

## **Effectiveness of Antenatal Corticosteroids in Reducing Neonatal Morbidity in Preterm Birth: A Systematic Review**

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**Abstract:** Background: The role of preterm birth in contributing to the neonatal's worldwide mortality and morbidity, remains one of the leading causes. The use of antenatal corticosteroids (ACS) greatly enhances the fetal lung maturation and decreases the incidence of these problems in newborns born before 37 weeks of gestation. In spite of the proven efficacy of ACS, there are still unresolved and many debated questions pertaining to the timing, dosing, and merits and risks in certain population subsets, especially in multiple gestations and late preterm births.

Methodology: Including primary research studies like RCTs, cohorts, and observational studies examining the effectiveness of ACS on the reduction of early neonatal morbidity and preterm births, is part of this systematic review. All studies included in this review underwent a detailed search of electronic data bases such as PubMed, Embase and the Cochrane Library. Only the studies published in the English language were incorporated. Based on the predetermined inclusion criteria, the selected data captured study type, the targeted population, the intervention, as well as any significant neonatal outcomes.

Results: Examination of 19 RCTs and numerous big cohort and observational studies showed that in preterm newborns, a single course of ACS significantly lowers the incidence of RDS, IVH, NEC, and neonatal death especially when given within 17 days before birth. The benefit was seen as early as two hours after administration and lasted up to two weeks. Though several courses of ACS did not yield extra benefits and were linked to lower birth weight and head circumference, a single course was still successful among varied maternal and neonatal subgroups. ACS lowered respiratory morbidity but raised the risk of newborn hypoglycemia in late preterm and early term populations. ACS was effective across several gestations and unaffected by maternal BMI.

Conclusion: Antenatal corticosteroids are quite successful in lowering neonatal morbidity and mortality in preterm births; the most benefit comes from doses just before delivery. The data favors the regular application of a single ACS class in women between 24 and 34 weeks gestation who are at danger of preterm birth. Regarding recurring courses and use in late preterm or early term pregnancies, where advantages have to be weighed against possible dangers including hypoglycemia and growth restriction, caution is advised.

### **Introduction**

One of the main causes of neonatal mortality and morbidity worldwide is preterm birth—that is, delivery before 37 weeks of gestation [1–3]. Complications resulting from preterm birth—including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC)—contribute significantly to both short- and long-term adverse

health outcomes in newborns [4, 5]. With a focus on actions that can increase newborn survival and lower morbidity, the management of pregnancies at risk of preterm delivery is still a key priority in perinatal medicine [6, 7].

Among women at risk of preterm birth, antenatal corticosteroids (ACS) have evolved as one of the most successful therapies [8,9]. ACS quickens fetal lung maturation and lowers the frequency and degree of RDS, IVH, and other consequences related with prematurity when given to pregnant women before expected preterm delivery [10,11]. Evidence from randomized controlled trials and systematic evaluations continually shows that a single course of antenatal steroids dramatically lowers the chance of newborn death, respiratory morbidity, and other severe outcomes in preterm infants [12,13]. Although recent data suggest that decreases in neonatal death and morbidity can occur as early as 2 hours after administration and last for up to two weeks, the advantages of ACS are most pronounced when administered between 24 hours and 7 days before birth [14].

Despite the widespread application of ACS therapy in obstetric practice, there are questions about the best timing, dosage regimens, and long-term safety of corticosteroid exposure, especially for newborns born at the extremes of gestational age or after repeated courses. Considering the evolution of perinatal healthcare efforts and the continuous emergence of fresh research, it is high time and warranted that a systematic review is worked on to consider the relevance of antenatal corticosteroids and their impact on the morbidity rates of neonates suffering from prematurity. Stressing on both immediate and protracted ramifications, the current research intends to assess and amalgamate the existing data on the impact of antenatal corticosteroids on reducing morbidity in neonates born preterm. Such an outcome is useful in determining the growing body of research dedicated to the optimal healthcare approach to pregnancies vulnerable to preterm birth and its clinical implications.

## **Methodology**

This research underwent a systematic review while complying with the benchmarking evidence synthesis procedure within the proof-based healthcare model. Upon search of the available electronic databases the Cochrane Library, Embase, and PubMed, and relevant studies were identified. The search strategy applied Medical Subject Headings (MeSH) and the relevant keywords pertaining antenatal corticosteroids, preterm birth, and neonatal mortality, and other relevant combinations. The search strategy was limited to English language publications and the relevant literature within the most recent available date. Inclusion criteria consisted of studies that analyzed the administration of antenatal corticosteroids in women who were deemed to be at risk of preterm birth and who subsequently reported on neonatal morbidity outcomes. Resulted studies had to be either observational studies or randomized controlled trials. Independent of each other, two reviewers examined the titles and abstracts of the studies; for studies that met the criteria for inclusion or were in doubt regarding the eligibility criteria, full-text papers were retrieved.

A standardized form was used to gather data on study design, population features, intervention specifics, control groups, and pertinent neonatal outcomes. Data extraction was done. The incidence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death were among the main results of interest. When available, secondary outcomes including long-term neurodevelopmental handicap were also kept track of.

Based on study design, appropriate tools were used to evaluate the quality of included studies—the Cochrane Risk of Bias instrument for randomized studies and the Newcastle-Ottawa Scale for observational research. Data synthesis was done qualitatively; quantitative meta-analysis was done when enough uniform data were ready. The findings were condensed to offer a general view of how effective antenatal steroids were in lowering neonatal mortality among premature newborns.

## Results

The current review included 19 studies (Figure 1, [8,9,14-30]), including ten studies which is randomized controlled trials [9,14–22], four large cohort and observational studies [23-26], and five subgroup and special population studies [8,27-30].

### Randomized Controlled Trials

Ten randomized controlled trials (RCTs) [9,14–22] found that antenatal corticosteroids (ACS) consistently lower neonatal respiratory morbidity and mortality throughout a range of preterm groups. A single course of ACS was linked to a major decrease in respiratory distress syndrome (RDS) and neonatal death in women at risk of preterm birth; the most noticeable benefit was seen when the treatment was given within 17 days before delivery. Studies focusing on late preterm infants found that betamethasone reduced the need for respiratory support; though an increased incidence of neonatal hypoglycemia was noted [17,22]. Evidence showing antenatal dexamethasone to be helpful in this group further supported the efficacy of ACS in late preterm birth [9,17].

Findings on successive ACS were conflicting. While another trial showed that multiple doses could lower RDS and severe lung disease without affecting growth at discharge [16], multiple courses did not produce more improvements in composite neonatal morbidity and were linked with lower birth weight, length, and head circumference [15,18,19]. In pregnancies complicated by preterm premature rupture of membranes (PPROM), no significant difference in major neonatal outcomes was seen between single and repeated courses of ACS [18].

Crucially, ACS administration showed quick advantages: reductions in mortality were seen as early as two hours post-administration in very premature newborns [14]. Trials in very preterm and early term cesarean populations likewise verified decreases in neonatal mortality and respiratory morbidity, respectively [21]. These RCTs give strong proof favoring the use of ACS to enhance neonatal outcomes in selected early term births (Table 1).

**Table 1. Randomized Controlled Trials**

Study (Year)	Design	Population	Sample Size	Key Outcomes	Main Findings
Murphy et al. (2008) [15]	RCT	Women 25–32 wks, undelivered after 14–21 days of initial ACS	1858	Composite neonatal morbidity, growth	Multiple courses of ACS did not improve outcomes; associated with lower birth weight, length, head circumference.
Norman et al. (2017) [16]	RCT	Women <34 wks, imminent birth	2598	RDS, neonatal death	ACS reduced RDS and neonatal death; optimal benefit when given 1–7 days before birth.
Gyamfi-Bannerman et al. (2016) [17]	RCT	Late preterm	2827	Respiratory outcomes	Betamethasone reduced respiratory support need; increased hypoglycemia.
El-Gawad et al. (2022) [18]	RCT	PPROM, single vs repeated ACS	200	Neonatal outcomes	No significant difference in major neonatal outcomes between single and repeated courses.
Sultana et al. (2023) [9]	RCT	Late preterm	Not stated	Preterm birth outcomes	Antenatal dexamethasone

					effective in late preterm birth.
Crowther et al. (2006)[19]	RCT	Women <32 wks, repeat doses	982	RDS, oxygen use, growth	Repeat doses reduced RDS and severe lung disease; no difference in growth at discharge.
Melamed et al. (2025)[14]	RCT	23–31 wks GA	7950	Mortality, neurologic injury	ACS reduced mortality as early as 2 hours post-administration.
Shivtej (2018) [20]	RCT	Preterm babies <37 wks	110	RDS	Complete course of ACS significantly reduced RDS.
Mwansa-kambafwile et al (2010) [21]	RCT	Very preterm	Not stated	Neonatal mortality, RDS	ACS reduced neonatal mortality and RDS.
DeBolt et al. (2022)[22]	RCT	Early term cesarean	Not stated	Respiratory morbidity	Betamethasone reduced respiratory morbidity in early term cesarean deliveries.

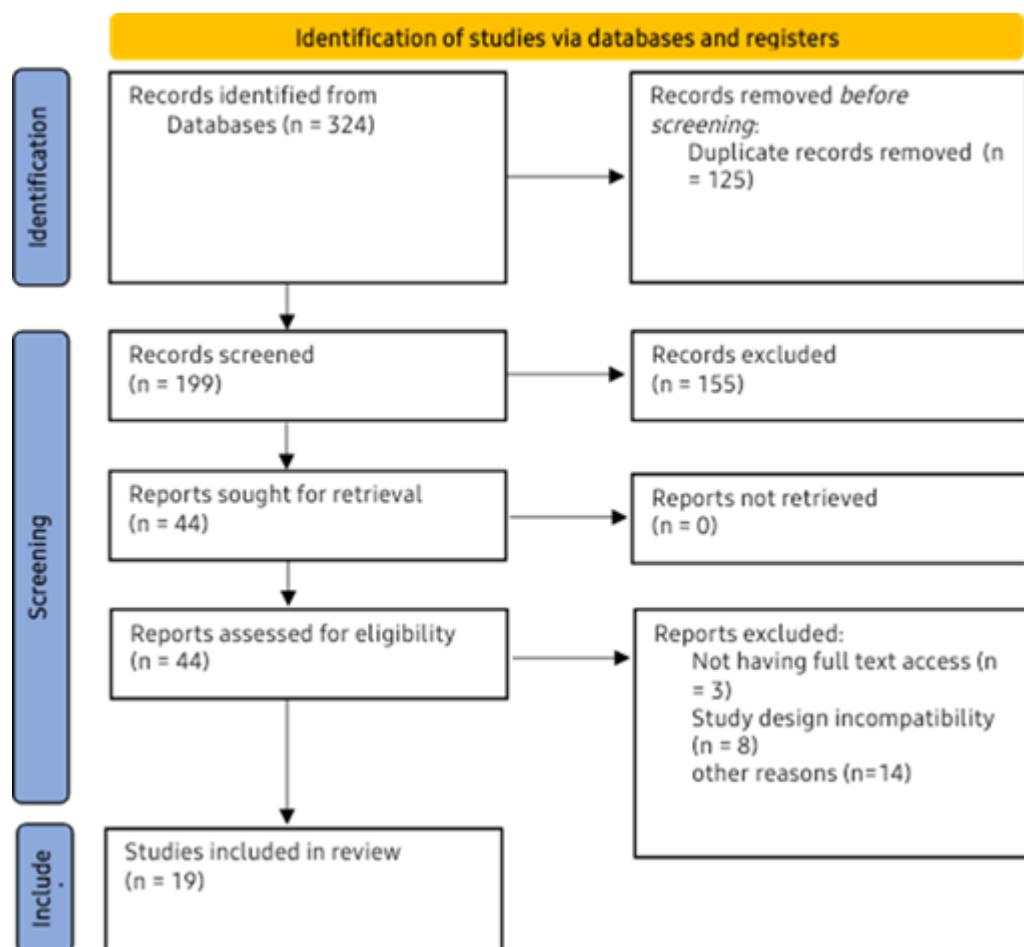


Figure 1: PRISMA flow for including studies

## Large Cohort and Observational Studies

Four large-scale cohort and observational studies [23-26] corroborate the findings of RCTs, indicating that ACS use in women at risk of preterm birth significantly reduces the incidence of RDS and composite neonatal morbidity, regardless of maternal diabetic status [23-26]. In extremely preterm infants (22–25 weeks gestation), ACS exposure was linked to lower rates of death and neurodevelopmental impairment at 18–22 months of age [23,24]. The timing of ACS administration relative to delivery was found to be critical; intervals greater than 14 days, particularly in infants born after 28 weeks, were associated with an increased need for ventilatory support and surfactant use [25]. Additionally, among very low birth weight infants, betamethasone was superior to dexamethasone or no steroids in reducing neonatal death and intraventricular hemorrhage (IVH) [26]. These studies reinforce the substantial benefits of ACS in diverse clinical settings and populations (Table 2).

Table 2. Large Cohort and Observational Studies					
Study (Year)	Design	Population	Sample Size	Key Outcomes	Main Findings
Battarbee et al. (2022) [23]	Cohort	23–33 wks, US hospitals	115,502	RDS, composite morbidity	ACS reduced RDS and morbidity in both diabetics and non-diabetics.
Tyson et al. (2008) [24]	Cohort	22–25 wks, NICHD Network	4446	Death, neurodevelopmental impairment	ACS reduced death and impairment at 18–22 months.
Ring et al. (2007) [25]	Cohort	26–34 wks, singletions	357	Ventilatory support, surfactant use	ACS-to-delivery interval >14 days increased need for support, especially >28 wks.
Lee et al. (2006) [26]	Cohort	VLBW infants, US	11,022	Neonatal death, IVH	Betamethasone reduced neonatal death compared to dexamethasone or no steroids.

## Subgroup and Special Population Studies

Subgroup analyses and studies [8,27-30] in special populations reveal that the effectiveness of ACS extends to multiple gestations and various maternal characteristics. ACS reduced the incidence of RDS in both twins and triplets, although the magnitude of effect varied by plurality [27]. Maternal body mass index (BMI) did not significantly influence the effectiveness of ACS, suggesting broad applicability across weight categories [28]. However, accurately predicting the timing of delivery after ACS administration remains challenging, with a substantial proportion of women delivering more than seven days after treatment [29].

Further, no significant differences were observed in the efficacy of ACS between twins and singletions in terms of morbidity and mortality [30]. In general preterm populations, a single course of ACS was associated with reductions in mortality, RDS, IVH, and necrotizing enterocolitis (NEC) [8]. These findings highlight the versatility and consistent benefit of ACS across various subgroups and clinical scenarios (Table 3).

Table 3. Subgroup and Special Population Studies					
Study (Year)	Design	Population	Sample Size	Key Outcomes	Main Findings
Blickstein et al. (2005) [27]	Observational	Twins, triplets vs singletions	167 twins, 157	RDS	ACS reduced RDS in twins and triplets.

			controls		though effect size varied by plurality.
Hashima et al. (2004) [28]	Observational	Obese vs non-obese women	243	Neonatal outcomes	BMI did not influence ACS effectiveness.
McLaughlin et al. (2003) [29]	Observational	Women <34 wks, Ireland	400	Timing of delivery after ACS	Many women delivered >7 days after ACS; timing accuracy is challenging.
Bae et al. (2023) [30]	Cohort	Twins/singletons, Korea	9531	Morbidity, mortality	No significant difference in ACS effect by plurality.
Bonanno et al. (2012) [8]	Cohort	Preterm infants	3885	Mortality, RDS, IVH, NEC	Single ACS course reduced all adverse outcomes.

## Discussion

Among preterm babies born before 34 weeks of gestation, the findings from this review confirm the well-known function of antenatal corticosteroids (ACS) in enhancing neonatal results [31–33]. Numerous randomized controlled trials and observational studies constantly show that a single course of ACS substantially lowers the risk of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and newborn mortality. With evidence suggesting that decreases in neonatal mortality and serious neurological damage may be seen as early as two hours after administration and persist for up to two weeks, the advantages of ACS are most clear when given 17 days before to delivery.

Still a major element, ACS should be given at the right time. Studies suggest that the maximum advantage is realized between 12 hours and 14 days, same with some earlier studies [34,35]. ACS exposure to birth gap Delays past this period can lessen the protective effects, especially on respiratory results. This stresses the need of exact prediction of preterm birth to maximize the effectiveness of ACS treatment.

Concerning several ACS courses, the data is contradictory. Although some studies show that repeat dosing may help to lower the frequency of RDS and the length of mechanical ventilation, questions remain regarding possible negative consequences on brain development and fetal growth. Animal research reveal that multiple courses may influence myelination in the developing brain, and clinical data point to links with lower birth weight, length, and head circumference [36,37]. Therefore, present guidelines advise limiting repeat courses to specifically chosen situations where the risk of preterm birth stays high following an initial course [38].

Rising focus has been on the administration of ACS in early term and late preterm (34–36 weeks). Randomized studies show that ACS can lower short-term respiratory morbidity in late preterm babies; but, this benefit is balanced by a higher incidence of neonatal hypoglycemia. Significantly, recent long-term follow-up research reveal that at six years of age, late preterm ACS exposure has no negative impact on neurodevelopmental results [39]. Still, when thinking about ACS in these gestational windows, close observation and clinical judgment are required given the risk of hypoglycemia, especially within the first 12 hours of life.

ACS's efficacy in many gestations, including twins and triplets, has been questioned.

While previous meta-analyses did not reach a conclusion, cohort studies and clinical practice guidelines, more recently, endorse the use of ACS for multiples, showing comparable reductions in neonatal mortality and morbidity as seen in singletons [40–42]. Factors such as body mass index (BMI) do not seem to substantially change the effectiveness of ACS, thus confirming its broad applicability across other regions.

Unlike cohorts, long-term follow up data ACS gives peace of mind due to evidence suggesting reduced rates of neurodevelopmental impairment in very preterm infants, and no increase in adverse neurocognitive or behavioral outcomes in childhood for those who underwent single course exposure to ACS [39]. However, ACS is cautionary in settings of use in pregnancies likely to end in term birth, as some studies suggest higher rates of neurocognitive deficits in this population.

## Conclusion

To summarize, the evidence continues to support the case for offering one course of ACS to women in the 24 to 34 weeks of gestation period at risk for preterm birth—along with the targeted timing of administration to shift the advantage as far forward as possible. The administration of repeat courses and timing of administration to late preterm or early term pregnancies should be individualized to minimize the tradeoffs between possible benefits and risks such as newborn hypoglycemia and likely developmental and neurodevelopmental impacts. Future inquiries should focus on improving the definition of optimal dosage, timing, and the long term safety of diverse populations and clinical settings.

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