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Antenatal corticosteroids for fetal lung maturation and prevention of respiratory distress syndrome: a systematic review

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ABSTRACT

Preterm birth remains a major global cause of neonatal morbidity and mortality, frequently leading to respiratory distress syndrome (RDS) due to pulmonary immaturity and surfactant deficiency. Antenatal corticosteroids (ACS) are widely used to accelerate fetal lung maturation and improve neonatal respiratory outcomes. The present systematic review evaluates the physiological mechanisms, clinical effectiveness, and current clinical recommendations for antenatal corticosteroid therapy in the prevention of neonatal RDS. A structured literature review was conducted following the PRISMA framework using major databases including PubMed, Google Scholar, Scopus, and Web of Science. Relevant studies evaluating the use of betamethasone or dexamethasone in pregnant women at risk of preterm birth were screened. Ten high-quality studies, including randomized controlled trials, cohort studies, and meta-analyses, were selected for qualitative synthesis. The findings consistently demonstrate that antenatal corticosteroid therapy significantly reduces the incidence of respiratory distress syndrome, neonatal mortality, intraventricular hemorrhage, and necrotizing enterocolitis. Several landmark trials also confirm benefits in both early and late preterm pregnancies. Physiologically, corticosteroids promote differentiation of type II pneumocytes, enhance surfactant synthesis, and improve pulmonary compliance, thereby facilitating postnatal lung function. Current international guidelines recommend administration of antenatal corticosteroids for women at risk of preterm delivery within seven days between 24 and 34 weeks of gestation. Overall, antenatal corticosteroid therapy remains a cornerstone of modern perinatal care. Future research should focus on optimizing dosing strategies and evaluating long-term neurodevelopmental outcomes associated with repeated exposure.

Keywords: Antenatal Corticosteroids; Fetal Lung Maturation; Neonatal Mortality; Preterm Birth; Respiratory Distress Syndrome.

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INTRODUCTION

Preterm birth remains a major global public health challenge and is a leading cause of neonatal morbidity and mortality worldwide. According to the World Health Organization, an estimated 15 million infants are born preterm each year, representing nearly 10% of all births globally, and complications related to prematurity account for a substantial proportion of neonatal deaths, particularly in low- and middle-income countries.[1] Preterm infants are highly vulnerable to a variety of complications due to the immaturity of multiple organ systems, among which respiratory distress syndrome (RDS) is one of the most common and life-threatening conditions.[2]

Respiratory distress syndrome, previously known as hyaline membrane disease, primarily affects premature neonates due to structural and biochemical immaturity of the lungs. The condition is mainly caused by inadequate production and

secretion of pulmonary surfactant by type II alveolar epithelial cells, which normally begins to increase during the late stages of gestation.[3] Surfactant plays a critical role in reducing surface tension within the alveoli and maintaining alveolar stability during respiration. In its absence, alveolar collapse (atelectasis), decreased lung compliance, impaired gas exchange, and progressive respiratory failure may occur shortly after birth.[4] The severity of RDS is inversely related to gestational age, with the highest incidence occurring in infants born before 32 weeks of gestation.[5]

The pathophysiology of neonatal RDS involves a complex interaction between surfactant deficiency, structural lung immaturity, inflammation, and impaired pulmonary circulation. Surfactant deficiency leads to increased surface tension within the alveoli, resulting in widespread atelectasis and ventilation-perfusion mismatch. Consequently, hypoxemia and hypercapnia develop, which further contribute to pulmonary vasoconstriction and respiratory compromise.[6] If not managed appropriately, severe RDS can lead to serious complications such as bronchopulmonary dysplasia, intraventricular hemorrhage, patent ductus arteriosus, and neonatal mortality.[7] Although advances in neonatal intensive care, including continuous positive airway pressure (CPAP), mechanical ventilation, and exogenous surfactant therapy, have significantly improved survival rates, preventive strategies remain essential to reduce disease burden and improve neonatal outcomes.[8]

One of the most important preventive interventions in modern perinatal medicine is the administration of antenatal corticosteroids (ACS) to pregnant women at risk of preterm delivery. Antenatal corticosteroid therapy promotes accelerated fetal lung maturation by stimulating surfactant production, enhancing structural development of the lungs, and improving pulmonary compliance.[9] Corticosteroids act by increasing the differentiation of type II pneumocytes and stimulating the synthesis of surfactant phospholipids and proteins, which are essential for effective lung function after birth.[10] In addition to their effects on the lungs, antenatal corticosteroids also contribute to the maturation of other fetal organ systems, including the cardiovascular and central nervous systems.[11]

The use of antenatal corticosteroids in obstetric practice was first established following the landmark randomized controlled trial conducted by Graham Liggins and Ross Howie in 1972, which demonstrated that administration of glucocorticoids to women at risk of preterm delivery significantly reduced the incidence of neonatal respiratory distress syndrome and mortality.[12] Since then, extensive clinical trials and meta-analyses have consistently confirmed the beneficial effects of antenatal corticosteroid therapy in improving neonatal outcomes.

Currently, the most used corticosteroids for antenatal therapy are betamethasone and dexamethasone, both of which readily cross the placenta due to their minimal mineralocorticoid activity and resistance to placental metabolism.[13] These corticosteroids promote lung maturation by stimulating surfactant synthesis, increasing lung compliance, enhancing antioxidant enzyme activity, and improving the structural development of alveoli and pulmonary vasculature.[14] Clinical evidence indicates that administration of antenatal corticosteroids significantly reduces the risk of respiratory distress syndrome, neonatal mortality, intraventricular hemorrhage, and necrotizing enterocolitis in preterm infants.[15]

Based on robust scientific evidence, several international guidelines recommend the use of antenatal corticosteroids for women at risk of preterm birth. Organizations such as the World Health Organization and the American College of Obstetricians and Gynecologists recommend administering antenatal corticosteroids between 24 and 34 weeks of gestation for women who are at risk of preterm delivery within seven days.[16] More recent research has also explored the benefits of corticosteroid therapy in late preterm pregnancies (34–36 weeks) and in special clinical situations such as multiple gestations and preterm premature rupture of membranes.[10]

Despite the well-established benefits of antenatal corticosteroid therapy, several important questions remain regarding the optimal timing of administration, the role of repeat or rescue courses, long-term neurodevelopmental outcomes, and potential adverse effects associated with excessive exposure.[17] Continued research is therefore essential to refine clinical guidelines and ensure the safe and effective use of antenatal corticosteroids in perinatal care.

This review aims to provide the physiological mechanisms, clinical effectiveness, current recommendations, and emerging evidence regarding antenatal corticosteroid therapy for fetal lung maturation and the prevention of respiratory distress syndrome in preterm neonates.

METHODS

Study Design and Reporting Guidelines: This review was conducted using a structured literature review approach to summarize the available scientific evidence on the role of antenatal corticosteroids in fetal lung maturation and the prevention of respiratory distress syndrome in preterm neonates. The review process was guided by the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework to ensure transparency and methodological rigor. Ethical approval was not

required, as this study was based exclusively on previously published literature.

Information Sources: A comprehensive literature search was conducted using major biomedical databases, including PubMed/MEDLINE, Google Scholar, Scopus, and Web of Science. These databases were selected because they provide extensive coverage of clinical and biomedical research related to obstetrics, neonatology, and pharmacotherapy.

Search Strategy: The search strategy was developed using a combination of Medical Subject Headings (MeSH) and free-text keywords related to antenatal corticosteroid therapy and neonatal respiratory outcomes. The primary search terms included *"antenatal corticosteroids," "betamethasone," "dexamethasone," "preterm birth," "fetal lung maturation,"* and *"respiratory distress syndrome."* These terms were combined using Boolean operators such as **AND** and **OR** to identify relevant studies. Additionally, reference lists of selected articles and relevant review papers were manually screened to identify additional eligible studies.

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria. Eligible studies included randomized controlled trials, cohort studies, clinical trials, and systematic reviews evaluating the use of antenatal corticosteroids in pregnant women at risk of preterm birth. Studies were included if they reported outcomes related to fetal lung maturation, incidence of neonatal respiratory distress syndrome, neonatal mortality, or other neonatal respiratory complications.

Studies were excluded if they were non-clinical studies, animal studies, case reports, conference abstracts without full text, or articles not published in English. Publications lacking sufficient outcome data or those unrelated to antenatal corticosteroid therapy were also excluded.

Study Selection

All retrieved articles were initially screened based on their titles and abstracts to assess relevance. Articles that appeared potentially relevant were then evaluated through full-text review to determine their eligibility for inclusion. Studies meeting the predefined eligibility criteria were included in the final review. Duplicate records were removed prior to screening.

Data Extraction

Relevant data from the included studies were extracted systematically. Extracted information included the author name, year of publication, study design, study population, intervention type (betamethasone or dexamethasone), gestational age at treatment, and key neonatal outcomes such as respiratory distress syndrome incidence, neonatal mortality, and respiratory complications.

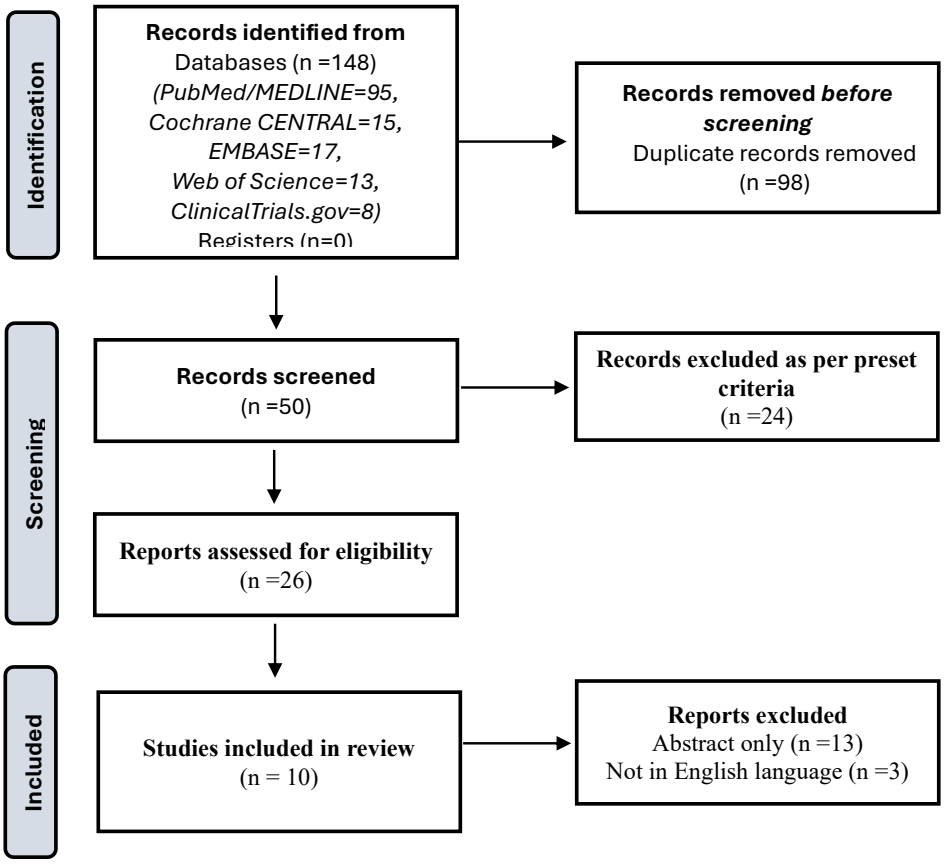

Figure 1: The PRISMA flow diagram of the selection of studies to be included in the systematic review.

Data Synthesis

Due to variations in study design, patient populations, and reported outcomes, a qualitative synthesis approach was used. The findings from the selected studies were summarized descriptively and presented in tabular form to highlight the key clinical outcomes associated with antenatal corticosteroid therapy. The evidence was interpreted in the context of current clinical recommendations and the physiological mechanisms underlying fetal lung maturation.

DISCUSSION

Antenatal corticosteroid therapy has been widely recognized as one of the most effective interventions for improving respiratory outcomes in preterm neonates. The landmark randomized controlled trial conducted by Graham C. Liggins and Ross N. Howie in 1972 first demonstrated that administration of antenatal glucocorticoids to women at risk of preterm delivery significantly reduced the incidence of neonatal respiratory distress syndrome (RDS) and neonatal mortality. This pioneering study established the biological basis for corticosteroid-induced fetal lung maturation and laid the foundation for subsequent clinical investigations.

Later research has continued to confirm the effectiveness and safety of antenatal corticosteroid therapy. A follow-up study by Caroline J. D. McKinlay and colleagues in 2015 evaluated long-term neurodevelopmental outcomes among children exposed to repeat antenatal corticosteroid courses. The study demonstrated that repeated corticosteroid exposure did not result in significant adverse neurodevelopmental outcomes while preserving the respiratory benefits observed during the neonatal period. These findings support the continued clinical use of corticosteroids in pregnancies at persistent risk of preterm birth.

Further evidence supporting antenatal corticosteroid therapy was provided by the multicentre randomized clinical trial conducted by Cynthia Gyamfi-Bannerman and colleagues in 2016. Their study specifically evaluated the administration of antenatal betamethasone in women at risk for late preterm delivery and reported a significant reduction in neonatal respiratory complications and need for respiratory support. These results expanded the therapeutic scope of corticosteroid administration beyond early preterm gestations.

Similarly, the randomized controlled trial by Caroline A. Crowther and collaborators in 2019 assessed the impact of repeat doses of antenatal corticosteroids in women who remained at risk of preterm birth. The study demonstrated improved respiratory outcomes and a lower incidence of severe RDS among neonates receiving repeat corticosteroid therapy, indicating that carefully monitored repeat dosing may provide additional neonatal respiratory protection.

Mechanistic insights into these clinical benefits were explored by Alan H. Jobe and Robert L. Goldenberg in 2018. Their research demonstrated that antenatal corticosteroids enhance fetal lung maturation by stimulating surfactant production, improving pulmonary compliance, and accelerating structural

Table 1: Summary of studies evaluating antenatal corticosteroids

Author	*Year*	*Study design*	*Study Focus*	*Outcome*	*References*
Liggins GC, Howie RN	1972	RCT	Antenatal glucocorticoid therapy	Reduce RDS and neonatal moratality	[12]
McKinlay CJD et al.	2015	Follow-up study	Repeat corticosteroid exposure	No adverse neurodevelopmental outcomes	[18]
Roberts D et al..	2016	Multicenter-RCT	Betamethasone in late preterm	Reduced respiratory complications	[19]
Crowther CA et al.	2019	RCT	Repeat ACS doses	Reduced severe RDS	[20]
Jobe AH, Goldenberg RL	2018	Clinical Research	Lung maturation mechanisms	Increased surfactant synthesis	[21]
Blankenship SA et al.	2020	Cohort study	SGA preterm infants	Reduced mortality	[22]
WHO ACTION Trials Collaborators	2022	Double-blind RCT	Dexamethasone therapy	Reduced respiratory morbidity	[23]
Walters AGB et al.	2023	RCT	Betamethasone vs placebo	Lower RDS incidence	[24]
Kibanga W et al.	2023	Observational study	Dexamethasone therapy	Reduce RDS incidence	[25]
Shittu KA et al.	2024	Clinical study	Late preterm ACS	Reduced respiratory morbidity	[26]

lung development. These physiological effects provide a clear biological explanation for the reduction in RDS observed in clinical trials.

More recent observational and cohort studies have further reinforced these findings across different neonatal populations. For instance, the cohort study by Samantha A. Blankenship and colleagues in 2020 reported that antenatal corticosteroid exposure was associated with reduced neonatal mortality and respiratory complications among small-for-gestational-age preterm infants. These results suggest that corticosteroid therapy may confer benefits even among high-risk neonatal subgroups.

Large international trials have also demonstrated the effectiveness of antenatal corticosteroids in low-resource settings. The WHO ACTION Trials Collaborators in 2022 conducted a double-blind randomized trial evaluating antenatal dexamethasone in women at risk of preterm birth and found significant reductions in neonatal respiratory morbidity and improved survival rates. These findings highlight the global applicability of corticosteroid therapy in improving neonatal outcomes.

More recent studies continue to support these observations. Clinical investigations by Andrew G. B. Walters (2023), Wilson Kibanga (2023), and Khalid A. Shittu (2024) consistently demonstrated reduced incidence of neonatal respiratory distress syndrome and improved respiratory outcomes following antenatal corticosteroid administration. Collectively, these studies reaffirm that antenatal corticosteroids remain a cornerstone therapy for preventing respiratory morbidity and mortality in preterm infants.

The accumulated evidence from randomized controlled trials, cohort studies, and international clinical investigations strongly supports the continued use of antenatal corticosteroids for fetal lung maturation. The consistent reduction in respiratory distress syndrome, need for respiratory support, and neonatal mortality across diverse populations underscores the critical role of this intervention in modern perinatal care.

Study Limitations

This review has several limitations. The included studies showed variability in study design, patient populations, and corticosteroid regimens, which may limit direct comparison of results. In addition, most studies primarily focused on short-term neonatal outcomes, while long-term effects of antenatal corticosteroid exposure were not consistently evaluated. Finally, only English-language publications from selected databases were included, which may have resulted in the exclusion of some relevant studies.

CONCLUSION

Antenatal corticosteroid therapy is a well-established and evidence-based intervention for promoting fetal lung maturation and reducing the incidence of respiratory distress syndrome in preterm neonates. Administration of corticosteroids such as betamethasone and dexamethasone in pregnant women at risk of preterm delivery significantly improves neonatal respiratory outcomes, reduces neonatal mortality, and lowers the risk of complications such as intraventricular hemorrhage and necrotizing enterocolitis.

Current clinical guidelines from organizations such as the World Health Organization (WHO) and the American College of Obstetricians and Gynecologists (ACOG) recommend the use of antenatal corticosteroids for pregnant women at risk of preterm birth between 24 and 34 weeks of gestation, particularly when delivery is expected within seven days. In selected cases, their use may also be considered in late preterm pregnancies based on clinical judgment and patient condition.

Overall, antenatal corticosteroid therapy remains a cornerstone of modern perinatal care. Adherence to established clinical guidelines and appropriate timing of administration can substantially improve neonatal survival and reduce respiratory complications in preterm infants. Continued research is needed to further refine optimal dosing strategies, evaluate long-term outcomes, and expand evidence-based recommendations for diverse clinical settings.

Author Contributions

All authors contribute equally to this research work.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this work.

Ethical Approval

Ethical approval was not required for this study, as it is a systematic review based exclusively on previously published data.

Informed Consent

Informed consent was not applicable, as no individual patient data were collected or analyzed in this study.

Data Availability Statement

All data analyzed in this study are included in the published articles identified through the systematic review and are available within the manuscript and its supplementary materials.

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