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Optimization of Antenatal Corticosteroid Therapy in Preterm Birth

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ABSTRACT

Antenatal corticosteroids (ACS) have been shown to reduce the risk of peripartal and neonatal mortality, as well as respiratory distress syndrome (RDS), and likely intracranial hemorrhage. The administration of ACS represents standard therapy in pregnant women at high risk of imminent preterm birth. The 2015 recommendations of the World Health Organization emphasize that ACS provide proven clinical benefits when administered under appropriate conditions but may also cause significant adverse effects if the indications and criteria are not fully met. The aim of this study was to present the course and outcome of pregnancy and neonatal outcomes in women who received ACS according to protocol. All pregnant women admitted with a diagnosis of threatened preterm birth during a six-month period were analyzed. A total of 141 pregnant women received ACS up to 34 weeks of gestation. The total number of preterm births during the same period according to the protocol of the maternity department was 193, of which 78 (40%) occurred before 34 weeks of gestation.The results showed that 52 (66.6%) women received ACS and delivered preterm, while in 24 (33.3%) women who delivered preterm ACS therapy had not been administered.

Keywords: preterm birth, corticosteroids, RDS, antenatal corticosteroids, neonate

Introduction

Preterm birth, defined as delivery before 37 completed weeks of gestation, represents one of the leading causes of neonatal morbidity and mortality worldwide. Complications associated with preterm birth account for a substantial proportion of neonatal deaths as well as long-term neurological and respiratory consequences[1]. Lung immaturity and the resulting respiratory distress syndrome (RDS) remain the primary cause of early neonatal mortality among preterm infants.

Antenatal administration of corticosteroids in women with threatened preterm birth is considered one of the most effective interventions in perinatal medicine. The first randomized controlled trial conducted by Liggins and Howie in 1972 demonstrated a significant reduction in the incidence of RDS in newborns whose mothers received corticosteroids prior to delivery[2]. Corticosteroids such as betamethasone and dexamethasone accelerate fetal lung maturation by stimulating surfactant synthesis, increasing the activity of enzymes involved in pulmonary epithelial maturation, and improving alveolar fluid absorption.

Systematic reviews and meta-analyses have confirmed that antenatal corticosteroids significantly reduce the risk of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death[3]. Recommendations for their use have been issued by leading professional organizations, including the World Health Organization and the American College of Obstetricians and Gynecologists, which recommend a single course of antenatal corticosteroids for pregnant women at high risk of preterm birth between 24 and 34 weeks of gestation, with consideration of administration in the late preterm period in selected cases[4,5].

Given the strong level of evidence and favorable benefit-risk ratio, antenatal corticosteroid therapy today represents the standard of care in the management of threatened preterm birth and a key intervention for reducing perinatal mortality and improving neonatal outcomes.

Although the effect of a single course of antenatal corticosteroids on fetal lung maturation is well established, clinical practice shows that in some women delivery does not occur within the optimal time frame of 7 days after administration. Since the maximal effect of corticosteroids on reducing the incidence of respiratory distress syndrome occurs within the first 7 days, the question has arisen regarding the justification for repeat administration in cases of persistent risk of preterm birth.

Randomized controlled trials have shown that a repeat (rescue) course of corticosteroids, administered at least 7 days after the initial course in women who remain at high risk of preterm birth before 34 weeks of gestation, reduces the incidence of RDS and severe neonatal respiratory complications[6]. Meta-analyses have confirmed a reduction in the need for mechanical ventilation and surfactant therapy without a significant increase in neonatal mortality[7].

However, earlier studies that included multiple repeated courses (more than two) reported reductions in birth weight and neonatal head circumference, raising concerns about potential long-term neurodevelopmental effects. Long-term follow-up of children in most studies did not demonstrate significant differences in neurocognitive outcomes, although caution with multiple courses is still recommended[7].

Recommendations from major professional bodies, including the American College of Obstetricians and Gynecologists and the Royal College of Obstetricians and Gynaecologists, suggest considering a single additional (rescue) course of antenatal corticosteroids in women before 34 weeks of gestation if ≥7 days have passed since the initial course and the risk of preterm birth within the following 7 days persists. Routine administration of multiple repeat courses is not recommended due to potential effects on fetal growth.

Therefore, current evidence suggests that a single repeat course in carefully selected clinical circumstances is safe and effective, while multiple

repeat courses should be avoided outside clearly defined indications.

Aim of the Study

To present the course and outcome of pregnancy and neonatal outcomes in women who received ACS according to protocol, with an analysis of the reasons for hospitalization and the time interval to delivery, defined as optimal or suboptimal (≥24 hours and ≤7 days).

Methodology

The study was conducted through a retrospective analysis of data obtained from the information system of the Clinic for Gynecology and Obstetrics. Inclusion criteria included all admissions to the Department of Reproductive Gynecology and Perinatology with a diagnosis of threatened preterm birth. The analyzed data included the reason for admission, cervical length, date of delivery, and Apgar score.

Results

During the six-month study period in 2024, a total of 141 pregnant women received antenatal corticosteroids (ACS) due to threatened preterm birth. Of these, 56 (39.7%) received ACS before 28 weeks of gestation, while 85 (60.3%) received therapy between 28 and 34 weeks of gestation.

The most common indication for hospital admission was cervical shortening, recorded in 56 women (39.7%), including 16 with a previously placed cerclage. The second most frequent indication was uterine contractions in 42 women (29.7%). Other indications included vaginal bleeding in 16 (11.3%), preterm premature rupture of membranes (PPROM) in 9 (6.3%), and other obstetric conditions in 15 (10.6%).

Among the women who received ACS, 112 (79.4%) delivered at our clinic, while 29 (20.6%) delivered at other institutions. Among deliveries at our clinic, 52 (46.4%) resulted in preterm birth, whereas 60 (53.6%) were term deliveries.

During the same period, a total of 193 preterm births were recorded in the maternity department overall, including 78 (40.4%) before 34 weeks of gestation. Among the 76 preterm births that occurred at our clinic, 52 (68.4%) mothers had received ACS, while 24 (31.6%) had not received antenatal corticosteroid therapy prior to delivery.

A detailed overview of maternal characteristics, indications for admission, and pregnancy outcomes is presented in Table 1, while the distribution of preterm births and exposure to ACS is shown in Table 2.

Table 1. Maternal characteristics, indications for admission, and pregnancy outcomes among women receiving antenatal corticosteroids (N = 141)

Variable	n (%)
Gestational age at ACS administration	
< 28 weeks	56 (39.7)
28–34 weeks	85 (60.3)
Indication for admission	
Cervical shortening	56 (39.7)
Cerclage present	16 (11.3)
Uterine contractions	42 (29.7)
Vaginal bleeding	16 (11.3)
PPROM	9 (6.3)
Other indications	15 (10.6)
Delivery location	
Study clinic	112 (79.4)
Other institutions	29 (20.6)
Pregnancy outcome (clinic deliveries)	
Preterm birth	52 (46.4)
Term birth	60 (53.6)

Table 2. Preterm births and antenatal corticosteroid exposure during the study period

Variable	n (%)
Total preterm births in the maternity department	193 (100)
Preterm births < 34 weeks	78 (40.4)
Preterm births at study clinic	76 (100)
Received ACS	52 (68.4)
Did not receive ACS	24 (31.6)

Table 3. Indication for admission and delivery outcome

Indication	Preterm birth	Term birth	Delivered elsewhere	Total
Cervical shortening	22	20	14	56
Uterine contractions	10	24	8	42

Discussion

In accordance with the 2015 recommendations of the World Health Organization, the use of antenatal corticosteroids should be clearly indicated and based on careful assessment of benefits and risks. Although ACS have proven clinical effectiveness in reducing respiratory morbidity in preterm infants, their inappropriate or non-selective use may be associated with significant adverse outcomes, particularly in low-resource settings.

Unexpected results from the ACT trial further raised concerns regarding the safety of widespread promotion of ACS use in population settings with limited resources. Strategies that encourage routine administration of ACS in women at risk of preterm birth may increase treatment coverage but also carry the risk of unnecessary exposure in women for whom therapy is not strictly indicated. At the population level, such an approach has been associated with increased perinatal mortality (RR 1.11; 95% CI 1.04–1.19), stillbirth (RR 1.11; 95% CI 1.02–1.21), and neonatal mortality within 28 days (RR 1.12; 95% CI 1.02–1.23). An increased risk of suspected maternal infection or inflammation was also reported (RR 1.49; 95% CI 1.32–1.68), while no significant difference in maternal mortality was observed compared with routine care. These findings suggest that uncritical implementation of recommendations may have the opposite effect in settings without adequate perinatal infrastructure.

The results of a systematic review and meta-analysis conducted by Kiran et al., which included 30 studies and more than 1.25 million children, further highlight the complexity of long-term outcomes. In extremely preterm infants, a single course of ACS was associated with a significant reduction in the risk of neurodevelopmental impairment (aOR 0.69; 95% CI 0.57–0.84). However, in infants born in the late preterm period an increased risk of neurocognitive disorders was observed (aHR 1.12; 95% CI 1.05–1.20), while in term infants exposure to ACS was associated with a higher risk of mental and behavioral disorders (aHR 1.47; 95% CI 1.36–1.60) as well as neurocognitive disorders (aHR 1.16; 95% CI 1.10–1.21). Since late preterm and term infants constituted a substantial proportion of the exposed population, these findings indicate the need for stricter candidate selection.

A prospective cohort study conducted by Nuran et al., including 595 women at risk of delivery between 34 and 36+6 weeks of gestation, showed that ACS administration in the late preterm period significantly reduced composite respiratory morbidity (aOR 0.63; 95% CI 0.40–0.99), the need for CPAP/HFNC therapy, and the incidence of transient tachypnea of the newborn. However, an increased incidence of neonatal hypoglycemia was also observed (aOR 1.64; 95% CI 1.04–2.59), without significant differences in severe respiratory distress, surfactant use, or length of hospitalization. These results confirm that the clinical benefit in this gestational group is limited and accompanied by potential metabolic complications.

A population-based cohort study conducted by Sarah et al., using US Vital Statistics data (2016–2020), analyzed outcomes in pregnant women with gestational diabetes mellitus (GDM) who delivered in the late preterm period. Exposure to ACS was associated with a higher rate of composite adverse neonatal outcomes, including the need for assisted ventilation and surfactant therapy. An increased risk of adverse maternal outcomes was also observed (aRR 1.34; 95% CI 1.18–1.52), including admission to intensive care, blood transfusion, and unplanned hysterectomy. Subgroup analyses confirmed a consistent trend of increased risk among exposed women.

Although the American College of Obstetricians and Gynecologists recommends ACS administration in women with GDM at risk of preterm birth, these recommendations are based on limited data because only a small proportion of women with GDM were included in key randomized trials. Current evidence suggests the need for individualized assessment of benefits and risks, particularly in populations with increased metabolic and perinatal risk.

Overall, contemporary evidence suggests that the benefit of ACS administration remains unequivocal in extremely preterm birth, whereas in late preterm birth and in certain high-risk groups, such as women with GDM, the balance between benefits and risks is considerably more complex. These findings highlight the need for more precise selection criteria, adequate diagnostics for assessing the real risk of preterm birth, and caution in routine therapy administration, particularly in settings with limited resources.

Conclusion

Improvement in the survival rate of preterm infants is largely based on advances and the rational use of antenatal corticosteroids.

The obtained data indicate the need for a more cautious approach when developing clinical protocols and making therapeutic decisions, particularly in resource-limited settings.

Although strategies that strongly promote the use of ACS in women at risk of preterm birth may increase their administration in the target population, they also carry the risk of unnecessary drug exposure in women without clear indications (Anke 2020). Future research should focus on differences in therapeutic regimens, evaluation of effectiveness in insufficiently studied groups such as multiple pregnancies and other high-risk obstetric categories, as well as the benefit-risk balance in very early or late preterm pregnancy.

In addition, long-term effects of ACS should continue to be monitored through existing studies that follow participants into childhood and adulthood. Particular emphasis should be placed on thoughtful and purposeful use of ACS based on careful clinical assessment.

Conflict of Interest:

The authors declare no conflicts of interest.

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