Antenatal corticosteroids for impending late preterm (34-36+6 weeks) deliveries—A systematic review and meta-analysis of RCTs

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Abstract

Background

Administration of antenatal corticosteroids (ANC) for impending preterm delivery beyond 34 weeks of gestation continues to be a controversial issue despite various guidelines for obstetricians and gynaecologists.

Objective

To compare outcomes following exposure to ANC for infants born between 34–36+6 weeks’ gestation.

Methods

A systematic review of randomised controlled trials (RCT) reporting neonatal outcomes after ANC exposure between 34–36+6 weeks’ gestation using Cochrane methodology. Databases including PubMed, Embase, Emcare, Cochrane Central library and Google Scholar were searched in May 2020. Primary outcomes: (1) Need for respiratory support (Mechanical ventilation, CPAP, high flow) or oxygen (2) Hypoglycemia. Secondary outcomes included respiratory distress syndrome (RDS), transient tachypnoea of newborn (TTN), need for neonatal resuscitation at birth [only in the delivery room immediately after birth (not in neonatal intensive care unit (NICU)), admission to NICU, mortality and developmental follow up. Level of evidence (LOE) was summarised by GRADE guidelines.

Main results

Seven RCTs (N = 4144) with low to high risk of bias were included. Only one RCT was from high income countries, Meta-analysis (random-effects model) showed (1) reduced need for respiratory support [5 RCTs (N = 3844); RR = 0.68 (0.47–0.98), p = 0.04; I² = 55%; LOE: Moderate] and (2) higher risk of neonatal hypoglycaemia [4 RCTs (N = 3604); RR = 1.61
Neonates exposed to ANC had reduced need for resuscitation at birth. The incidence of RDS, TTN and surfactant therapy did not differ significantly. None of the included studies reported long-term developmental follow up.

Conclusions
Moderate quality evidence indicates that ANC exposure reduced need for respiratory support, and increased the risk of hypoglycaemia in late preterm neonates. Large definitive trials with adequate follow up for neurodevelopmental outcomes are required to assess benefits and risks of ANC in this population.

Introduction
Administration of antenatal corticosteroids (ANC) is standard practice for threatened preterm delivery between 24–34 weeks’ gestation. Based on the evidence from randomised controlled trials (RCTs), most of the Obstetric and Gynaecological College/Society guidelines recommend ANC between 24–34 weeks of gestation [1–3]. However administration of ANC beyond 34 weeks of gestation continues to be a controversial issue, more so for late preterm gestations from 34 to 36\(\frac{1}{2}\) weeks.

Late preterm neonates (LPNs) represent ~70% of total preterm births, which account for ~10% of total births [4]. Compared to neonates born at term (37–40 weeks’ gestation), LPNs are at risk of complications such as the need for resuscitation at birth, respiratory distress, hypothermia, and hypoglycaemia. Considering the size of their population, LPNs impose an enormous burden on the health system [5]. A population-based prospective study from UK (N = 1146) found that LPNs are more likely to require resuscitation (17.5% vs 7.4%), respiratory (11.8% vs 0.9%) and nutritional support (3.5% vs 0.3%) and less likely to be fed breast milk (64.2% vs 72.2%) compared to term neonates [6]. Furthermore, LPNs are at six to sevenfold higher risk of complications including transient tachypnoea of newborn (TTN) and respiratory distress syndrome (RDS) compared to term neonates [7, 8]. Admission to the neonatal intensive care unit (NICU) for such complications inevitably means separating the mother-infant dyad with the risk of lactation failure and increased parental anxiety. The average duration of hospital stay has been reported to be longer (8.8 vs. 2.2 days), accounting for 10-fold higher cost of care in LPNs vs. term neonates [9]. Overall, the importance of reducing the enormous health burden especially due to respiratory complications in LPNs cannot be overemphasised.

Based on the results of the Antenatal Late Preterm Steroids (ALPS) study, the American College of Obstetricians and Gynaecologists’ (ACOG) guidelines recommend ANC between 34–36\(\frac{1}{2}\) weeks of gestation for reducing neonatal respiratory morbidity, particularly TTN [2, 10]. A recent systematic review and meta-analysis including 3 RCTs (n = 3200) found that ANC reduced the risk of TTN (RR: 0.72, 95% CI: 0.56 to 0.92), severe RDS (RR: 0.60, CI: 0.33–0.94), and need for surfactant (RR: 0.61CI: 0.38 to 0.99) in LPNs. However, the risk of hypoglycaemia was significantly higher (RR: 1.61, CI: 1.38–1.87) in neonates exposed to ANC [11].

Data on these outcomes was available from only 2 of the 3 included RCTs with the ALPS study accounting for 2800 of the 3200 neonates included in this meta-analysis [10]. Importantly, none of these trials reported neonatal long-term neurodevelopmental outcomes.
Considering the difficulties in balancing short-term gains vs. potentially serious long-term adverse effects there is no international consensus for prophylactic ANC at 34 to 36 weeks’ gestation despite the ACOG recommendations [12, 13]. Given the clinical significance of this issue, we aimed to conduct a systematic review on the effects of ANC on LPNs.

Materials and methods

The Cochrane methodology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct and report this systematic review respectively [14, 15]. Ethics approval was not required. We have not registered the protocol with PROSPERO or any other database.

Participants

Inclusion criteria. Neonates born between (34–36+6 weeks) of gestation.

Exclusion criteria. Major chromosomal and congenital anomalies.

Intervention. Antenatal glucocorticosteroids of any type (e.g. Betamethasone, Dexamethasone), dose (single/multiple), and duration vs. placebo/control.

Outcomes. Primary. (1) Need for any respiratory support (Mechanical ventilation, CPAP, high flow) or oxygen (2) Hypoglycaemia: Blood glucose level <2.6 mmol/l or as defined by the authors of included studies.

Secondary. (1) Need for resuscitation at birth: Requirement of any intervention including positive pressure ventilation, CPAP, facial oxygen (defined as the free flow of oxygen near the nostrils by a catheter or mask) only in the delivery room immediately after birth (not in NICU) (2) Admission to NICU (3) TTN: Tachypnoea, chest x-ray showing increased perihilar intestinal marking or fluid in the fissure. (4) RDS: Clinical signs of respiratory distress such as tachypnoea, rib recessions, grunt, requirement of oxygen, with reticulogranular pattern on chest x-ray (5) Mortality: Death before discharge from the NICU during the first admission after birth (6) Need for mechanical ventilation (7) Need for surfactant: (8) Developmental follow up outcomes (9) Adverse effects including sepsis, and seizures.

Search strategy. We searched MEDLINE (from 1966), EMBASE (from1980), CINAHL and Cochrane Central Register of Controlled Trials initially in Dec 2019 and May 2020 for published studies. We used the following search terms in various combinations: a) Population: Neonate(s), newborn(s), infant, premature, late preterm b) Intervention: Antenatal corticosteroids, adrenocortical stimulating hormone, Betamethasone, Celestone, Dexamethasone, c) Publication type: “Randomized controlled Trial, Controlled Trial”, or “Clinical Trial”. Online abstracts of Pediatric Academic Society (PAS) meetings were reviewed from 2002. Abstracts of conference proceedings including Perinatal Society of Australia and New Zealand (PSANZ), European Academy of Paediatric Societies, and the British Maternal and Fetal Medicine Society were searched in EMBASE. We searched ‘Google Scholar’ for articles that might not have been cited in the standard medical databases. The reference lists of identified studies and reviews were searched to identify additional eligible studies. We also searched www.clinicaltrials.gov and Australian New Zealand trial registry (www.anzctr.org.au) for ongoing studies. No language restriction was applied. Reviewers MD, SP and RM (librarian) conducted the literature search independently.

Study selection. Both reviewers (MD and SP) independently selected studies for inclusion in the review. First, the records were screened according to the titles and abstracts. Full texts of the selected articles were then retrieved and assessed for inclusion according to the pre-specified selection criteria.
Data extraction and management. Reviewers MD and SP extracted the data independently, using a data collection form. We included the information about authors, year of publication, the country where the study was conducted, setting, inclusion and exclusion criteria, participants characteristics, type of steroids (betamethasone or dexamethasone) used, outcome measures (need for respiratory support, hypoglycaemia, RDS, TTN, neonatal resuscitation, admission to neonatal unit, mortality and developmental follow up) and their definitions. We checked the number of participants allocated to each arm, methods of analysis, loss to follow up and reasons for the same. For dichotomous outcomes, the number of patients with the event and the number of patients analysed in each treatment group was recorded. For continuous outcomes, we recorded the mean and standard deviations. Both reviewers verified the information about study design and outcomes. Discrepancies were resolved by discussion and consensus.

Assessment of Risk of Bias (ROB). Both reviewers (MD and SP) assessed the ROB in each included trial for the following seven components: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases. For each of these components, they assigned ratings of high, low or unclear ROB [16]. Differences in judgements were resolved by discussion.

Data synthesis. Meta-analysis was conducted using Review Manager 5.4 [Cochrane Collaboration, Nordic Cochrane Centre], with ‘intention to treat analysis’. Heterogeneity between trials was assessed by visual examination of the forest plot to check for overlapping of confidence intervals (CI), Chi² test and I² statistics. We used random-effects model (REM) assuming high heterogeneity. However, results were also compared using fixed-effect model (FEM). Categorical and continuous measures of effect size were expressed as risk difference (RR) (Mantel Haenszel method) and mean difference (MD) (Inverse Variance method) respectively. Sensitivity analysis was planned for studies with low ROB. Subgroup analyses were planned by neonatal gestation at birth (34, 35, 36 weeks), mode of delivery (vaginal or caesarean section) and presence of maternal gestational diabetes.

Assessment of publication bias. We planned to assess publication bias using a funnel plot [17].

Grading the evidence and summary of findings. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for assessment and Grade pro guidelines development tool to create the summary of findings table for reporting the level of evidence (LOE) [18, 19]. Evidence from RCTs was considered as high quality. We graded the evidence in the following domains: ROB, inconsistency, indirectness, imprecision and publication bias. The evidence was downgraded one level for serious and two levels for very serious limitation.

Results
The literature search retrieved 830 potentially relevant citations (Fig 1). Total of 203 citations were removed as duplicate. After carefully reviewing the abstracts and titles 598 citations were excluded. Total 29 citations were read in details and 22 were excluded for reasons mentioned in the flow chart. Finally, 7 RCTs including 4144 neonates whose mothers received ANC between 34–36+6 weeks’ gestation were eligible for inclusion in the systematic review [10, 20–25]. The type, dose and duration of ANC prophylaxis varied in these 7 RCTs (Dexamethasone: 4, Betamethasone: 3). Five studies provided data for the primary outcome of need for any respiratory support [10, 20–22, 25] whereas only 4 reported on hypoglycemia [10, 20, 21, 25]. The ALPS study by Gyamfi-Bannerman provided data for all outcomes included in this review [10]. The
Characteristics of the included studies are shown in Table 1. The trials by Gyamfi-Bannerman and Porto carried low ROB in most of the domains [10, 20] whereas those by Attawattanakul, Balci, Kasab, Mirzamoradi and Ontela, carried high to unclear ROB [21–25] (Fig 2).

Primary outcomes

1. Need for any respiratory support: Five RCTs that included 3844 neonates (ANC: 1941, Control: 1903) reported this outcome [10, 20–22, 25]. Need for any respiratory support was significantly less in the ANC vs. control group neonates [ANC: 11% vs. Control: 16%]. Meta-analysis confirmed these findings [RR = 0.68(0.47–0.98), p = 0.04; Heterogeneity: Chi² = 8.84, I² = 55%; LOE: Moderate] (Fig 2). The number needed to treat (NNT) for preventing one case of respiratory support was 20 (Fig 3).

2. Hypoglycaemia: Four studies that reported this outcome included 3604 neonates (ANC: 1821, Control: 1783) [10, 20, 21, 25]. Incidence of hypoglycaemia was significantly high in
the ANC vs. control group (ANC: 20% vs. Control: 12.5%). Meta-analysis confirmed these findings \[RR = 1.61(1.38–1.87), p<0.00001; Heterogeneity: \chi^2 = 0.40, I^2 = 0%; LOE: High\] (Fig 3). The number needed for harm for hypoglycemia was 13 (Fig 4).

**Secondary outcomes**

1. **Need for resuscitation at birth** [only in delivery room immediately after birth (not in NICU)]: The data for this outcome was available from 6 studies that included 3871 neonates (ANC: 1948, Control: 1923) [10, 21–25]. Need for resuscitation at birth was significantly less in the ANC vs. control group neonates [ANC: 10% vs. Control: 16.5%]. Meta-analysis
confirmed these findings [RR = 0.63(0.42–0.95), p = 0.03; Heterogeneity: Chi² = 8.73, I² = 43%; LOE: Low]. (S1 Fig) NNT for this outcome was 16.

2. Admission to NICU: Six studies that reported this outcome included 3944 neonates (ANC: 1991, Control: 1953) [10, 20–22, 24, 25]. There was no difference in admission to NICU in the ANC vs. control group neonates (ANC: 32% vs. Control: 38%). Meta-analysis confirmed these findings [RR = 0.84 (0.59–1.19), p = 0.32; Heterogeneity: Chi² = 18.44, I² = 73%; LOE: Low]. (S2 Fig)
3. **TTN**: The incidence of TTN was reported in 5 RCTs including 3844 neonates (ANC: 1941, C: 1903) [10, 20–22, 25]. TTN was less in the ANC vs. control group (ANC: 10% vs. Control: 11.5 but was not statistically significant [RR = 0.90 (0.66–1.24) p = 0.53; $\chi^2 = 7.57$, $I^2 = 47%$; LOE: Low]. (S3 Fig)

4. **RDS**: All seven studies reported this outcome included 4143 neonates (ANC: 2090, C: 2053) [10, 20–25]. Incidence of RDS was less in the ANC vs. control group (ANC: 4% vs. Control: 7%) but was not statistically significant [RR = 0.64 (0.35–1.17), p = 0.15; $\chi^2 = 13.55$, $I^2 = 56%$; LOE: Low]. (S4 Fig)

5. **Mortality**: Three studies that reported this outcome included 3200 neonates (ANC: 1821, Control: 1783) [10, 20, 24]. Mortality was similar in the ANC vs. control group neonates (ANC: 1% vs. Control: 1%). Meta-analysis confirmed these findings [RR = 0.94 (0.04–23.80), p = 0.97; Heterogeneity: $\chi^2 = 2.27$, $I^2 = 56%$; LOE: Very Low]. (S5 Fig)

6. **Need for mechanical ventilation**: The data for this outcome was available from 4 studies that included 3650 neonates (ANC: 1845, Control: 1805) [10, 20–22]. Need for mechanical

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**Fig 3. Effect of ANC on need for any respiratory support.**

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**Fig 4. Effect of ANC on hypoglycemia.**

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ventilation was 21% in ANC vs. 27% in control group. Meta-analysis showed no difference between the two groups \( [RR = 0.78 (0.51–1.19), p = 0.25; \text{Heterogeneity: } \text{Chi}^2 = 1.09, I^2 = 0\%; \text{LOE: Moderate}] \). (S6 Fig)

7. **Need for Surfactant:** The data for this outcome was available from 3 studies that included 3340 neonates (ANC: 1690, Control: 1650) [10, 20, 22]. Need for surfactant was 1.5% in ANC vs. 3.2% in control group. Meta-analysis showed no difference between the two groups \( [RR = 0.45(0.11–1.84), p = 0.27; \text{Heterogeneity: } \text{Chi}^2 = 3.95, I^2 = 49\%; \text{LOE: Very Low}] \). (S7 Fig)

8. **Developmental follow up:** None of the included studies reported data on this outcome.

9. **Adverse effects:** Apart from neonatal hypoglycaemia none of the included studies reported any other adverse effects such as neonatal sepsis, and seizures.

**Sensitivity analysis.** Results of the sensitivity analysis including only studies with low ROB (Gyamfi- Bannerman and Porto et al) showed no difference in any respiratory support between ANC vs. control group, hypoglycaemia was more, whereas need for resuscitation at birth and surfactant therapy were significantly less in ANC group [10, 20] (S1 Table).

**Subgroup analysis.** This was not possible due to lack of stratified data based on gestational age, mode of delivery and maternal diabetes.

**Analysis using fixed effect model.** The results of this comparative analysis showed that majority of the outcomes including both primary outcomes were similar with both models. However, the fixed effect model showed admission to NICU, need for surfactant, RDS and TTN were significantly less in ANC group. (S2 Table)

**Summary of findings table and publication bias.** For the primary outcome of need for any respiratory support, the evidence was graded as moderate whereas it was deemed high for hypoglycaemia. For secondary outcomes the evidence was deemed as very low to moderate. (Table 2) Publication bias couldn’t be ruled out due to a small number of trials [26].

**Quality of evidence GRADE**

1. **High:** Risk of bias: not serious, Inconsistency: Not Serious, Indirectness: Not serious, Imprecision: Not serious, Other considerations: None
2. **Moderate**: Risk of bias: not serious, Inconsistency: Serious, Indirectness: Not serious, Imprecision: Not serious, Other considerations: None
3. **Moderate**: Risk of bias: not serious, Inconsistency: Not Serious, Indirectness: Not serious, Imprecision: serious, Other considerations: None
4. **Low**: Risk of bias: Serious, Inconsistency: Serious, Indirectness: Not serious, Imprecision: Not serious, Other considerations: None
5. **Low**: Risk of bias: Not Serious, Inconsistency: Serious, Indirectness: Not serious, Imprecision: serious, Other considerations: None
6. **Low**: Risk of bias: Serious, Inconsistency: Not Serious, Indirectness: Not serious, Imprecision: serious, Other considerations: None
7. **Very Low**: Risk of bias: serious, Inconsistency: Serious, Indirectness: Non serious, Imprecision: Serious, Publication bias: Not serious
Table 2. Summary of finding for pooled data as per GRADE guidelines.

| Outcome                        | Absolute risk | Relative effect | Number of participants | Quality of evidence |
|--------------------------------|---------------|-----------------|------------------------|---------------------|
| **Effect of ANC on**           |               |                 |                        |                     |
| Any respiratory support        | 160 per 1,000 | RR 0.68 (0.47 to 0.98) | 3844 (5 RCTs)          | Moderate*           |
| Hypoglycemia                   | 125 per 1000  | RR 1.61 (1.38 to 1.87) | 3604 (4 RCTs)          | High                |
| Need for resus at birth (only in delivery room immediately after birth (not in NICU)] | 165 per 1,000 | RR 0.63 (0.42 to 0.95) | 3871 (6 RCTs) | Low*                  |
| Admission to NICU              | 381 per 1,000 | OR 0.84 (0.59 to 1.19) | 3944 (6 RCTs)          | Low*                |
| TTN                            | 114 per 1,000 | RR 0.90 (0.66 to 1.24) | 3844 (5 RCTs)          | Low**               |
| RDS                            | 68 per 1,000  | RR 0.64 (0.35 to 1.17) | 4143 (7 RCTs)          | Moderate*           |
| Mortality                      | 1 per 1,000   | RR 0.94 (0.04 to 23.80) | 3200 (3 RCTs) | Very Low* |
| Need for mechanical ventilation| 27 per 1,000  | RR 0.78 (0.51 to 1.19) | 3650 (4 RCTs) | Moderate* |
| Need for Surfactant            | 32 per 1000   | RR 0.45 (0.11 to 1.84) | 3340 (3RCT)           | Very Low* |

Abbreviations: ANC: Antenatal corticosteroids, CI: Confidence interval, GRADE: Grading of Recommendations Assessment, Development and Evaluation, NICU: Neonatal intensive care unit, RDS: respiratory distress syndrome, RR: Relative risk, RCT: Randomised control trial, TTN: Transient tachypnoea of newborn

8. **Very Low**: Risk of bias: not serious, Inconsistency: Serious, Indirectness: Non serious, Imprecision: Very serious, Other considerations: None

**Discussion**

Our systematic review showed that exposure to ANC was beneficial in reducing the need for respiratory support but with the increased risk of hypoglycemia in neonates born at late pre-term gestation. Exposure to ANC also reduced the need for resuscitation at birth. ANC had no impact on RDS, TTN, admission to NICU, need for mechanical ventilation, surfactant therapy and mortality. None of the included trials reported long term follow up data.

Respiratory morbidities in LPNs relate to developmental immaturity of the lungs. The mechanisms for benefits of ANC include enhanced alveolar differentiation with the induction of type 2 pneumocytes and activation of endothelial nitric oxide synthase [27, 28]. It is postulated that similar to term gestation, ANC exposure at late preterm gestation accelerates coordinated organ development sequence in response to endogenous rise in fetal glucocorticoids [29, 30]. Experimental studies show that the improvement in lung function after ANC exposure are due to an increase in the absorption of fetal lung fluid, thinning of alveolar septae, and synthesis of surfactant proteins and phospholipids [30, 31].

The benefits of ANC need to be considered in the context of their potential adverse effects. ANC exposure is associated with reduced brain mass, delayed myelination, decreased maturation of peripheral nerves, increased impairment of hypothalamopitutory axis and impaired programmed apoptosis in animal studies [30, 32–34]. A follow-up study of participants from ASTECS trial reported two-fold increase in teacher-reported low academic ability in children.
(age 8–15 years) exposed to betamethasone as term infants born by an elective caesarean section. There were no significant differences in general health, behaviour and academic achievements between exposed vs. unexposed groups. However, only 51% response rate diminishes the validity of these finding [35].

A recent population-based study from Finland using nationwide registries of all (term and preterm) singleton live births found that ANC exposure was associated with a significant increase [adjusted hazard ratio (aHR): 1.33; 95% CI (1.26–1.41] in mental and behavioural disorders in children at 5.8 (interquartile-range, 3.1–8.7) years. The incidence of these disorders was high in term neonates exposed to ANC vs. controls [aHR: 1.38; (95% CI: 1.21–1.58)]. The incidence of these adverse outcomes was higher (14.59% vs 10.71%) but statistically non-significant [aHR: 1.00; (95% CI: 0.92–1.09)] in preterm neonates [36].

It is important to consider the implications of our results for clinical practice. The NNT to prevent one case of any respiratory support and need for resuscitation at birth was 20 and 16 respectively. In comparison, the NNT for harm was 13 for neonatal hypoglycaemia. LPNs are at high risk of hypoglycaemia due to poor substrate and underdeveloped compensatory response. The increased risk of neonatal hypoglycaemia might be due to transient hyperinsulinaemia following maternal hyperglycaemia in response to ANC [37].

The definition of neonatal hypoglycaemia varied in the RCTs included in our review. The ALPS study defined it as blood glucose <2.2mmol/L [10]. This raises the possibility that many neonates with hypoglycaemia may have been missed considering the widely accepted definition of hypoglycaemia is blood glucose <2.6 mmol/L. Hypoglycaemia is an independent predictor of poor neurodevelopmental outcomes in neonates. A large prospective cohort study from Sweden (n = 101,060) found that, in infants with early moderate hypoglycaemia (<6 hours after birth, blood glucose <2.2mmol/L), the risk of any adverse neurological or neurodevelopmental outcome and cognitive developmental delay was increased by two [OR 1.94 (1.30–2.89)] and three [OR 3.17 (1.35–7.43)] fold respectively compared to normoglycaemic infants [38].

A recent systematic review of non-RCTs (N = 1395) showed that neonatal hypoglycaemia was associated with visual-motor impairment (n = 508; OR = 3.46, 95% CI = 1.13–10.57) and executive dysfunction (n = 463; OR = 2.50, 95% CI = 1.20–5.22) in early childhood. In mid-childhood, the odds of neurodevelopmental impairment (n = 54; OR = 3.62, 95% CI = 1.05–12.42), low literacy (n = 1,395; OR = 2.04, 95% CI = 1.20–3.47) and numeracy (n = 1,395; OR = 2.04, 95% CI = 1.21–3.44) were significantly higher [39].

Inability to predict spontaneous preterm birth means inevitable unwarranted exposure to ANC in a significant number of late preterm pregnancies, which do not result in late preterm delivery. The ALP study reported that 16% of pregnancies with ANC exposure went on to deliver at term gestation [28]. Overall, potential long-term neurodevelopmental adverse effects of ANC must receive due attention considering that none of the included trials till date have reported such data.

The limitations of using Apgar scores as a primary outcome need to be discussed. Apgar score at 1 minute does not correlate with mortality and long-term neurodevelopmental outcomes [40]. Apgar scores can be low in otherwise well preterm neonates with no evidence of perinatal asphyxia [40–42]. Moreover, being a continuous measure, it is much more likely that differences would be noted regardless of their clinical importance.

The strengths of our review include its robust methodology, inclusions of only RCTs, large sample size and use of GRADE guidelines for summarizing the level of evidence. We conducted sensitivity analysis excluding the studies with high ROB. Compared to the previous systematic review we have provided data from 4 more RCTs (n~1000), all from developing countries. The provision of the NNT for both, benefit and harm, is important for guiding
research and clinical practice. The limitations of our review include the fact that the pooled results are still influenced by the large ALPS trial [10]. The included RCTs differ in the definitions of various outcomes, type of steroids, and their dosage. Furthermore, analysis stratified by gestation, mode of delivery or maternal diabetic status was not possible.

Conclusions

Our systematic review showed that exposure to ANC was beneficial in reducing the need for respiratory support but with an increased risk of hypoglycemia in neonates born at late preterm gestation. Exposure to ANC also reduced the need for resuscitation at birth.

In summary, moderate to low-quality evidence indicates that ANC exposure reduced the need for respiratory support and increased the risk of neonatal hypoglycaemia in LPNs. ANC reduced need for resuscitation at birth in LPNs. The increased risk of neonatal hypoglycaemia is a serious concern. Pragmatic and adequately powered multicentre RCTs with long-term follow up assessing neonatal neurodevelopmental outcomes are needed to assess the efficacy and safety of ANC. Stratification by gestation, mode of delivery, maternal diabetes and other risk factors for respiratory distress is desirable in such trials. Pending results of such trials rigorous monitoring, treatment, and follow up of LPNs exposed to ANC is critical, more so in the context of hypoglycemia.

Supporting information

S1 Fig. Effect of ANC on need for resuscitation at birth.
(TIF)

S2 Fig. Effect of ANC on admission to nursery.
(TIF)

S3 Fig. Effect of ANC on TTN.
(TIF)

S4 Fig. Effect of ANC on RDS.
(TIF)

S5 Fig. Effect of ANC on mortality.
(TIF)

S6 Fig. Effect of ANC on mechanical ventilation.
(TIF)

S7 Fig. Effect of ANC on need for surfactant.
(TIF)

S1 Table. Results of sensitivity analysis based on ROB.
(DOCX)

S2 Table. Results of analysis by fixed and random effects model.
(DOCX)

S3 Table. Compliance of PRISMA guidelines.
(DOC)

S1 File. Search strategy.
(DOCX)
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**Submission declaration:** All authors declare that the work submitted has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder.

**Author Contributions**

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**References**

1. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung matura-
   tion for women at risk of preterm birth. Cochrane Database Syst Rev. 2017; 3:CD004454. https://dx.doi.
   org/10.1002/14651858.CD004454.pub3 PMID: 28321847.

2. Practice CoO. Committee Opinion No. 713: antenatal corticosteroid therapy for fetal maturation. Obstet-
   rics and gynecology. 2017; 130(2):e102. https://doi.org/10.1097/AOG.0000000000002237 PMID:
   28742678.

3. Skoll A, Boutin A, Bujold E, Burrows J, Crane J, Geary M, et al. No. 364-Antenatal corticosteroid therapy
   for improving neonatal outcomes. Journal of Obstetrics and Gynaecology Canada. 2018; 40(9):1219–39.
   https://doi.org/10.1016/j.jogc.2018.04.018 PMID: 30268316.

4. Delnord M, Zeitlin J. Epidemiology of late preterm and early term births—An international perspective.
   Semin Fetal Neonatal Med. 2019; 24(1):3–10. Epub 2018/10/13. https://doi.org/10.1016/j.siny.2018.09.
   001 PMID: 30309813.

5. Raju T. The "Late Preterm" Birth—Ten Years Later. Pediatrics. 2017; 139(3). Epub 2017/02/06. https://
   doi.org/10.1542/peds.2016-3331 PMID: 28148728.

6. Boyle EM, Johnson S, Manktelow B, Seaton SE, Draper ES, Smith LK, et al. Neonatal outcomes and
   delivery of care for infants born late preterm or moderately preterm: a prospective population-based
   study. Archives of disease in childhood Fetal and neonatal edition. 2015; 100(6):F479–F85. Epub 2015/
   04/01. https://doi.org/10.1136/archdischild-2014-307347 PMID: 25834169.

7. Shapiro-Mendoza CK, Tomaszek KM, Kotchuck M, Barfield W, Nannini A, Weiss J, et al. Effect of
   late-preterm birth and maternal medical conditions on newborn morbidity risk. Pediatrics. 2008; 121(2):
   e223–32. Epub 2008/02/05. https://doi.org/10.1542/peds.2006-3629 PMID: 18245397.

8. Barfield W LK. Late Preterm Infants. Weisman L KM, editor: Up to date; 2020 23/06/2020.

9. McLaurin KK, Hall CB, Jackson EA, Owens OV, Mahadevia PJ. Persistence of morbidity and cost differ-
   ences between late-preterm and term infants during the first year of life. Pediatrics. 2009; 123(2):653–9.
   Epub 2009/01/28. https://doi.org/10.1542/peds.2008-1439 PMID: 19171634.
10. Gyamfi-Bannerman C, Thorn EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, et al. Antenatal Beta-methasone for Women at Risk for Late Preterm Delivery. N Engl J Med. 2016; 374(14):1311–20. https://dx.doi.org/10.1056/NEJMoa1516783 PMID: 26842679.

11. Sacconne G, Berghella V. Antenatal corticosteroids for maturity of term or near term fetuses: systematic review and meta-analysis of randomized controlled trials. BMJ-British Medical Journal. 2016; 355:10. https://doi.org/10.1136/bmj.j0544 PMID: 27733360.

12. Jobe AH, Goldenberg RL. Antenatal corticosteroids: an assessment of anticipated benefits and potential risks. Am J Obstet Gynecol. 2018; 219(1):62–74. Epub 2018/04/10. https://doi.org/10.1016/j.ajog.2018.04.007 PMID: 29630886.

13. Kamath-Rayne BD, Rozance PJ, Goldenberg RL, Jobe AH. Antenatal corticosteroids beyond 34 weeks gestation: What do we do now? Am J Obstet Gynecol. 2016; 215(4):423–30. Epub 2016/06/28. https://doi.org/10.1016/j.ajog.2016.06.023 PMID: 27342043.

14. Lefebvre C ME GJ. Searching for studies. Cochrane handbook for systematic reviews of interventions New York: Wiley. 2011; Version 5.1.0.

15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of internal medicine. 2009; 151(4):W-65-W-94.

16. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. Bmj. 2011; 343:d5928. Epub 2011/10/20. https://doi.org/10.1136/bmj.d5928 PMID: 22008217.

17. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj, 2011; 343:d4002. Epub 2011/07/26. https://doi.org/10.1136/bmj.d4002 PMID: 21784880.

18. Guyatt GH, Oxman AD, Santesio N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing Summary of Findings tables—binary outcomes. Journal of clinical epidemiology. 2013; 66(2):158–72. https://doi.org/10.1016/j.jclinepi.2012.01.012 PMID: 22609141.

19. Schünemann H BJ, Guyatt G, Oxman A. GRADE handbook for grading quality of evidence and strength of recommendations. www.guidelinedevelopment.org/handbook. October 2013.

20. Porto AM, Coutinho IC, Correia JB, Amorim MM. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. Bmj, 2011; 342:d1696. https://dx.doi.org/10.1136/bmj.d1696 PMID: 21487057.

21. Ontela V, Dorairaian G, Bhat VB, Chinnakali P. Effect of Antenatal Steroids on Respiratory Morbidity of Late Preterm Newborns: A Randomized Controlled Trial. J Trop Pediatr. 2018; 64(6):531–8. https://dx.doi.org/10.1093/tropmed/fty001 PMID: 29365196.

22. Mirzamoradi M, Hasani Nejhad F, Jamali R, Heidar Z, Bakhtiyari M. Evaluation of the effect of antenatal betamethasone on neonatal respiratory morbidities in late preterm deliveries (34–37 weeks). Journal of Maternal Fetal and Neonatal Medicine. 2018. http://dx.doi.org/10.1080/14767058.2018.1554051

23. Kassab F. The effect of antenatal steroids on fetal outcome after the 34 weeks of pregnancy in women at high risk of preterm labor. AAMJ. 2013; 10(4):262–72.

24. Balci O, Ozdemir S, Mahmoud AS, Acar A, Colakoglu MC. The effect of antenatal steroids on fetal lung maturation between the 34th and 36th week of pregnancy. Gynecologic and obstetric investigation. 2010; 70(2):95–9. https://doi.org/10.1159/000295898 PMID: 20234136.

25. Attawattanakul N, Tansupswatdikul P. Effects of antenatal dexamethasone on respiratory distress in late preterm infant: a randomized controlled trial. Thai Journal of Obstetrics and Gynaecology. 2015; 23(1):25–33.

26. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. Bmj, 2011; 343:d4002. Epub 2011/07/26. https://doi.org/10.1136/bmj.d4002 PMID: 21784880.

27. Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol. 1995; 173(1):254–62. Epub 1995/07/01. https://doi.org/10.1016/0002-9378(95)90210-4 PMID: 7631700.

28. Haviv HR, Said J, Mol BW. The place of antenatal corticosteroids in late preterm and early term births. Semin Fetal Neonatal Med. 2019; 24(1):37–42. Epub 2018/10/17. https://doi.org/10.1016/j.siny.2018.10.001 PMID: 30322825.

29. Liggins GC. The role of cortisol in preparing the fetus for birth. Reprod Fertil Dev. 1994; 6(2):141–50. Epub 1994/01/01. https://doi.org/10.1071/rd9940141 PMID: 7991781.

30. McKinlay CJ, Dalziel SR, Harding JE. Antenatal glucocorticoids: where are we after forty years? J Dev Orig Health Dis. 2015; 6(2):127–42. Epub 2014/12/04. https://doi.org/10.1017/S2040174414000579 PMID: 25466556.
31. Polglase GR, Nitsos I, Jobe AH, Newnham JP, Moss TJ. Maternal and intra-amniotic corticosteroid effects on lung morphometry in preterm lambs. Pediatr Res. 2007; 62(1):32–6. Epub 2007/05/23. https://doi.org/10.1203/PDR.0b013e3180686433 PMID: 17515831.

32. Huang WL, Beazley LD, Quinlivan JA, Evans SF, Newnham JP, Dunlop SA. Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol. 1999; 94(2):213–8. Epub 1999/08/04. https://doi.org/10.1016/s0029-7844(99)00265-3 PMID: 10432130.

33. Antonow-Schlorke I, Helgert A, Gey C, Coksayan T, Schubert H, Nathanielsz PW, et al. Adverse effects of antenatal glucocorticoids on cerebral myelination in sheep. Obstet Gynecol. 2009; 113(1):142–51. Epub 2008/12/24. https://doi.org/10.1097/AOG.0b013e3181921924 PMID: 19104370.

34. Kapoor A, Petropoulos S, Matthews SG. Fetal programming of hypothalamic-pituitary-adrenal (HPA) axis function and behavior by synthetic glucocorticoids. Brain Res Rev. 2008; 57(2):586–95. Epub 2007/08/25. https://doi.org/10.1016/j.brainresrev.2007.06.013 PMID: 17716742.

35. Stutchfield PR, Whitaker R, Gliddon AE, Hobson L, Kotecha S, Doull IJ. Behavioural, educational and respiratory outcomes of antenatal betamethasone for term caesarean section (ASTECS trial). Arch Dis Child Fetal Neonatal Ed. 2013; 98(3):F195–200. Epub 2013/02/21. https://doi.org/10.1136/archdischild-2012-303157 PMID: 23424017.

36. Räikkönen K, Gissler M, Kajantie E. Associations Between Maternal Antenatal Corticosteroid Treatment and Mental and Behavioral Disorders in Children. Jama. 2020; 323(19):1924–33. Epub 2020/05/20. https://doi.org/10.1001/jama.2020.3937 PMID: 32427304.

37. Kamatkar S, Jobe A. Antenatal Late Preterm Steroids (ALPS): are we ready to accept it? J Perinatol. 2017; 37(6):624–5. Epub 2017/03/24. https://doi.org/10.1038/jp.2017.25 PMID: 28333158.

38. Wickström R, Sköld B, Petersson G, Stephansson O, Altman M. Moderate neonatal hypoglycemia and adverse neurological development at 2–6 years of age. Eur J Epidemiol. 2018; 33(10):1011–20. Epub 2018/07/22. https://doi.org/10.1007/s10654-018-0425-5 PMID: 30030683.

39. Shah R, Harding J, Brown J, McKinlay C. Neonatal Glycaemia and Neurodevelopmental Outcomes: A Systematic Review and Meta-Analysis. Neonatology. 2019; 115(2):116–26. Epub 2018/11/09. https://doi.org/10.1159/000492659 PMID: 30408811.

40. The Apgar Score. Pediatrics. 2015; 136(4):819–22. Epub 2015/09/30. https://doi.org/10.1542/peds.2015-2651 PMID: 26416932.

41. Catlin EA, Carpenter MW, Bramn BST, Mayfield SR, Shaul PW, Goldstein M, et al. The Apgar score revisited: influence of gestational age. J Pediatr. 1986; 109(5):865–8. Epub 1986/11/01. https://doi.org/10.1016/s0022-3476(86)80715-6 PMID: 3772665.

42. Hegyi T, Carbone T, Anwar M, Ostfeld B, Hiatt M, Koons A, et al. The agpar score and its components in the preterm infant. Pediatrics. 1998; 101(1 Pt 1):77–81. Epub 1998/01/17. https://doi.org/10.1542/peds.101.1.77 PMID: 9417155.