Research Article

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Use of antenatal corticosteroids: effects, benefits and potential risks

Abstract

Preterm birth (PTB) is a major global cause of neonatal morbidity and mortality, and its incidence has remained largely unchanged. Antenatal corticosteroids (ACS) are the most effective intervention for improving outcomes in pregnancies at risk of PTB, enhancing fetal lung maturation and reducing respiratory and neurological complications. A single ACS course is recommended before 34 weeks, although interest has expanded to late preterm and periviable gestations. While short-term respiratory benefits in late preterm infants are well documented, uncertainties remain regarding optimal timing, dosing, and long-term developmental effects. Both endogenous and exogenous glucocorticoids play key in fetal maturation but can influence neurodevelopmental programming when exposure exceeds physiologic levels. ACS affects the fetal HPA axis, placental function, neural stem/progenitor cells, and epigenetic regulation, with potential implications for later cognitive, behavioral, and metabolic outcomes. Repeated ACS courses offer no clear neonatal benefit and may reduce birth weight or increase neurodevelopmental risks. Given the importance of administering ACS within 2–7 days before delivery, accurate prediction of imminent PTB is essential. Emerging predictive models and ongoing large cohort studies are expected to refine gestational age specific recommendations. ACS remains a cornerstone of PTB management, requiring individualized, evidence-based use.

Keywords: antenatal corticosteroids, preterm birth, perinatal and neonatal, prematurity

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Introduction

Preterm birth (PTB) remains a major global health challenge and the leading cause of perinatal morbidity and mortality. Despite advances in perinatal and neonatal care, its worldwide incidence has remained largely unchanged for decades. Each year, approximately 15 million infants are born preterm, representing 5–7% of births in high-income countries and significantly higher proportions in developing countries.[1] In 2010, PTB accounted for about 11% of all live births globally.[2] Reducing prematurity remains a key public health priority. Survival rates have increased, and morbidity has decreased because of technologic advances in perinatal and neonatal medicine.[3]

According to the World Health Organization's International Classification of Diseases, 10th Revision (ICD-10), PTB is defined as delivery between 22 and 37 completed weeks of gestation, corresponding to 154–259 days. It is a major determinant of neonatal mortality and morbidity and has long-term adverse consequences for health.[4,5] PTB is a complex syndrome with multifactorial aetiologies that can be classified into two groups: spontaneous PTBs (70% of all PTB) and iatrogenic PTBs (30% of all PTB).[3,6]

Surviving preterm neonates have increased risks of multiple short- and long-term morbidities, including respiratory distress syndrome, bronchopulmonary dysplasia, necrotising enterocolitis, sepsis, intraventricular haemorrhage, cerebral palsy, feeding difficulties, and sensory impairment. Preterm birth also places substantial psychological and financial burdens on families and health systems.[7–9]

Although the highest morbidity and mortality occur before 34 weeks, late preterm infants (34–36^{+6} weeks of gestation) are more common and still face significantly higher risks than term neonates. The 37weeks of gestation cutoff is somewhat arbitrary, as early-term births (37–38 weeks of gestation) also have increased adverse outcomes compared with full term (39–40 weeks of gestation).[7]

Preterm birth is classified as spontaneous (preterm labour or prelabour membrane rupture) or provider-initiated (induction or caesarean for maternal or fetal indications). Despite numerous associated risk factors, the aetiology of spontaneous preterm birth remains incompletely understood.

Antenatal corticosteroid (ACS) administration is one of the few proven interventions for pregnant women at high risk of preterm birth. Corticosteroids cross the placenta, stimulate fetal alveolar surfactant production, improve responsiveness to postnatal surfactant therapy, and enhance overall lung compliance and respiratory function. Their clinical benefit was first demonstrated in the landmark randomized controlled trial by Liggins and Howie (1972), which reported significant reductions in respiratory distress syndrome and intraventricular haemorrhage among preterm infants exposed to antenatal betamethasone.[10]

Since then, ACS therapy, consisting of either two 12 mg intramuscular doses of betamethasone 24 hours apart or four 6 mg intramuscular doses of dexamethasone every 12 hours, has been shown to reduce the risks of previous reported neonatal complication. ACS has thus become the global standard of care for pregnant patients at risk of preterm birth. Nevertheless, more than five decades after the landmark trial, key uncertainties remain regarding optimal gestational age, timing, dosing, clinical setting, and long-term effects.[11,12]

Based on this evidence, a single course of ACS for women at risk of preterm delivery before 34 weeks of gestation is recommended by major international authorities, including the U.S. National Institutes of Health, the American College of Obstetricians and Gynecologists (ACOG), Society for Maternal-Fetal Medicine (SMFM), and the Royal College of Obstetricians and Gynaecologists (RCOG).[4,10,13–15]

ACS is regarded both as a crucial fetal-maternal intervention and as a potential contributor to controversial effects on fetal brain development and the future risk of chronic disease. Recent scientific literature has explored these dual perspectives, particularly the influence of endogenous and exogenous steroids on neurodevelopment.

Neurodevelopmental programming of glucocorticoid signaling

Although brain maturation extends into early adulthood, critical in utero neurodevelopmental processes are highly susceptible to external insults. Prenatal exposure to drugs, infections, or maternal stress can disrupt endogenous signaling pathways, including those regulating gene expression and neurodevelopment.

These exposures may alter the hypothalamic–pituitary–adrenal (HPA) axis and glucocorticoid signaling, leading to lasting effects on endocannabinoid pathways, brain structure, and behavior.[16,17]

Endogenous steroids and fetal brain

The placenta is a distinct organ linking the mother and fetus, two physiologically related yet separate compartments. Maternal total and free ACTH levels rise progressively during pregnancy, partly due to placental ACTH production, which increases circulating concentrations 2-3 times. Beyond its known effects on fetal type II pneumocytes, ACS also affects placental villi. Recent evidence demonstrates that ACS may be associated with abnormal villous development, placental infarction, and reduced vascular reactivity, suggesting that chronic hypoxia and accelerated villous maturation may contribute to preterm labor.[18]

By 8–10 weeks of gestation, the fetal pituitary-adrenal axis is functional, and the adrenal glands secrete significant amounts of DHEAS (dehydroepiandrosterone sulfate). The fetal zone of the adrenal cortex is the primary site of steroidogenesis before birth, using placental pregnenolone and progesterone as precursors. Fetal cortisol concentrations remain 5-10 times lower than maternal levels.[19] Corticosteroids are essential for normal fetal brain development. The fetal brain expresses mineralocorticoid receptors, concentrated in the hippocampus, and glucocorticoid receptors, distributed throughout the limbic system, hypothalamic paraventricular nucleus, and cerebral cortex. Under stress, rising fetal cortisol increases glucocorticoids activation, whereas mineralocorticoids predominate under basal conditions.[20]

Exogenous steroids and fetal brain

Glucocorticoid receptors are the primary targets for exogenous synthetic glucocorticoids such as betamethasone and dexamethasone. These agents may influence brain development by altering glucocorticoid expression, with effects dependent on dose, timing, and duration of ACS. Animal studies show that dexamethasone can impair neurogenesis and induce apoptosis, particularly in the developing hippocampus, leading to structural changes, reduced brain weight, and long-term decreases in neuronal populations. Glucocorticoids also affect oligodendrocyte maturation, accelerating early myelination but reducing it later in development.[21,22]

Prenatal stress and glucocorticoid exposure contribute to "fetal programming" which influences susceptibility to preterm birth and may increase the long-term risk of neurological and metabolic disorders. Regulation of fetal exposure to both endogenous glucocorticoids (via the placenta) and exogenous glucocorticoids (via ACS) is therefore critical.[23]

We reviewed the guidelines for prenatal ACS use in pregnancies at high risk of preterm delivery and emphasize the need to consider ACS as a personalized therapeutic approach.

Antenatal administration of corticosteroids

Recent research has expanded the use of ACS beyond the traditional 24+0/7– 33+6/7 weeks of gestation window recommended by ACOG and SMFM. Interest has focused on late preterm (34 0/7–36 6/7 weeks) and periviable (<24 weeks) gestations, where most preterm births occur and neonatal survival continues to improve.[24,25]

The ALPS (Antenatal Late Preterm Steroids) trial (>2800 singleton pregnancies) demonstrated that betamethasone significantly reduced severe respiratory morbidity, transient tachypnea, surfactant use, and bronchopulmonary dysplasia, without increasing neonatal mortality. Although hypoglycemia was more frequent, it did not prolong hospitalization. A subsequent Cochrane review confirmed reduced respiratory distress syndrome risk (RR 0.75, 95% CI 0.60–0.95).[12,26]

Despite short-term benefit, concerns have persisted regarding potential long-term neurodevelopmental risks, supported by animal studies and observational data. A large meta-analysis (>1 million children) reported small increases in neurocognitive or psychological disorders after ACS exposure in late preterm and term births. However, long-term follow-up from ALPS showed no differences in cognitive or behavioral outcomes at 7 years, consistent with the original Liggins and Howie cohort.[12,26]

Professional guidelines remain inconsistent: ACOG/SMFM recommend ACS use up to 36 6/7 weeks of gestation, whereas WHO, FIGO, SOGC, and RCOG restrict use to ≤34 weeks.[12,25]

Recent trials from India evaluated late preterm ACS use. Yenuberi et al. found that betamethasone did not reduce neonatal respiratory distress in infants born at 34 0/7–36 6/7 weeks (4.9% vs. 4.8%; RR 1.03, 95% CI 0.57–1.84). A multicenter trial of dexamethasone reported similar outcomes for severe respiratory distress and mortality. Both studies were stopped early due to futility or low event rates. These results contrast with ALPS, likely due to differences in study design, inclusion of twin gestations, term deliveries, population characteristics, and healthcare settings.[12,27,28]

Improving neonatal care has led to resuscitation attempts as early as 21–22 weeks of gestation Retrospective U.S. data (>10,000 births) showed reduced mortality or neurodevelopmental impairment with ACS at 23 weeks of gestation (adjusted OR 0.58). Meta-analysis among infants resuscitated at 22 weeks of gestation showed survival nearly doubled with ACS exposure. Although survival improves, morbidity among survivors remains extremely high, necessitating shared decision-making with neonatology.[12]

ACS benefit is greatest when delivery occurs 2–7 days after administration, yet optimal timing is achieved in only 13–48% of cases. Predictors of optimal timing include PPROM, cervical dilation, cervical length <2 cm, preterm labor symptoms, and medically indicated delivery. Several predictive models (APOSTEL-II, De Silva et al., QUiPP, QUIDS) incorporate clinical factors and/or quantitative fetal fibronectin to estimate delivery risk within 7 days. Their generalizability is currently limited, and the risk threshold at which ACS should be withheld remains unclear.[12]

The standard betamethasone regimen is12 mg intramuscularly administered 24 hours apart. Because most patients who receive ACS remain pregnant for more than seven days after treatment, later studies assessed the effects of repeat ACS courses on neonatal outcomes. Findings have been inconsistent, but expert consensus advises against administering more than two courses, citing evidence of reduced birth weight, increased rates of small for gestational age infants, and possible adverse neurodevelopmental effects

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associated with repeated exposure. Evidence indicates potential harm from repeated ACS courses, including reduced birth weight and possible neurodevelopmental effects. Recent trials evaluating lower betamethasone dosing found that a half-dose regimen was not superior to the standard dose for preventing neonatal respiratory morbidity. Studies comparing 12-h versus 24-h dosing intervals show inconsistent results and possible increased risk of necrotizing enterocolitis with shorter intervals, requiring further investigation.[12,14,15]

Discussion

Recent evidence indicates that ACS can modify fetal hormonal regulation, with HPA axis sensitivity differing by exposure type. Neural stem/progenitor cells (NSPCs), essential for brain development, are highly responsive to glucocorticoids. Exposure may influence their long-term proliferation and differentiation, although many ACS effects support critical maturation in preterm infants.[29]

Maternal glucocorticoid levels rise from 12 weeks of gestation due to increasing hypothalamic and placental CRH, creating a positive feedback loop. Placental enzyme 11β-hydroxysteroid dehydrogenase type-2(HSD11B2) inactivates cortisol, maintaining fetal cortisol concentrations 10–13 times lower than maternal levels. In threatened preterm birth, synthetic glucocorticoids, betamethasone and dexamethasone, which are 25 times more potent than cortisol and not metabolized by HSD11B2 cross the placenta freely and effectively promote fetal organ maturation.[30]

ACS reduces the risk of previous reported neonatal complications, but potential long-term metabolic, cardiovascular, and neurobehavioral consequences remain under investigation. Altered HPA axis reactivity has been reported in ACS-exposed low birthweight preterm infants, suggesting possible independent ACS effects. Furthermore, elevated maternal cortisol levels after ACST administration in pregnancy are associated with more emotional disorders in girls at seven years of age. Betamethasone remains the preferred agent due to lower mortality and fewer adverse effects, and WHO guidelines (2022) allow ACS use in selected term pregnancies.[23,31,32]

Exogenous glucocorticoids act directly on the developing brain, where glucocorticoids are highly expressed in the hippocampus. Reduced hippocampal neuronal density has been observed in ACS-exposed preterm infants. ACS effects on neurogenesis, glycogenesis, and NSPCs vary with dosing and may contribute to later cognitive and behavioral outcomes. Maternal stress can induce glucocorticoids-gene methylation, and ACS may similarly cause persistent epigenetic alterations leading to heightened HPA reactivity into adolescence.[23,31–33]

Fetal Doppler data on cerebral hemodynamics after ACS are inconsistent: betamethasone shows minimal effect, whereas dexamethasone may transiently reduce middle cerebral artery PI and RI.28 Other studies report no significant middle cerebral artery changes; growth-restricted fetuses were excluded.[23]

Fetal adrenal function begins at 8 weeks of gestation, with significant cortisol synthesis after 22 weeks of gestation. Both endogenous and exogenous corticosteroids modulate neurodevelopment and late gestation maturation by suppressing proliferation and enhancing terminal differentiation. P-glycoprotein expression from 12 weeks of gestations provides partial blood-brain barrier protection. In the fetal brain, corticosteroids act via mineralocorticoid and glucocorticoid receptors, which exert distinct regulatory roles.[32,34]

Glucocorticoid receptors are highly expressed in the placenta and fetal brain particularly in hippocampal neurons and glial cells. Although the developmental trajectory of these receptors in the human fetus remains unclear, mineralocorticoid receptors have a ten-fold higher affinity for endogenous glucocorticoids and regulate basal HPA activity, whereas glucocorticoids mediate acute stress responses. Exogenous corticosteroids preferentially bind glucocorticoids, a mechanism central to fetal maturation. The adverse effects of ACS on neurodevelopment may result from elevated fetal corticosteroid exposure via placental transfer, stimulation of the fetal HPA axis, or corticosteroid-induced placental CRH production.[23,32,34]

Fetal susceptibility to corticosteroid excess is genetically regulated and aligns with the concept of fetal programming. Prenatal glucocorticoid overexposure from maternal stress or ACS has been associated with increased risks of schizophrenia, attention deficit hyperactivity disorder, antisocial behavior, post-traumatic stress disorder, anxiety, and learning disorders, potentially mediated through altered mesolimbic dopaminergic signaling and HPA dysregulation. Hypoxia and inflammation can downregulate placental 11β-HSD2, increasing fetal glucocorticoid exposure and reducing hippocampal glucocorticoid expression.[23,32]

Long-term outcomes after multiple ACS courses remain unclear. Early trials reported reduced birth size without neonatal benefit, whereas later follow-up showed no differences in mortality or disability at 5 years. Some sex-specific effects have been noted, including impaired learning and attention in girls after repeated betamethasone exposure, while dexamethasone-exposed infants showed no increase in muscular hypotonia.[35,36]

Conclusion

ACS therapy has substantially improved outcomes for preterm infants, with emerging benefits in both late preterm and periviable gestations. Long-term safety data remain limited, and large cohorts' study may address remaining uncertainties. The most critical research priority is optimizing ACS timing through practical and accurate preterm-birth prediction models, including machine-learning approaches, with gestational age specific recommendations.

Considering the available evidence and current clinical practice guidelines, it is essential to accurately assess the likelihood and timing of preterm birth in order to administer an appropriate dose of ACS in a timely manner. Equally important is the need to avoid unwarranted repeat courses of ACS. When repeat administration is clinically indicated, the interval between courses should not be less than 14 days.

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Conflicts of interest

The authors declare that they have no competing interests.

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