and include behavioural, social, environmental, genetic, biological, medical and iatrogenic (caused by treatment or diagnostic) factors such as infertility treatment (Institute of Medicine (US) 2007). Disclosed or undisclosed attempts at late abortion may add considerably to the burden of preterm birth in some settings (Mandondo 2018).

Preterm birth is a major cause of neonatal mortality and morbidity, particularly those related to respiratory immaturity (Blencowe 2012; Liu 2015). Respiratory distress syndrome (RDS) related to inadequate surfactant production in the lung alveoli and incomplete lung development, occurs in as many as one-third of babies born before 32 weeks, and is a major cause of death and disability (Roberts 2017). Survivors of preterm birth are at increased risk of long-term neurological disability (Roberts 2017). Many individually-randomised trials since 1972 have shown a reduction in mortality with antenatal administration of corticosteroids to the mother (and thus, transplacentally to the fetus) (Roberts 2017). The most common corticosteroids used are betamethasone or dexamethasone in divided doses 12 to 24 hours apart. Questions remain regarding timing of treatment (Crowther 2016; Park 2016; Wapner 2016) and the ethics of care at the border of viability (Ecker 2016). An observational study of 6925 multiple-birth infants found that antenatal corticosteroids (ACS) exposure in extremely preterm infants was associated with reduced mortality but not the composite of neurodevelopmental impairment or death (Boghossain 2016). ACS have also been used to reduce respiratory morbidity following elective caesarean section at term (Nada 2016). However, adverse effects of ACS have been described, particularly reduced head growth (Braun 2013) and growth impairment (Zephyrin 2013). A risk-benefit analysis study has estimated that when multiple courses of ACS are initiated beyond 29 weeks' gestation, there is a suggestion of more risk than benefit (Zephyrin 2013). A fundamental limitation in the precision of ACS administration is the lack of accurate methods of predicting preterm birth (Son 2017). It is clear that ACS have both beneficial and harmful effects, and the possibility exists that in certain clinical settings the harmful effects might outweigh the benefits. Most of the evidence on ACS is from studies in high-income settings, as reported in the Cochrane Review on '*Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth*', and may not be applicable to low-income settings (Roberts 2017).

Description of the intervention

In high-income settings, use of ACS for women at risk of preterm birth between 24 and 34 weeks' gestation is generally considered the standard of care, while the benefits in low-income settings have not been evaluated (Jobe 2018). There is also evidence of some benefit for later preterm births and elective caesarean sections (Jobe 2018; Nada 2016). However, concern about long-term metabolic and cardiovascular effects on the offspring, and the fact that in many cases anticipated preterm birth does not materialise, resulting in unnecessary exposure of babies, has led to concern regarding the extent of ACS use (Jobe 2018). In the protocol we stated that this review would include randomised studies of interventions which allow the comparison of the effects of more liberal use of ACS versus more restrictive use. These might include, for example, individual patient randomisation to more liberal versus more restrictive treatment protocols; cluster-randomised studies of more liberal versus more restrictive policies for ACS use; or educational interventions to alter the use of ACS versus usual care. Given the current emphasis on comprehensive coverage for pregnancies at risk for preterm birth as the standard of care, included studies might have more restrictive policies as the intervention arm. However for the purpose of this review, strategies intended to increase use of ACS will be regarded as the intervention, and those with less intended use of ACS as the control group.

How the intervention might work

Virtually all medical interventions have beneficial and harmful effects. There are many ways in which the results of randomised trials may be misleading (Heneghan 2017). We suggest that randomised trials tend to over-estimate the benefits relative to adverse effects for several reasons.

1. Beneficial effects are more likely to be measured, as many adverse effects are unknown and difficult to predict. Even known adverse effects receive less attention than beneficial effects, and studies are rarely powered for adverse effects.
2. The time-frame of randomised trials are generally geared towards the expected beneficial effects, whereas adverse effects may have longer time-frames.
3. Investigator bias and interpretation of results tends to operate in favour of beneficial effects.
4. Publication bias tends to operate in favour of beneficial effects.
5. Fraud and invested interests more often operate in favour of beneficial effects.
6. Randomised trials frequently use proxy outcomes because the outcome of interest (e.g. death) is too infrequent to be measured. Assumed associations of proxy outcomes with the outcome of interest are not always valid. For example, an intervention such as ACS might in certain circumstances reduce respiratory morbidity but increase death.

In the case of ACS research over the past four decades, more emphasis has been given to the beneficial effects than to adverse effects. However, there has been concern about some measured adverse effects such as reduced fetal head growth; neonatal hypoglycaemia; and maternal leukocytosis, which peaks at 24 hours (Bauer 2016).

Clinical priority has been placed on avoiding at all costs the birth of a preterm baby without the protection of ACS. Because of the 48-hour window needed for effectiveness, the tendency has been to administer corticosteroids to all women considered at some risk of preterm birth before 34 weeks' gestation. Common situations are women with early onset pre-eclampsia and suspected preterm

labour. In both these examples, birth frequently does not follow within a week. This results in large proportions of babies being exposed unnecessarily to corticosteroids (Jobe 2018), and it is possible that the adverse effects of corticosteroids in these babies might outweigh the beneficial effects in those babies who are born within a week of treatment.

Because of concern about known and potential unknown adverse effects, a more conservative policy may be adopted. For example:

1. as conservative management of early onset pre-eclampsia frequently succeeds in delaying birth for 10 to 14 days, administration of corticosteroids is delayed until a decision for delivery has been taken or is imminent;
2. in the case of suspected preterm labour, corticosteroids are delayed until objective cervical changes have been documented, indicating a high level of certainty that preterm birth is imminent.

The benefit of such policies is that unnecessary exposure to corticosteroids is avoided in those women who do not give birth within seven days or before 34 weeks' gestation. The risk is that in some cases delivery may be too rapid to allow the 48-hour window to complete the full course of corticosteroids. This review seeks to address the balance between these benefits and risks.

Why it is important to do this review

Current guidelines encourage the use of ACS in women at risk of preterm labour, as this has been shown to reduce adverse effects linked to prematurity, including perinatal death, neonatal death, and RDS, compared to placebo or no treatment, as reported in the Cochrane Review by Roberts and colleagues (Roberts 2017). Another Cochrane Review found benefits for repeat doses of ACS in women who are still at risk of preterm birth seven days after the initial dose (Crowther 2015), while the current evidence did not show a long-term harmful effect. However, included studies in both reviews were mostly conducted in high-income settings (Vogel 2017). The current review was focused on intervention strategies to optimise ACS use to achieve intended clinical benefits for preterm infants. In view of the disproportional burden of preterm birth and its complications in low-income countries, there have been global efforts to increase the coverage of ACS in low-income settings (Massawe 2018). However, the complexity of implementing such strategies in uncontrolled settings may affect the potential effectiveness and safety of ACS. Limitations such as the lack of accurate estimation of gestational age and accurate prediction of preterm birth may blunt or even reverse the effectiveness demonstrated in clinical trials. Under some circumstances, mortality from known and unknown adverse effects of ACS may outweigh the beneficial effects. It is of considerable importance to global health to objectively review data of specific relevance to this hypothesis, as well as formulating a research agenda to generate more robust evidence.

OBJECTIVES

To determine the relative benefits and risks of individual patient protocols, health service policies, educational interventions or other strategies which aim to optimise the use of antenatal corticosteroids (ACS) for anticipated preterm birth.

METHODS

Criteria for considering studies for this review

Types of studies

We included cluster-randomised controlled trials (RCTs). Individually-randomised and quasi-randomised trials were eligible for inclusion but none were identified. We included studies published in abstract form only if sufficient information was available. We did not include cross-over studies.

Types of participants

For clinical outcomes such as actual treatment with antenatal corticosteroids (ACS) or perinatal mortality: women at risk of preterm birth and their babies, or defined antenatal populations exposed to divergent policies with respect to ACS use.

For process outcomes of health service interventions, such as attitudes to ACS use: health workers.

Types of interventions

Strategies to optimise the use of ACS, including:

1. strategies aiming to promote the use of ACS;
2. strategies aiming to restrict the use of ACS.

Strategies considered included, but were not limited to the following:

1. education and training;
2. health service policies;
3. treatment protocols.

ACS efficacy trials were not considered eligible and are the subject of other Cochrane Reviews.

Types of comparisons

1. Strategies to promote ACS use versus usual care
2. Strategies to restrict ACS use versus usual care
3. Comparison of various strategies

Types of outcome measures

In the absence of published core outcomes for ACS use, we adapted the core outcome set developed for studies of preterm birth prevention (identified * below) (van 't Hooft 2016).

Primary outcomes

1. Perinatal death (as defined by trial authors)
2. Offspring mortality*, early neurodevelopmental morbidity*, or late neurodevelopmental morbidity* (composite outcome)

Secondary outcomes

Neonatal/childhood

1. Antenatal corticosteroid treatment (babies)
2. Offspring mortality* or severe neonatal morbidity as defined by trial authors (composite outcome)
3. Stillbirth
4. Neonatal death
5. Gestational age at birth*

6. Birthweight*
7. Head circumference
8. Neonatal intensive care unit admission
9. Respiratory morbidity*
10. Gastrointestinal morbidity*
11. Early neurodevelopmental morbidity*
12. Late neurodevelopmental morbidity*
13. Cerebroventricular haemorrhage (as defined by trial authors)
14. Infection*
15. Harm to offspring from intervention*
16. Chronic lung disease (as defined by trial authors)
17. Childhood illness

Maternal

1. Antenatal corticosteroid treatment (women)
2. Appropriate antenatal corticosteroid treatment
3. Inappropriate antenatal corticosteroid treatment
4. Prelabour rupture of membranes*
5. Caesarean section
6. Chorioamnionitis (as defined by trial authors)
7. Maternal infection or inflammation* (as defined by trial authors)
8. Maternal mortality*
9. Death or severe morbidity (as defined by trial authors)
10. Hospital stay
11. Maternal satisfaction (as defined by trial authors)
12. Postnatal depression (as defined by trial authors)
13. Baby not breast fed
14. Harm to mother from intervention*

Health services

1. Health staff attitude to use
2. Caregiver satisfaction
3. Cost

Search methods for identification of studies

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

We searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (26 September 2019).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) (26 September 2019) for unpublished, planned and ongoing trial reports using the search methods described in Appendix 1.

Searching other resources

We searched the reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two of the review authors (ACR and GJH) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion.

We created a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

Two review authors extracted data (ACR and GJH or OTO). We resolved discrepancies through discussion. We entered data into Review Manager software (RevMan 2014) and checked it for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (ACR and GJH or OTO) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion.

Risk of bias for individually- and cluster-RCTs

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively-numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered studies to be at low risk of bias if they were blinded, or if we judged that the lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we have about other possible sources of bias.

We assessed whether each study is free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. When more data are available, we will explore the impact of the level of overall bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Additional risk of bias for cluster-RCTs

For cluster-RCTs we assessed the possibility of recruitment bias, baseline imbalance, loss of clusters and incorrect analysis. Had we included individually-randomised RCTs, we would have assessed

the compatibility of all included cluster-RCTs with individually-randomised RCTs, according to the *Handbook* (Higgins 2011).

Assessment of the certainty of the evidence using the GRADE approach

We assessed the certainty of evidence using the GRADE approach as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating to the primary outcomes for all comparisons.

We used GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create a 'Summary of findings' table. We produced a summary of the intervention effect and a measure of certainty for the following outcomes using the GRADE approach. In the absence of published core outcomes for ACS use, we adapted the core outcome set developed for studies of preterm birth prevention (identified * below) (van 't Hooft 2016).

1. Perinatal death
2. Offspring mortality*, early neurodevelopmental morbidity*, or late neurodevelopmental morbidity*
3. Offspring mortality* or severe neonatal morbidity as defined by trial authors
4. Neonatal death
5. Stillbirth
6. Appropriate ACS treatment
7. Inappropriate ACS treatment
8. Maternal infection or inflammation* (as defined by trial authors)
9. Maternal mortality*

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we planned to use the mean difference (MD) where outcomes were measured in the same way between trials and the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

For outcomes where authors have sufficiently adjusted results for clustering (stillbirth, perinatal death, neonatal death), we included the adjusted effect estimates and standard errors using the generic inverse-variance method in Revman. For outcomes where authors did not sufficiently adjust their results for clustering (ACS treatment in mothers, appropriate ACS treatment, inappropriate ACS treatment, Caesarean section, maternal infection and maternal mortality), we adjusted the sample size and event rates to take account of cluster design effect using the methods described in the *Handbook* (Section 16.3.4 or 16.3.6) using an intra cluster correlation co-efficient (ICC) of 0.001 as reported in (Althabe 2015) for neonatal death. For future updates of the review, if the ICC from the included trial is not available, we will derive an ICC from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. In this version of the review, we included only cluster-RCTs. For future updates of the review, if we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a subgroup analysis to investigate the effects of the randomisation unit.

Dealing with missing data

For included studies, we noted levels of attrition, but did not find high levels of missing data. In future updates of this review, we will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and we analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We did not pool data in meta-analysis. For future updates of this review, we will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either the Tau^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity. We will explore and report on clinical heterogeneity related to participants, interventions and comparisons by summarising characteristics of studies in table format.

Assessment of reporting biases

We did not pool data in meta-analysis. For future updates of this review, we will investigate reporting biases using funnel plots if more than 10 studies are included in the meta-analysis.

Data synthesis

We were not able to pool results in meta-analysis, but reported on them in a narrative manner. In future updates of this review, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity

sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials.

If we use random-effects analyses, we will present the results as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

We were not able to perform subgroup analysis as we did not pool data. In future updates of this review, if we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

We will carry out the following subgroup analyses.

1. Cluster-randomisation versus individual-randomisation (for all outcomes)
2. Low-middle income settings versus high-income settings
3. Interventions targeting only ACS use versus more complex interventions including ACS use

The primary outcomes will be used in subgroup analyses other than the randomisation unit.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We were not able to perform sensitivity analyses. In future updates of this review, we will conduct sensitivity analyses to explore the effect on results of trial quality by temporarily removing from our analysis those studies with high risk of bias related to inadequate allocation concealment and high rates of attrition. Sensitivity analysis will be restricted to the review's primary outcomes.

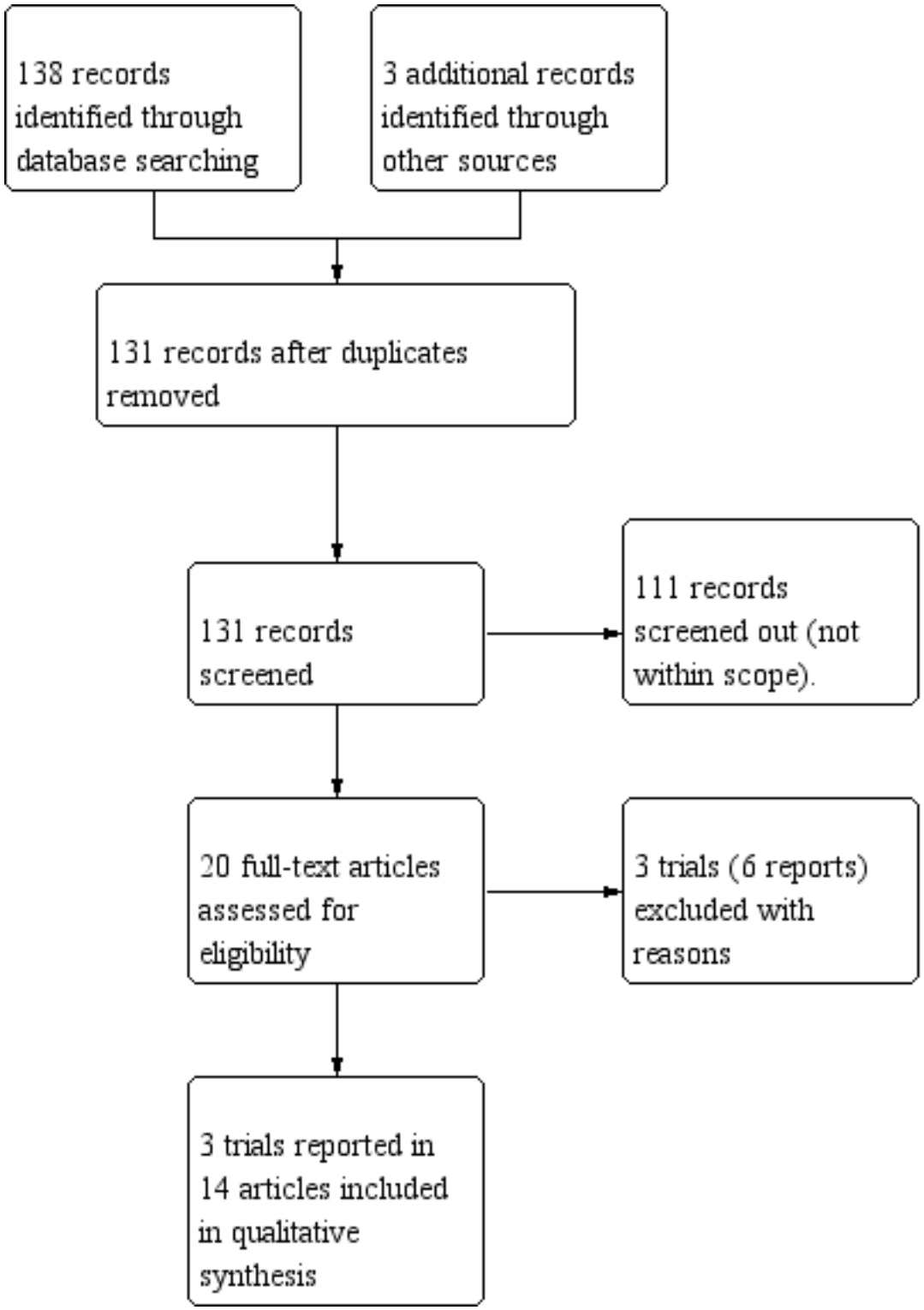
RESULTS

Description of studies

Results of the search

The search yielded 141 study records. After removal of duplicates, we screened 131 titles and abstracts for inclusion. Of these, we screened full texts of 20 study reports. We excluded three studies (six reports) and included three studies (reported in 14 articles) (Althabe 2015; Gülmezoglu 2007; Leviton 1999). See: Figure 1. All three studies assessed strategies to increase the use of ACS. We did not identify any studies that assessed strategies to restrict the use of antenatal corticosteroids (ACS).

Figure 1. Study flow diagram.



Included studies

We included three trials. The first, by Leviton and colleagues (Leviton 1999), was conducted from 1995 to 1996, shortly after the National Institutes of Health (NIH) in the USA released a consensus statement on the use of ACS in women at risk of preterm labour. The trial assessed whether active dissemination of the recommendations resulted in an increased uptake of ACS therapy. The second, the WHO Reproductive Health Library (WHO RHL) trial (Gülmezoglu 2007), assessed whether a multifaceted educational intervention to promote the use of the WHO RHL had an effect on obstetric practices in Mexico and Thailand. The intervention

was delivered between October 2001 and October 2002. The third trial, the Antenatal Corticosteroids Trial (ACT) (Althabe 2015) aimed to promote the use of ACS in low- and middle-income countries (LMICs) through a multifaceted intervention from October 2011 to March 2014. See Characteristics of included studies.

Design

All three trials were cluster-RCTs. In Leviton 1999, hospitals affiliated to the Albert Einstein College of Medicine (AECOM) and the National Perinatal Information Centre (NPIC) in the USA were randomised to either intervention or control. In the WHO RHL trial (Gülmezoglu 2007), hospitals with more than 1000 deliveries per year and not linked to a university or other academic institution were randomised to intervention or control group, stratified by country, type of hospital and number of births per year. In the ACT trial (Althabe 2015), conducted at seven sites affiliated to the Global Network for Women's and Children's Health Research, clusters comprised distinct geographical rural and semi-urban settings that had established a birth registry with more than 300 births per year, including births at home and at healthcare facilities.

Sample sizes

Leviton 1999 randomised 27 hospitals, 13 to the active dissemination group and 14 to the usual dissemination group. Records of 6798 eligible women were reviewed, 3516 at baseline and 3283 at follow-up. The WHO RHL trial (Gülmezoglu 2007), randomised a total of 40 hospitals, 22 to the multifaceted intervention and 18 to the control group. The ACT trial (Althabe 2015), randomised 102 clusters, 51 to both the intervention and the control groups. In the intervention group, 48,219 women and 48,698 births, and in the control group, 51,523 women and 52,007 births were analysed.

Setting

The trial by Leviton 1999 was conducted in the USA and included only tertiary care hospitals with neonatal intensive care unit (NICU) facilities. The WHO RHL trial (Gülmezoglu 2007) was conducted in Northern Thaliland and Mexico City and included hospitals that were not affiliated with universities or academic institutions. The ACT trial (Althabe 2015) was conducted in Argentina, Zambia, Guatemala, India (Belgaum and Nagpur regions), Pakistan and Kenya, including distinct geographical rural and semi-urban settings. Healthcare facilities included hospitals and clinics. Homebirths were also included.

Participants

Leviton 1999 included tertiary care hospitals with NICU facilities that had at least 100 eligible cases in the baseline year, no existing protocol on antenatal corticosteroid therapy and did not participate in any other ACS-related research. Eligible participants were women giving birth at 34 weeks' gestational age or less and included spontaneous labour, prelabour rupture of membranes and preterm delivery due to a medical condition. The WHO RHL trial (Gülmezoglu 2007), included hospitals that were not associated with a university or another academic institution and had more than 1000 deliveries per year. At each hospital, clinical practice data were collected from 1000 consecutive deliveries or for a six-month period, whichever was reached sooner. No further description of participants was reported.

In the ACT trial (Althabe 2015), each site included areas which provided antenatal care via clinics and/or hospitals by nurses, physicians and traditional birth attendants, although the amount of care taking place in different setting varied across sites. In the intervention group (n = 48,219), 49% of all women delivered at hospital, 28% delivered in a clinic, and 22% delivered at home or in another location. In the control group (n = 51,523), 53% of women delivered at hospital, 23% delivered in a clinic, and 24% delivered at home or another location. In the intervention group, 40% of deliveries were attended by a physician compared to 45% in the control group. Furthermore, more deliveries in the intervention group were attended by a nurse (38%) compared to the control group (30%). All areas included in the trial had established a birth registry and recorded at least 300 births annually. Pregnant women were enrolled by 20 weeks gestational age and birth outcomes were recorded. Maternal baseline characteristics were similar in both groups.

Interventions and comparisons

All three trials evaluated multifaceted interventions that aimed to promote the use of ACS.

Leviton and colleagues (Leviton 1999) compared an active dissemination strategy of recommendations on the use of ACS with usual dissemination. Usual dissemination comprised the release of the final consensus statement by the NIH on the use of ACS; an opinion statement on the use of ACS by the American College of Obstetricians and Gynaecologists, emailed to its members; NIH brochures on the consensus statement, mailed to healthcare institutions, universities, medical societies and obstetricians; a JAMA publication on the NIH recommendations; a second publication in the American Journal of Obstetrics and Gynaecology; and dissemination through lectures, word-of-mouth discussions and available literature. The active dissemination strategy comprised five additional components, namely 1) selecting an influential physician and nurse co-ordinator at each intervention hospital, who liaised with colleagues on high-risk cases and facilitated the active dissemination strategies; 2) a grand rounds lecture by a nationally respected expert, recommending that the majority of women at risk for preterm birth should receive ACS, and hand-outs of the consensus statement, research articles and samples of sticker prompts and chart reminders; 3) a chart reminder system, comprising brightly coloured reminders inside all eligible charts and stickers outside of charts, to prompt physicians to consider prescribing ACS; 4) an hour-long informal discussion with the influential physician, obstetricians and residents to discuss and agree on management of four scenarios where ACS might be useful (spontaneous preterm labour, prelabour rupture of membranes, early gestational care without prior antenatal care, and complicated pregnancy); and 5) monitoring and providing feedback on administration of ACS and chart reminders to the influential physician.

The WHO RHL trial (Gülmezoglu 2007) compared a multifaceted intervention with no intervention. The intervention comprised 1) a meeting with the director of the hospital or the heads of department of obstetrics and gynaecology to ensure buy-in; 2) provision of the RHL, computers and printers to facilitate access to knowledge; 3) selection of a hospital RHL co-ordinator from existing staff members, to assist staff with using the RHL and to liaise with the research team if problems arose; 4) RHL information and advocacy materials such as brochures and posters to promote

awareness about the RHL among staff members; and 5) three interactive workshops. The first workshop provided information on the project and the role of the WHO, introduced the RHL and covered principles of evidence-informed decision-making; the second workshop covered the contents of the RHL; and the third workshop focused on how to implement change.

The ACT trial (Althabe 2015) compared a multifaceted intervention designed to promote the use of ACS at all levels with standard care, which included training in neonatal care and a recommendation to refer women at high risk of preterm birth to hospitals. The intervention comprised three components, namely 1) provision of ACS kits that comprised ready-to use boxes containing corticosteroid vials, syringes, gloves and instructions for administration; 2) various items to improve identification of women at high risk of preterm labour and referral to hospitals including posters as reminders in areas of care, pregnancy discs to estimate the date of delivery in cases where the date of the last menstrual period was known, and uterine height tape to estimate gestational age and therefore identify women at high risk of preterm labour; and 3) training of birth attendants to improve the administration of ACS, in identifying women at high risk of preterm labour, appropriately using the preterm kit (giving a single course of four doses of 6 mg dexamethasone 12 hourly), and referring women to a health centre or contacting a skilled birth attendant if necessary.

Outcomes

Leviton and colleagues (Leviton 1999) measured use of ACS before the consensus conference and at follow-up, after the dissemination strategies. The WHO RHL trial (Gülmezoglu 2007) assessed changes in 10 selected clinical practices, of which one, ACS use in women with preterm birth, was relevant to this review. The primary outcome in the ACT trial (Althabe 2015) was 28-day neonatal mortality among infants less than the fifth percentile for birthweight, which was taken as a proxy for preterm birth. Secondary outcomes were measured in infants with low birthweight and their mothers, and in all infants and included ACS use, perinatal mortality (defined as stillbirths from 20 weeks' gestational age and neonatal deaths before seven days), neonatal mortality, neonatal weight and maternal infection. Only outcomes measured in all infants were included in this review. Process outcomes included number of women receiving ACS, number of doses and number of referrals. A full list of all secondary outcomes is provided in the Characteristics of included studies.

Funding

All three trials declared funding sources. The trial by Leviton and colleagues was funded by 'The Patient Outcomes Research Team on Low Birthweight contract 290-92-0055 from the Agency for Health Care Policy and Research' (Leviton 1999); the RHL WHO trial was funded by the 'UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP)' (Gülmezoglu 2007); and the ACT trial was funded through the 'Eunice Kennedy Shriver National Institute of Child Health and Human Development' (Althabe 2015).

Conflicts of interest

Leviton and colleagues did not report any conflicts of interests (Leviton 1999); authors of the RHL WHO trial declared that four of the five authors were editors of the WHO Reproductive Health Library since its inception in 1997 (Gülmezoglu 2007); while authors of the ACT trial declared no conflicts of interest (Althabe 2015).

Excluded studies

We excluded three studies (McGoldrick 2016; Patel 2017; WHO 2019). McGoldrick 2016 focused on barriers and enablers to ACS use (qualitative study), Patel 2017 focused on identifying women at high risk of preterm birth, and WHO 2019 is a protocol of ACS use compared with placebo in low-resource settings. (see Characteristics of excluded studies) .

Risk of bias in included studies

See Figure 2 for a summary of 'Risk of bias' assessments across trials and Figure 3 for a summary of 'Risk of bias' assessments for each included trial.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

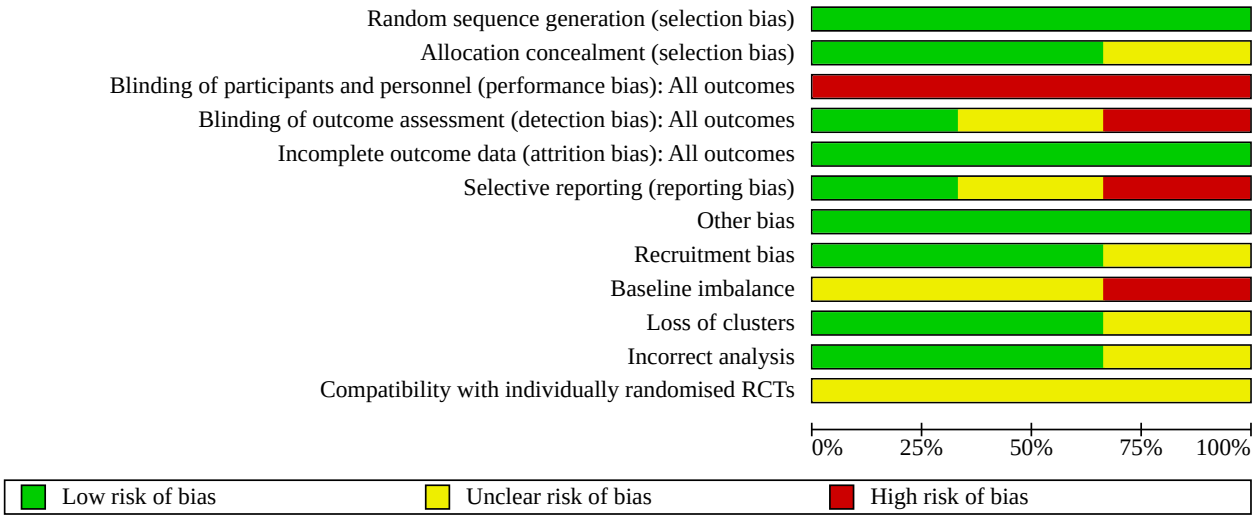
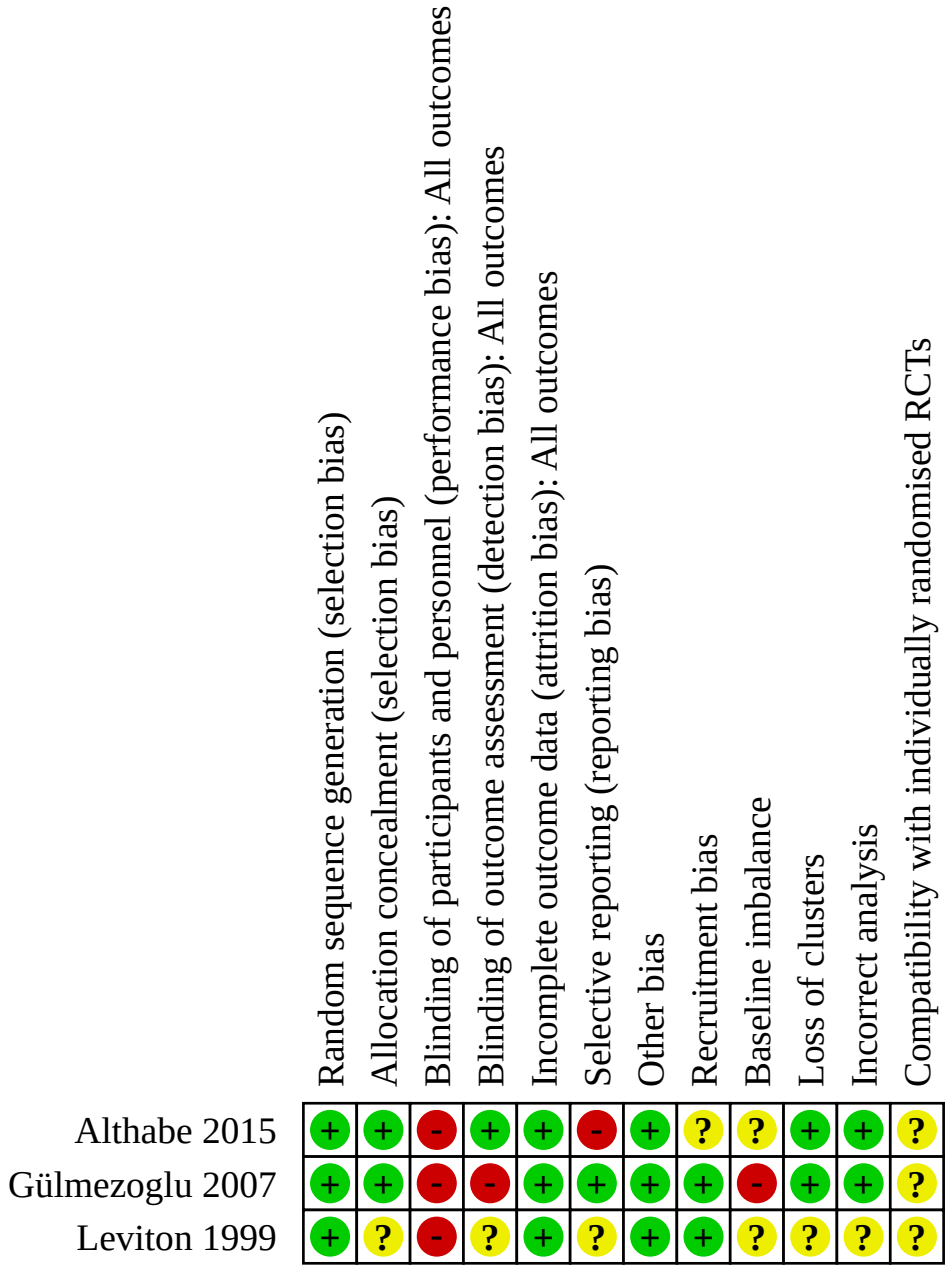


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged all three trials (Althabe 2015; Gülmezoglu 2007; Leviton 1999) to have used adequate methods for generation of the random sequence (low risk of bias). In addition, the WHO RHL trial (Gülmezoglu 2007), used adequate methods to conceal allocation through central allocation at the WHO in Geneva and only informing country investigators of their allocated group after having collected baseline data. In Leviton 1999 authors did not report on methods used to conceal allocation and we therefore assessed risk of bias related to allocation concealment to be unclear. In the ACT trial (Althabe 2015), all clusters were randomised by the data co-ordinating centre at the beginning of the trial and we therefore judged the methods to be adequate for allocation concealment (low risk of bias).

Blinding

We judged all trials to have high risk of performance bias, as none of the three trials were able to blind personnel and participants, due to the nature of the interventions. We judged the ACT trial (Althabe 2015) to have low risk of detection bias, as they used a team independent of the research team to collect outcome data. In the WHO RHL trial (Gülmezoglu 2007), field workers not involved in the implementation of the intervention collected outcome data in postnatal wards, however, the charts contained reminder systems and field workers were able to consult the mothers if information was missing. We therefore judged this trial to have high risk of detection bias. Leviton 1999 did not report who collected outcome data and we therefore judged risk of bias to be unclear.

Incomplete outcome data

We judged all three trials to be at low risk of attrition bias. in the ACT trial, attrition rates were similar between groups and less than 20% overall. In the control group, one of the 51 control sites withdrew due to external factors unrelated to the trial, but this occurred before participants were recruited (Althabe 2015). In the WHO RHL trial, no hospitals were lost to follow-up (Gülmezoglu 2007), and in Leviton 1999 all hospitals that were randomised were included in the analysis.

Selective reporting

It was unclear whether there was risk of reporting bias linked to selective outcome reporting in Leviton 1999, as no protocol was available. The WHO RHL trial (Gülmezoglu 2007) reported on all pre-specified outcomes and was judged as low risk of bias for this domain. We judged risk of reporting bias in the ACT trial (Althabe 2015) to be high. In the protocol, low birthweight infants were defined as birthweight below the 10th percentile, while in the trial report, it was defined as below the fifth percentile. There was thus a difference between the cut-offs for birthweight between the protocol and trial report (difference ranging from 0 g to 200 g). In addition, there was post-hoc analysis to explore the reasons for unexpected findings of increased mortality at the cluster level. This was unlikely to have introduced bias but might have affected the interpretation of results.

Other potential sources of bias

All three included trials were judged as having low risk for other bias. We were unable to pool any data in meta-analysis and planned subgroup analyses were not possible.

Additional risk of bias for cluster-RCTs

Recruitment bias

We judged the trial by Leviton 1999 and the WHO RHL trial (Gülmezoglu 2007) as having low risk of recruitment bias. In the ACT trial (Althabe 2015), participants were recruited after allocation of clusters due to the pragmatic nature of the trial. It is not clear whether this introduced bias and we thus judged the risk of recruitment bias to be unclear.

Baseline Imbalance

In the WHO RHL trial (Gülmezoglu 2007), there was an imbalance in the median number of doctors per hospital in Mexico (20 versus 14), and we therefore judged the risk of bias to be high. In the ACT trial (Althabe 2015) we judged the risk of bias due to baseline imbalances at cluster level to be unclear, as there was a difference between intervention and control clusters in the year before the trial in terms of the number of births attended by physicians and nurses - in the intervention clusters, fewer women had births attended by physicians and more births attended by nurses compared to the control clusters. Leviton 1999 did not report characteristics of included hospitals and it is therefore unclear whether there was risk of bias due to baseline imbalances.

Loss of clusters

We judged risk of bias related to loss of clusters to be low in the ACT trial (Althabe 2015) and the WHO RHL trial (Gülmezoglu 2007), while Leviton 1999 did not report on loss of clusters and we therefore made a judgement of unclear risk of bias.

Incorrect analyses

We judged risk of bias to be low for the ACT trial (Althabe 2015) and the WHO RHL trial (Gülmezoglu 2007). Results were adequately adjusted for clustering in the ACT trial (Althabe 2015), and analysed at cluster level in the WHO RHL trial (Gülmezoglu 2007). Leviton 1999 analysed data at patient and hospital level and it is not clear whether they adjusted results at patient level. We therefore judged the risk of bias to be unclear for this domain.

Comparability with individually-randomised RCTs

We judged risk of bias to be unknown for all three trials, as we did not include an individually randomised trial as comparison.

Effects of interventions

See: **Summary of findings 1** Strategies to increase use of antenatal corticosteroids versus routine (usual) care for optimising antenatal corticosteroid administration for anticipated preterm birth

Comparison 1: Strategies aiming to promote the use of antenatal corticosteroids versus usual care

All three included trials compared strategies that aimed to promote the use of ACS with standard care.

Primary outcomes

1. Perinatal death

ACT (Althabe 2015) was the only included trial that reported on perinatal death. A strategy aiming to promote the use of ACS in rural and semi-urban settings in low- and middle-income countries probably increases the risk of perinatal death at population level (risk ratio (RR) 1.11, 95% confidence interval (CI) 1.04 to 1.19; 1 study; n = 100,705; moderate-certainty evidence; Analysis 1.1).

2. Offspring mortality*, early neurodevelopmental morbidity*, or late neurodevelopmental morbidity*

None of the included trials reported on this outcome.

Secondary outcomes

Neonatal/childhood

1. Antenatal corticosteroid treatment (babies)

None of the included trials reported on this outcome.

2. Offspring mortality* or severe neonatal morbidity as defined by trial authors

None of the included trials reported on this outcome.

3. Stillbirth

The ACT trial (Althabe 2015) was the only included trial that reported on stillbirth. A strategy aiming to promote the use of ACS in rural and semi-urban settings in low- and middle-income countries probably increases the risk of stillbirth at population level (RR 1.11, 95% CI 1.02 to 1.21; 1 study; n = 100,705; moderate-certainty evidence; Analysis 1.2).

4. Neonatal death

The ACT trial (Althabe 2015) was the only included trial that reported on neonatal death. A strategy aiming to promote the use of ACS in rural and semi-urban settings in low- and middle-income countries probably increases the risk of neonatal death before 28 days at population level (RR 1.12, 95% CI 1.02 to 1.23; 1 study; n = 100,705; moderate-certainty evidence; Analysis 1.3).

5. Gestational age at birth

None of the included trials reported on this outcome.

6. Birthweight

None of the included trials reported on this outcome.

7. Head circumference

None of the included trials reported on this outcome.

8. Neonatal intensive care unit admission

None of the included trials reported on this outcome.

9. Respiratory morbidity

None of the included trials reported on this outcome.

10. Gastrointestinal morbidity

None of the included trials reported on this outcome.

11. Early neurodevelopmental morbidity

None of the included trials reported on this outcome.

12. Late neurodevelopmental morbidity

None of the included trials reported on this outcome.

13. Cerebroventricular haemorrhage

None of the included trials reported on this outcome.

14. Infection

None of the included trials reported on this outcome.

15. Harm to offspring from intervention

None of the included trials reported on this outcome.

16. Chronic lung disease

None of the included trials reported on this outcome.

17. Childhood illness

None of the included trials reported on this outcome.

Maternal

1. Antenatal corticosteroid treatment (women)

All three trials (Althabe 2015; Gülmezoglu 2007; Leviton 1999) reported on the use of ACS. Two trials (Althabe 2015; Leviton 1999) found that active promotion of ACS resulted in an increased use of ACS, while one trial (Gülmezoglu 2007) did not find a difference in the rate of ACS administration. However, we were not able to pool results, since all trials reported results related to this outcome differently.

In Leviton 1999, authors reported results both at patient and at hospital level. They found that, at patient level, use of ACS increased by 75% from baseline to after the conference (follow-up) in the usual dissemination group, compared to an increase of 108% in the active dissemination group, a 33% difference between groups. At hospital level, there was a 68% increase in the use of ACS at follow-up in the usual dissemination groups compared to a 113% increase in the active dissemination group, a difference of 45%.

The WHO RHL trial (Gülmezoglu 2007) analysed results at hospital level. Results differed between hospitals. In Mexico, changes in ACS administration varied from -42.9% to 92.3%. ACS use increased in eight of the 13 intervention hospitals, compared to three of the nine control hospitals. The difference in the ACS administration rate at follow-up was 5.3% (95%CI -18.6 to 29.2; P = 0.64).

In Thailand, changes in ACS use varied from -20.3% to +36.0%, with four of the nine hospitals in the intervention group and five of nine hospitals in the control group showing an increase in the use of ACS.The difference in the ACS administration rate at follow-up was 3.8% (95%CI -12.7 to 20.4; P = 0.63).

In ACT (Althabe 2015), 5571/45,439 (12%) women in the intervention group compared to 746/48,187 (2%) in the control group received ACS. (RR 7.94, 95% CI 7.14 to 8.83; 1 study; n = 93,626); Analysis 1.4).

2. Appropriate antenatal corticosteroid treatment

Appropriate ACS treatment, defined as the proportion of women who received ACS and delivered a preterm infant (out of all women who delivered a preterm infant), was reported in the ACT trial (Althabe 2015). Among women who delivered a less-than-5th-percentile infant (proxy for preterm infant), 1052/2327 (45%) in the intervention group and 215/2062 (10%) in the control group received ACS (RR 4.34, 95%CI 3.59 to 5.25; 1 study; n = 4389; low-certainty evidence; Analysis 1.5)

3. Inappropriate antenatal corticosteroid treatment

Inappropriate ACS treatment, defined as the proportion of women who received ACS and did not deliver a preterm infant (out of all women who did not deliver a preterm infant) was reported in the ACT trial (Althabe 2015). Among women who did not deliver a less-than-5th-percentile infant (proxy for preterm infant), 4519/43,112 (10%) in the intervention group and 531/46,125 (1%) in the control group received ACS (RR 9.11, 95%CI 8.04 to 10.33; 1 study; n = 89,237; low-certainty evidence; Analysis 1.6).

4. Prelabour rupture of membranes

None of the included trials reported on this outcome.

5. Caesarean section

The ACT trial (Althabe 2015) was the only included trial that reported on caesarean sections. A strategy aiming to promote the use of ACS in rural and semi-urban settings in low- and middle-income countries probably has little or no effect on the risk for caesarean section (RR 1.00, 95% CI 0.95 to 1.04; 1 study; n = 99,738; Analysis 1.7).

6. Chorioamnionitis (as defined by trial authors)

None of the included trials reported on this outcome.

7. Maternal infection or inflammation

The ACT trial (Althabe 2015) was the only included trial that reported on maternal infection. A strategy aiming to promote the use of ACS in rural and semi-urban settings in low- and middle-income countries may increase the risk of maternal infection (RR 1.49, 95% CI 1.32 to 1.68; 1 study; n = 99,742; low-certainty evidence; Analysis 1.8).

8. Maternal mortality

The ACT trial (Althabe 2015) was the only included trial that reported on maternal mortality. A strategy aiming to promote the use of ACS in rural and semi-urban settings in low- and middle-income countries may make little or no difference to maternal mortality (RR 1.11, 95% CI 0.64 to 1.92; 1 study; n = 99,742; low-certainty evidence; Analysis 1.9).

9. Death or severe morbidity

None of the included trials reported on this outcome.

10. Hospital stay

None of the included trials reported on this outcome.

11. Maternal satisfaction

None of the included trials reported on this outcome.

12. Postnatal depression

None of the included trials reported on this outcome.

13. Baby not breast fed

None of the included trials reported on this outcome.

14. Harm to mother from intervention

None of the included trials reported on this outcome.

Health services

1. Health staff attitudes to use

None of the included trials reported on this outcome.

2. Caregiver satisfaction

None of the included trials reported on this outcome.

3. Cost

None of the included trials reported on this outcome.

Comparison 2: Strategies aiming to restrict the use of antenatal corticosteroids versus routine care

We did not include any studies addressing this comparison.

DISCUSSION

Summary of main results

We included three studies in this review but were unable to pool the data in meta-analysis due to outcomes not being reported across all studies, or outcome results being reported in different ways. The main source of data in this review is from the ACT trial (Althabe 2015). In the protocol for this review (see Differences between protocol and review), we planned to report all settings and subgroup by low-middle versus high-income countries; these planned analyses were not possible in this version of the review, although adding further studies in future updates may allow us to carry out planned subgroup analyses.

Two of the three trials found that strategies to promote the use of antenatal corticosteroids (ACS) led to an increased use of corticosteroids in pregnant women at risk of preterm birth, while one trial did not find a difference in the rate of ACS administration. In low-resource settings, strategies to promote the use of ACS may increase steroids use among the target population, but may also carry a substantial risk of unnecessary steroids exposure to women in whom ACS is not indicated.

In low-resource settings, strategies to promote the use of ACS probably increase the risk of stillbirth, perinatal death, and neonatal death before 28 days; may increase the risk of maternal infection; and may make little or no difference to the risk of maternal mortality; at the population level (see Summary of findings 1).

Overall completeness and applicability of evidence

Our results are mostly based on one large cluster-RCT (Althabe 2015) that included close to 100,000 participants and was conducted at multiple sites across various low- and middle-income countries (LMICs), in low-resource semi-urban and rural settings. The primary outcome for this trial was 28-day neonatal mortality in infants less than the fifth percentile birthweight (a proxy for preterm birth). Among this group of infants, there was no difference in 28-day neonatal mortality (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.87 to 1.06), stillbirth (RR 0.99, 95% CI 0.90 to 1.09) and perinatal mortality (RR 0.97, 95% CI 0.91 to 1.04).

The unexpected findings of increased perinatal mortality rates among all live births (regardless of birthweight) raised concerns among the investigators, who performed subsequent secondary analyses to better understand the findings. When they stratified results according to trial sties, they found that neonatal death rates in the intervention compared to control groups were significantly higher in Zambia (RR 1.77, 95% CI 1.42 to 2.20), Kenya (RR 1.47, 95% CI 1.02 to 2.12) and in Nagpur, India (RR 1.36, 95% CI 1.09 to 1.71). In Belgaum, India, they found a marginally significant increase in neonatal death rates (RR 1.13, 95% CI 0.99 to 1.27), while they did not find a significant increase in Pakistan (RR 0.93, 95% CI 0.82 to 1.07), Guatemala (RR 0.86, 95% CI 0.72 to 1.03) and Argentina (RR 1.06, 95% CI 0.54 to 2.09) (Althabe 2015). The high mortality rates at the African sites were accompanied by high rates of possible serious bacterial infection in the neonates (based on clinical observation). Furthermore, they found that mortality rates for infants less than the 25th percentile birthweight were similar in intervention and control groups, but increased significantly in the intervention group in infants at or above the 25th percentile birthweight.

Authors also assessed whether other intervention components linked to the quality of care might have contributed to the high neonatal mortality rates in the intervention groups, but concluded that ACS more than other components might have contributed to this harmful effect. The most probable contributor to the harmful effects observed at the population level was hypothesised to be related to the nine-fold risk of inappropriate exposure of ACS in the intervention compared to control clusters.

The two trials conducted in high-resource settings only assessed coverage of ACS (Gülmezoglu 2007; Leviton 1999).

Quality of the evidence

We judged the certainty of evidence to be moderate for the outcomes perinatal death, 28-day neonatal mortality and stillbirth; and low for the outcomes maternal infection and maternal mortality (Summary of findings 1). We downgraded the certainty of evidence due to study limitations related to high risk of performance bias and bias relating to selective outcome reporting. In addition, we downgraded the certainty of evidence for appropriate ACS treatment, inappropriate ACS treatment, and maternal infection for indirectness, and maternal mortality for imprecision.

Potential biases in the review process

We followed a rigorous and systematic process, as per the standard methods described in the *Cochrane Handbook* (Higgins 2011). This includes a comprehensive search of published and unpublished studies with no language restriction. We were not able to pool data in meta-analyses, nor assess publication bias, as only one of the three included RCTs provided data for important outcomes. Indeed, our findings are based on a single randomised controlled trial (RCT). However, this was a multi-centre trial across six LMICs, with 99,742 participants.

Agreements and disagreements with other studies or reviews

This is the first systematic review to assess strategies that optimise the use of antenatal corticosteroids. The Cochrane Review on effectiveness of antenatal corticosteroids (Roberts 2017) found that administration of ACS compared to placebo or no treatment, significantly decreased perinatal death and respiratory distress syndrome (RDS), a severe complication from preterm birth. The review did not find a difference between groups in risk of maternal mortality and infection. However, these findings are based on evidence from high-resource, hospital settings in few middle- and mostly high-income countries. A further Cochrane Review on ACS administration before elective caesarean section at term found that ACS probably decrease the risk of RDS and admission to neonatal intensive care units. The review found no difference in the risk of neonatal death and no adverse maternal events were reported in included studies (Sotiriadis 2018).

Another systematic review (Saccone 2016) assessed the effects of ACS in late preterm deliveries (gestational age at or greater than 34 weeks) on RDS. The review included three trials on women with imminent late preterm delivery, and three trials on women undergoing planned caesarean section. These individually-randomised trials were conducted in hospitals in middle- and high-income countries, and found that ACS decreased the risk for RDS in both groups. There was no difference in the risk of neonatal death with very few events across trials. The review did not include any maternal outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

In low-resource settings, strategies to actively promote the use of antenatal corticosteroids (ACS) in women at risk of preterm birth may increase ACS use in the target population but may also carry a substantial risk of unnecessary exposure of ACS to women in whom ACS is not indicated. At the population level, these effects are associated with increased risks of stillbirth, perinatal death, neonatal death before 28 days, and maternal infection.

Due to the safety concerns that emerged from the findings of the ACT trial, the WHO issued its 'recommendations on interventions to improve preterm birth outcomes' (WHO 2015) to reflect a more conservative approach for ACS use. WHO recommends administration of ACS for women at risk of preterm labour (between 24 and 34 weeks' gestational age) provided the following conditions are met: 1) being able to accurately assess gestational age, 2) considering preterm delivery to be imminent, 3) absence of clinical evidence of maternal infection, 4) having adequate capacity to safely manage preterm labour and birth, and 5) availability of adequate care for the preterm infant.

The findings of this review support a more conservative approach to clinical protocols and clinical decision-making in low-resource settings, along the lines of these WHO recommendations, which take into account both the established clinical efficacy of ACS when used in the correct clinical situation and context, and the possibility of important adverse effects when certain pre-conditions are not met.

Implications for research

There is a need to assess the effectiveness of ACS in low-resource settings. The WHO-ACTION-I (Antenatal CorticosTeroids for Improving Outcomes in preterm Newborns) trial (WHO 2019) is currently ongoing. This is a multi-centre, multi-country trial, recruiting participants in hospitals in India, Bangladesh, Pakistan, Nigeria and Kenya where the WHO criteria for ACS administration can be reasonably met. Although the trial falls within the scope of the Cochrane Review on the effectiveness of ACS (Roberts 2017), the findings would support whether or not the specified requirements for ACS use make a difference to ACS efficacy in low-resource settings.

Given the unanticipated results of the ACT trial (Althabe 2015), further research on strategies to optimise the use of ACS in low-resource settings is justified, to confirm or refute the findings of ACT. Such research should consider application of innovative approaches for appropriate selection of eligible population for ACS use (e.g. simple and scalable methods to ensure accurate gestational age assessment and confirm high likelihood of preterm birth); provide minimum neonatal care packages to care for preterm infants; optimise the use of complementary interventions such as magnesium sulphate for fetal neuroprotection, and tocolytics when appropriate; and reduce uncontrolled or indiscriminate scale up of ACS in vulnerable populations.

Further research would also be welcomed across all settings to allow for planned subgroup analysis across settings, which was specified in the protocol for this review .

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Althabe 2015

Study characteristics	
Methods	Antenatal Corticosteroid Trial (ACT): 30-month 2-arm, parallel cluster-RCT. Conducted at 7 sites of the Global Network for Women's and Children's Health Research in 6 countries. After randomisation, but before the intervention, a survey was done in all study clusters to identify participating health facilities and birth attendants.
Participants	Pregnant women in selected clusters - data were collected on all women who delivered in the study clusters and provided consent. Clusters (n = 102): distinct geographical rural and semi-urban settings in Argentina, Zambia, Guatemala, India (Belgaum and Nagpur regions), Pakistan and Kenya. All health providers in the intervention clusters (349 health facilities) were trained before the start of the trial. Clinical setting and providers in selected clusters: each site included areas which provided antenatal care via clinics and/or hospitals by nurses, physicians and traditional birth attendants although the amount of care taking place in different setting varied across areas. The location of birth also varied across areas with between 6% to 99% of births taking place in hospital settings (as opposed to clinic or home settings). All areas included in the trial had established a birth registry and recorded at least 300 births annually; registry administrators aimed to enrol all pregnant women by 20 weeks' gestation and to record birth outcomes.
Interventions	Intervention: (51 clusters randomised and analysed, 48,219 women analysed) Multifaceted intervention designed to increase the use of antenatal corticosteroids at all levels, consisting of:

Althabe 2015 *(Continued)*

1. Provision of antenatal corticosteroid kits (ready-to-use boxes containing corticosteroid vials, syringes, gloves, instructions for administration)
2. Components to improve identification and referral of women at high risk of preterm labour (women before 36 weeks' gestation with signs of labour, preterm premature rupture of membranes, pre-eclampsia or eclampsia, bleeding as high risk of preterm labour):
   a. posters as reminders in areas of care
   b. pregnancy discs to estimate date of delivery if LMP is known
   c. uterine height tape for identification of women at high risk of preterm birth and unknown gestational age
3. Components to improve the administration of antenatal corticosteroids to eligible women by training birth attendants:
   a. to identify women eligible for antenatal corticosteroids
   b. appropriately use the preterm kit (if allowed to administer injections, to give a single course of 4 doses of 6 mg of dexamethasone 12 hourly)
   c. refer the women to a health centre or contact skilled birth attendant when necessary

Control: (51 clusters randomised, 50 clusters analysed, 51,523 women analysed)

Standard care

Training in neonatal care given to all sites.

Training also included a recommendation of referral to hospital for women at high risk of preterm birth (but this was not supported by transport or other strategies).

Outcomes

All mortality outcomes were obtained via the Global Networks' Maternal and Neonatal Health Registry (MNH Registry) based in each cluster. Data were collected by birth registry administrators.

Primary outcome

1. 28-day neonatal mortality among infants less than the 5th percentile for birthweight (proxy for preterm birth)

Secondary outcomes

Outcome measures in infants with LBW and their mothers:

1. Rate of antenatal corticosteroid use
2. Maternal infection from birth up to 7 and 42 days postpartum
3. Perinatal mortality rate (stillbirths > 20 weeks gestational age or > 500 g and neonatal deaths before 7 days)
4. Early neonatal mortality rate at 7 days after birth
5. Mean neonatal weight at 7 and 28 days
6. Neonatal and perinatal mortality rates by country
7. Neonatal and perinatal mortality rates by type of setting (health based deliveries versus community based deliveries)
8. Infant mortality rate at 42 days postpartum

Outcome measures in all infants and mothers:

1. Early neonatal mortality (7 days after birth)
2. Neonatal mortality at 28 days after birth
3. Maternal infection from birth up to 7 days postpartum
4. Maternal infection from birth up to 42 days postpartum
5. Infant mortality rate at 42 days after birth

Process measures:

1. Number of women receiving corticosteroids and number of doses
2. Number of referrals

Althabe 2015 *(Continued)*

3. Number of health providers trained
4. Number of kits distributed
5. Health providers' opinion about the kits
6. Number of kits fully used (all doses administered) at site
7. Number of kits partially used (1-3 doses of dexamethasone) at site

Notes	Time period 1 October 2011 to 20 March 2014 Trial registration number: NCT01084096 Funding source declared: Eunice Kennedy Shriver National Institute of Child Health and Human Development. Conflict of interests: declared no conflict of interests. Author contacted to request details of how random sequence was generated: Response obtained, random sequence was computer generated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence (correspondence with author)
Allocation concealment (selection bias)	Low risk	Quote: "The data coordinating centre (RTI International, Durham, NC, USA) randomly assigned eligible clusters (1:1) to intervention or control using a stratified randomisation procedure to account for Global Network site, neonatal mortality, and treatment group in Global Network Emergency Obstetric and Neonatal Care trial." Strata contained 2 or 4 clusters. All clusters randomised at the start of the study.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Staff at the data coordinating centre informed investigators at each site of the randomisation allocation during the preparatory period to allow time for staff training for the intervention before the start of the trial. The nature of the trial precluded masking of group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "To reduce bias, the MNH Registry team obtained outcome data independently of the intervention teams." Not reported whether the Registry team was aware of group allocation. Perinatal death is an objective outcome which will not be influenced by knowledge of group allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates similar between groups and less than 20% overall Intervention group: 1501 women lost to follow-up Control group: 1833 women lost to follow-up Reasons for loss to follow-up were not provided 1 of the 51 control sites withdrew due to external factors not related to the trial.
Selective reporting (reporting bias)	High risk	In the protocol, low birthweight infants were defined as birthweight below the 10th percentile, while in the trial report, it is defined as below the 5th percentile. There is thus a difference between the cut-offs for birthweight between the protocol and trial report (difference ranging from 0 g to 200 g). There was post-hoc analysis to explore the reasons for unexpected findings of

Althabe 2015 *(Continued)*

		increased mortality at the cluster level. This was unlikely to have introduced bias (but might have affected the interpretation of results).
Other bias	Low risk	No other source of bias identified.
Recruitment bias	Unclear risk	Participants recruited after allocation of clusters but this was due to the pragmatic nature of the trial. Not clear whether this introduced bias.
Baseline imbalance	Unclear risk	Quote: "In the year before the trial, fewer women in the intervention clusters than in the control clusters had deliveries attended by physicians, and more deliveries in the intervention clusters than in the control clusters were attended by nurses"
Loss of clusters	Low risk	One cluster in the control group withdrew due to unrest and staff concerns about safety - not related to trial.
Incorrect analysis	Low risk	Results adjusted for clustering
Compatibility with individually randomised RCTs	Unclear risk	No individually-randomised RCTs for comparison.

Gülmezoglu 2007

Study characteristics	
Methods	Cluster-randomised trial in Mexico city and Northeast region of Thailand Hospitals with > 1000 deliveries per year and not directly associated with a university or academic institution were eligible
Participants	22 hospitals in Mexico City and 18 in the Northeast region of Thailand. At each hospital, data from 1000 consecutive deliveries at baseline and follow-up
Interventions	Intervention: over a period of 6 months between October 2001 and October 2002 - Multifaceted intervention comprising 1) meeting with hospital director/heads of obstetrics and gynaecology departments 2) provision of WHO Reproductive Health Library (RHL), computers, printers 3) Selection of hospital RHL co-ordinator from staff 4) RHL information/advocacy materials such as brochures and posters and 5) 3 interactive workshops using the WHO RHL. - Workshop 1: Information about project, WHO's role, principles of evidence-informed desicion-making, presenting RHL - Workshop 2: RHL contents - Workshop 3: How to implement change - All staff (doctors, midwives, interns and students) included in all 3 workshops Control: The control hospitals did not receive any intervention. Dates of follow-up were not given.
Outcomes	Changes in 10 selected clinical practices as recommended in RHL starting approximately 4 to 6 months after the third workshop (10-12 months from the first workshop). Clinical practice data were collected at each hospital from 1000 consecutively delivered women, or for a 6-month period, whichever was reached sooner.

Gülmezoglu 2007 *(Continued)*

1. Social support during labour
2. MgSO4 for eclampsia
3. Corticosteroids to women with preterm birth
4. Selective episiotomy
5. Uterotonic use after birth
6. Breastfeeding on demand
7. External cephalic version
8. Iron/folate supplementation
9. Antibiotic use at caesarean section
10. Vacuum extraction for assisted birth

Notes	ISRCTN14055385 Conflict of interest: AMG, JV, PL and AL are editors of the WHO Reproductive Health Library since its inception in 1997 to date. Funding: UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random allocation sequence was produced centrally by WHO in Geneva, assigning hospitals at random in each stratum to intervention or control. Quote: "For each stratum, random permutations were produced using a SAS® random number generator, with the starting number taken independently for each stratum."
Allocation concealment (selection bias)	Low risk	Country investigators were informed of the allocation status of the hospitals after collection of baseline data were completed and when the first workshop had to be organised as required in the protocol. Quote: "The allocation was concealed until knowledge of the assignment was required operationally to implement the intervention. Thus, country investigators were informed of the allocation status of the hospitals after collection of baseline data, when the first intervention workshop had to be organized."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding was not possible. The hospital staff were unaware of the primary outcome practices.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding was not possible. Field workers not involved in the implementation of the trial collected outcome data in the postnatal wards from hospital records, but the mothers could be consulted if information was missing in the records.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up of hospitals.
Selective reporting (reporting bias)	Low risk	All outcomes reported on.
Other bias	Low risk	No other source of bias identified.
Recruitment bias	Low risk	No source of recruitment bias identified, hospitals informed of allocation after baseline data were collected

Gülmezoglu 2007 *(Continued)*

Baseline imbalance	High risk	Imbalace in the median number of doctors per hospital in Mexico (20 versus 14).
Loss of clusters	Low risk	No loss of clusters.
Incorrect analysis	Low risk	Analysis appears appropriate - unit of analysis was the hospitals
Compatibility with individually randomised RCTs	Unclear risk	No individually-randomised RCTs for comparison.

Leviton 1999

Study characteristics	
Methods	Cluster-randomised controlled trial Hospitals from the Albert Einstin College of Medicine (AECOM) affiliated hospitals and hospitals from the National Perinatal Information Centre (NPIC) randomised to intervention and control groups Data were abstracted from medical records at baseline (12 months before consensus conference, March 1993 to February 1994) and after (12 months after consensus conference, April 1995 to July 1996)
Participants	27 hospitals (8 AECOM and 22 NPIC); All hospitals were tertiary care facilities with neonatal intensive care unit facilities Criteria for inclusion of hospitals: at least 100 eligible cases in baseline care; no standing protocol on ACS; not participating in other ACS related research Eligible participants: all women giving birth at 34/52 or less, including cases of spontaneous labour, PROM, and preterm delivery indicated by medical conditions No data on women who received ACS but did not deliver prematurely
Interventions	Control: usual dissemination (n = 14) - NIH Consensus Conference in February 1994, final statement released May 1994 - American College of Obstetricians and Gynaecologicsts' opinion statement on ACS mailed to members in December 1994 - End January 1995, NIH brochures on consensus statement mailed to medical care institutions, universities, medical societies and obstetricians. - JAMA published the NIH recommendations in February 1995 - 2nd publication in American Journal of Obstetrics and Gynaecology July 1995 - Lectures, word-of-mouth discussions, available literature Intervention: active dissemination (n = 13) comprised 5 components 1. Influential physician and nurse co-ordinator at each hospital. Liaised with colleagues who managed high risk cases. Facilitated the active dissemination strategies at treatment hospitals, in partnership with nurse co-ordinators 2. Grand rounds lecture on ACS by a nationally respected expert. Emphasising that the majority of women at risk for preterm delivery should receive ACS. Those attending received consensus conference statement, key research articles and citations, samples of a sticker prompt and chart reminder

Leviton 1999 *(Continued)*

3. Chart reminder system to prompt physicians to consider prescribing therapy on a timely basis. Reminders were inserted in eligible charts as soon as possible after admission. These were brightly coloured and large. Outside of flagged charts also had brightly coloured sticker
4. Group discussions by influential physician. 1-hour long, informal group discussions with hospital's obstetricians and residents, discussing 4 case scenarios in which ACS might be administered (spontaneous preterm labour, PROM, early gestational age and no prenatal care, complicated pregnancy). Goals were to gain consensus on basic management, elicit reasons why corticosteroids would/would not be used, draw out differences in management strategies in accordance with the scenarios)
5. Monitoring of care provided feedback to physicians. Nurse co-ordinators kept logs of preterm admissions and deliveries to determine whether charts had reminder systems whether ACS was administered and when. Influential physicians received reports.

Outcomes	Primary outcome: use of antenatal corticosteroids
Notes	Time period: March 1993 to July 1996 Trial registration number: not reported Funding source: the Patient Outcomes Research Team on Low Birthweight contract 290-92-0055 from the Agency for Health Care Policy and Research, Rockville, Md Conflict of interests: not reported Author contacted to request missing information related to methods and results, but email address no longer valid and not able to find alternative address.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random table of numbers was used to allocate hospitals
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not possible. Physicians in the active dissemination hospitals were aware of the study, whereas in the control hospitals only the hospital leadership were aware.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All hospitals that were randomised were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	Low risk	No other source of bias identified
Recruitment bias	Low risk	Hospitals recruited before randomisation
Baseline imbalance	Unclear risk	Quote: "A difference between intervention and control cases in frequency of abnormal fetal conditions or fetal distress was significant at patient level". "During the after conference year, 2 differences in hospital case mix emerged between intervention and control institutions. Based on hospital census (not

Leviton 1999 *(Continued)*

		sampling), treatment hospitals had a larger proportion of the lowest GA cases in the after-conference year because 3 control hospitals reduced their proportions of such cases, while 1 treatment hospital increased its proportion of these cases. In addition, in the after-conference year the average proportion of reported PROM cases increased in all hospitals but increased significantly more in treatment than in control hospitals". "The change in case mix did not cause increased use of the therapy in the active dissemination group"
Loss of clusters	Unclear risk	One hospital refused participation after randomisation
Incorrect analysis	Unclear risk	Unclear whether results at patient level were adjusted for clustering
Compatibility with individually randomised RCTs	Unclear risk	No individually-randomised RCTs for comparison.

ACS: antenatal corticosteroids;**GA:** gestational age; **LBW:** low birth weight; **LMP:** last menstrual period; **MgSO4:** magnesium sulphate; **NIH:** National Institutes of Health; **PROM:** premature rupture of membranes; **RCT:** randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
McGoldrick 2016	Comparing methods to identify barriers and enablers to administration of ACS as well as a qualitative study on barriers and enablers to ACS
Patel 2017	This study is about identifying women at high risk of preterm birth
WHO 2019	Protocol. Comparing ACS to placebo and not various strategies to one another

ACS: antenatal corticosteroids.

DATA AND ANALYSES

Comparison 1. Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care

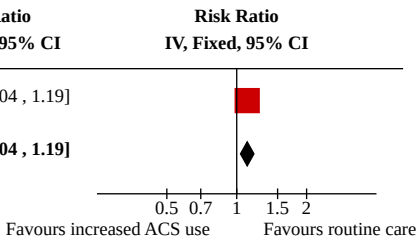
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Perinatal death	1	100705	Risk Ratio (IV, Fixed, 95% CI)	1.11 [1.04, 1.19]
1.2 Stillbirth	1	100705	Risk Ratio (IV, Fixed, 95% CI)	1.11 [1.02, 1.21]
1.3 Neonatal death (as defined by trial authors)	1	100705	Risk Ratio (IV, Fixed, 95% CI)	1.12 [1.02, 1.23]
1.4 Antenatal corticosteroid treatment (mothers)	1	50197	Risk Ratio (M-H, Fixed, 95% CI)	7.94 [7.14, 8.83]
1.5 Appropriate ACS treatment (women)	1	2209	Risk Ratio (M-H, Fixed, 95% CI)	4.34 [3.59, 5.25]
1.6 Inappropriate ACS treatment (women)	1	44910	Risk Ratio (M-H, Fixed, 95% CI)	9.11 [8.04, 10.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Casaerean section	1	50197	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.95, 1.04]
1.8 Maternal infection	1	50197	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.32, 1.68]
1.9 Maternal mortality	1	50197	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.64, 1.92]

Analysis 1.1. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 1: Perinatal death

Study or Subgroup	log[RR]	SE	Increased ACS use Total	Routine care Total	Weight	Risk Ratio IV, Fixed, 95% CI
Althabe 2015 (1)	0.104	0.034	48698	52007	100.0%	1.11 [1.04 , 1.19]
Total (95% CI)			**48698**	**52007**	**100.0%**	**1.11 [1.04 , 1.19]**

Heterogeneity: Not applicable
Test for overall effect: Z = 3.06 (P = 0.002)
Test for subgroup differences: Not applicable

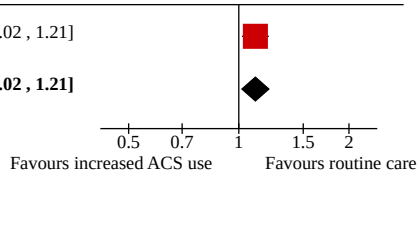


Footnotes
(1) Adjusted RR reported in paper

Analysis 1.2. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 2: Stillbirth

Study or Subgroup	log[RR]	SE	Increased ACS use Total	Standard care Total	Weight	Risk Ratio IV, Fixed, 95% CI
Althabe 2015 (1)	0.1044	0.0431	48698	52007	100.0%	1.11 [1.02 , 1.21]
Total (95% CI)			**48698**	**52007**	**100.0%**	**1.11 [1.02 , 1.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.42 (P = 0.02)
Test for subgroup differences: Not applicable

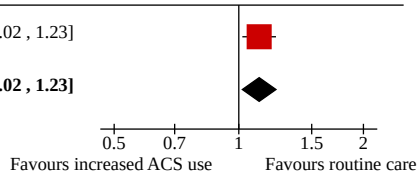


Footnotes
(1) Adjusted RR reported in paper

Analysis 1.3. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 3: Neonatal death (as defined by trial authors)

Study or Subgroup	log[RR]	SE	Increased ACS use Total	Standard care Total	Weight	Risk Ratio IV, Fixed, 95% CI
Althabe 2015 (1)	0.1133	0.0477	48698	52007	100.0%	1.12 [1.02 , 1.23]
Total (95% CI)			**48698**	**52007**	**100.0%**	**1.12 [1.02 , 1.23]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.38 (P = 0.02)
Test for subgroup differences: Not applicable

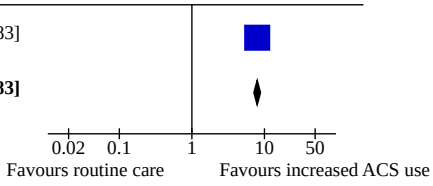


Footnotes
(1) Adjusted RR reported in paper

Analysis 1.4. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 4: Antenatal corticosteroid treatment (mothers)

Study or Subgroup	Increased ACS use Events	Total	Routine care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Althabe 2015 (1)	2803	24267	377	25930	100.0%	7.94 [7.14 , 8.83]
Total (95% CI)		**24267**		**25930**	**100.0%**	**7.94 [7.14 , 8.83]**
Total events:	2803		377			

Heterogeneity: Not applicable
Test for overall effect: Z = 38.29 (P < 0.00001)
Test for subgroup differences: Not applicable

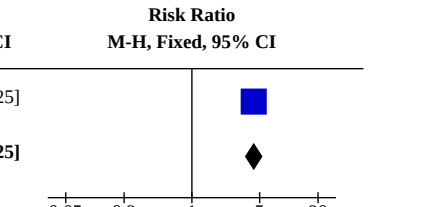


Footnotes
(1) Results adjusted for clustering. ICC 0.001, DE=1.987

Analysis 1.5. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 5: Appropriate ACS treatment (women)

Study or Subgroup	Increased ACS use Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Althabe 2015 (1)	529	1171	108	1038	100.0%	4.34 [3.59 , 5.25]
Total (95% CI)		**1171**		**1038**	**100.0%**	**4.34 [3.59 , 5.25]**
Total events:	529		108			

Heterogeneity: Not applicable
Test for overall effect: Z = 15.20 (P < 0.00001)
Test for subgroup differences: Not applicable

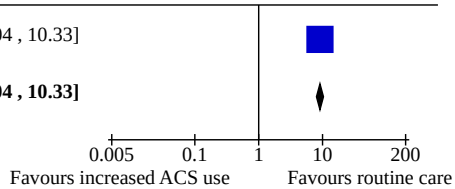


Footnotes
(1) Results adjusted for clustering. ICC 0.001, DE=1.987

Analysis 1.6. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 6: Inappropriate ACS treatment (women)

Study or Subgroup	Increased ACS use Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Althabe 2015 (1)	2274	21697	267	23213	100.0%	9.11 [8.04 , 10.33]
Total (95% CI)		**21697**		**23213**	**100.0%**	**9.11 [8.04 , 10.33]**
Total events:	2274		267			

Heterogeneity: Not applicable
Test for overall effect: Z = 34.53 (P < 0.00001)
Test for subgroup differences: Not applicable

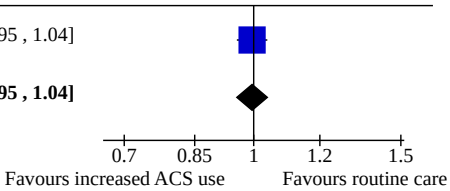


Footnotes
(1) Results adjusted for clustering. ICC 0.001, DE=1.987

Analysis 1.7. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 7: Casaerean section

Study or Subgroup	Increased ACS use Events	Total	Routine care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Althabe 2015 (1)	3590	24267	3853	25930	100.0%	1.00 [0.95 , 1.04]
Total (95% CI)		**24267**		**25930**	**100.0%**	**1.00 [0.95 , 1.04]**
Total events:	3590		3853			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.84)
Test for subgroup differences: Not applicable

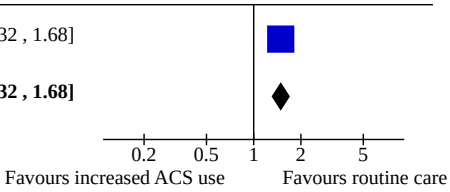


Footnotes
(1) Results adjusted for clustering. ICC 0.001, DE=1.987

Analysis 1.8. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 8: Maternal infection

Study or Subgroup	Increased ACS use Events	Total	Routine care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Althabe 2015 (1)	607	24267	436	25930	100.0%	1.49 [1.32 , 1.68]
Total (95% CI)		**24267**		**25930**	**100.0%**	**1.49 [1.32 , 1.68]**
Total events:	607		436			

Heterogeneity: Not applicable
Test for overall effect: Z = 6.39 (P < 0.00001)
Test for subgroup differences: Not applicable

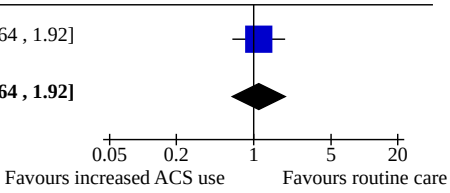


Footnotes
(1) Results adjusted for clustering. ICC 0.001, DE=1.987

Analysis 1.9. Comparison 1: Strategy of aiming to increase use of antenatal corticosteroids versus routine (usual) care, Outcome 9: Maternal mortality

Study or Subgroup	Increased ACS use Events	Total	Routine care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Althabe 2015 (1)	26	24267	25	25930	100.0%	1.11 [0.64 , 1.92]
Total (95% CI)		**24267**		**25930**	**100.0%**	**1.11 [0.64 , 1.92]**
Total events:	26		25			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



Footnotes
(1) Results adjusted for clustering. ICC 0.001, DE=1.987

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

Each line was run separately

ICTRP

antenatal AND steroids

antenatal AND corticosteroids

ClinicalTrials.gov

Advanced search

Interventional Studies | Preterm | Corticosteroid

Interventional Studies | Preterm | Steroids

HISTORY

Review first published: Issue 5, 2020

CONTRIBUTIONS OF AUTHORS

GJH conceived the review. GJH and AR wrote the first draft of the protocol and conducted initial study selection, data extraction and analysis. OTO revised the protocol and conducted additional data analysis and extraction. AR wrote the first draft of the manuscript. GJH and OTO provided critical input. All authors have approved the final version of this manuscript.

DECLARATIONS OF INTEREST

G Justus Hofmeyr: none known

Anke C Rohwer was partly supported by the Research, Evidence and Development Initiative (READ-It) project (project number 300342-104). READ-It is funded by aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.

Olufemi T Oladapo: co-ordinated the development of the WHO recommendations on interventions to improve newborn outcomes published in 2015, and is the Project Co-ordinator for the WHO ACTION trials.

SOURCES OF SUPPORT

Internal sources

- Centre for Evidence-based Health Care, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa

External sources

- Research, Evidence and Development Initiative (READ-It) project, UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was published in PROSPERO, and not the Cochrane Library. We added two outcomes to the GRADE 'Summary of findings' table (appropriate ACS treatment and inappropriate ACS treatment) as these are considered critical outcomes for policy decision making.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Developed Countries; Developing Countries; Inappropriate Prescribing; Infant, Premature; Perinatal Death; *Premature Birth; Randomized Controlled Trials as Topic; Stillbirth [epidemiology]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy