The benefits of antenatal corticosteroids (ACS) when judiciously administered are indisputable. The administration of ACS to combat the effects of prematurity is firmly established as the standard of care. However, as stated by the World Medical Association in the Declaration of Helsinki, “even the best proven interventions must be evaluated continuously through research for their safety, effectiveness, efficacy, accessibility and quality.” We cannot overlook the fact that ACS are not a totally benign treatment; ACS exert a wider array of metabolic, endocrine, and immune effects than any other known biological ligand. Although the intended primary target of ACS may be the fetal lungs, corticosteroids have pleiotropic effects, and other organ systems are clearly affected. These include the developing fetal brain, which contains a high level of corticosteroid receptors.

Corticosteroids are necessary for fetal brain development, and markedly influence neurogenesis, synaptogenesis, and myelination. It is important to note, however, that for these normative processes to occur in the fetus, a hypocortisolic milieu that is several times lower than the maternal level must be present. Protective mechanisms are in place to avoid excessive levels of endogenous maternal cortisol because of the potential for the disruption of fundamental neurodevelopmental processes with subsequent development of maladaptive signals. Both the placenta and the fetal brain have a high level of expression of the 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2), an enzyme that converts endogenous corticosteroids in inactive metabolites. However, the potent exogenous corticosteroids, betamethasone and dexamethasone, are not considerably metabolized by 11β-HSD-2, and when administered antenatally, will easily cross the placenta, exposing the fetal brain to supraphysiological corticosteroid levels.

Data from randomized controlled trials (RCT) on the long-term effects of ACS on the fetal brain are limited. The interpretation of available RCT data is further hampered by both insufficient power to detect significant differences in rare events and the lack of an unexposed control group in many of the studies in which multiple courses of ACS were given. A much larger volume of observational data linking ACS exposure to various long-term adverse outcomes is now available. These outcomes include delayed development and psychiatric problems at 7 to 8 years of age, anxiety and depression at the age of 29 to 36 years, and abnormal electroencephalogram patterns in adults. However, it has to be remembered that such observational reports describe associations rather than proximate cause and are subject to bias from undetected and undetectable confounders. Given these constraints, it would be unwise to discourage the appropriate use of ACS for infants delivered between 23- and 34-weeks gestation. In preterm infants of this gestational age range, the long-established short-term benefits of ACS are likely to override any potential long-term adverse effects. However, if the short-term benefits of ACS are minimal (as in late preterm administration) or absent (as in term-born infants), the balance between benefits and harm may change.

The principal question facing us with regard to the late preterm use of ACS is whether the demonstrated immediate benefit, predominately for otherwise self-limited respiratory morbidity, outweighs the still unclearly defined long-term neurodevelopmental and metabolic risks. The fetal brain is critically vulnerable during the 34 to 36 weeks gestational period. In this period, the oligodendrocytes responsible for myelin synthesis undergo their most rapid growth, and 50% of the cortical volume and 25% of the cerebellar volume have yet to form. It has been reported that ACS administration at 34 to 36 weeks’ gestation leads to a reduction of neurotrophin-3 levels that is independent of other obstetrical variables. Neurotrophins are a family of neuronal growth factors critical for fetal brain development. When very preterm infants are exposed to ACS, the neurotrophin levels increase, possibly explaining the lower rates of intraventricular hemorrhage and better neurodevelopmental outcomes. However, when late preterm infants are exposed to ACS, neurotrophin-3 is down-regulated, raising the concern that normal gray and/or white matter development may be adversely affected with long-term consequences. The
proposed mechanism is via steroid-induced neuronal death. Because of these concerns, a number of authors urged caution regarding the administration of ACS after 34 weeks’ gestation.

After the publication of the well-conducted randomized trial of ACS in the late preterm period (the ALPS trial), between 2016 and 2019, late preterm ACS administration was recommended by obstetrical societies worldwide. These recommendations have however been widely reconsidered in light of some recently published data. The Green-top Guideline No. 74 (2022) from the Royal College of Obstetricians and Gynaecologists does not extend the recommendation for late preterm ACS beyond 34 6/7 weeks’ gestation. In addition, the recommendation for late preterm ACS was entirely removed from the European Consensus Guidelines on the Management of Respiratory Distress Syndrome in 2019. The 2021 guideline by the International Federation of Gynecology and Obstetrics (FIGO) specifically advises against routine use of ACS after 34 weeks’ gestation, and the World Association of Perinatal Medicine equally advises against routinely giving ACS after 34 weeks’ gestation in its 2022 clinical practice guideline because of an uncertain risk–benefit ratio. The 2019 Guideline of the German, Austrian, and Swiss Societies of Gynecology and Obstetrics takes the same approach. Thus, there is universal interest in the results of the 3-year follow-up of the children enrolled in the ALPS trial. Hopefully, these high—evidence level randomized data will allow us to reframe the late preterm ACS discussion around the uncertain risk of developmental delay. Adding to the debate are data from the World Health Organization ACTION Trials Collaborators study (2022).¹ This double-blind, placebo-controlled, randomized trial of late preterm ACS showed no benefit for perinatal or neonatal morbidity and mortality and was stopped before completion because of lower-than-expected prevalence of the primary outcomes and slow recruitment.

A growing body of evidence suggests that term-born children exposed in utero to ACS are at increased risk for short- and long-term adverse outcomes, even following as little as a single prenatal course administered at any gestational age. In a retrospective cohort study of 5330 singleton term-born infants exposed to ACS for threatened preterm labor compared with term-born infants whose mothers had also experienced threatened preterm labor but who had not received ACS, the ACS-exposed infants had increased odds of neonatal intensive care unit admission and small-for-gestational-age birthweights.²

An increasing number of reports now suggest that, in addition to adverse short-term outcomes, there may also be long-term adverse effects when ACS administration is followed by term delivery. One concerning report described an alteration of diurnal cortisol regulation at 8 to 10 years of age, which persisted even when adjusted for covariates. This has been hypothesized to result from interference with the normal development of the hypothalamic-pituitary-adrenal axis, which leads to an abnormal, flattened diurnal cortisol slope lacking the cortisol awakening peak. A similar slope has been reported in children who experienced perinatal adversity and in preterm children treated with postnatal corticosteroids. Alteration in cortisol regulation is associated with cognitive delay, mental health issues, and an increased risk of metabolic, cardiac, and autoimmune diseases later in life. Term-born children exposed to ACS have been shown to have substantially increased cortisol reactivity to acute psychosocial stress, and this persists up to 14 to 18 years of age when compared with non—ACS-exposed children. Such individuals may well be at increased vulnerability to stress-related disorders later in life, including metabolic syndrome, depression, abnormal behavior, and memory impairment.

Almost 15,000 ACS-exposed children were compared with unexposed peers in Finland in a population-based retrospective study. A higher adjusted hazard ratio for mental and behavioral disorders was noted in the exposed children who were followed up to 12 years of age.³ The calculated number needed to harm (NNH) was 38.8. It is important to note that this NNH is comparable to the number needed to treat of 38.5 reported for the beneficial effect on neonatal mortality for optimally administered ACS before 34 weeks’ gestation. In the Finnish study, the increased risk for mental and behavioral disorders was considerably greater in children born at term, whereas the difference did not reach statistical significance in children born preterm. The association persisted within term-born sibling pair comparisons, suggesting that unmeasured familial confounders were unlikely to be present.

In an extended analysis of the same cohort, a considerably higher adjusted hazard ratio for speech and language disorders, scholastic skill disorders, motor function disorders, epilepsy, and cerebral palsy has been noted in term-born children exposed to ACS.⁴ The authors concluded that ACS exposure in term-born children may be associated with harms across a wide spectrum of symptomatic severity, warranting careful consideration of ACS in women who may not be likely to deliver before term.

A 2022 systematic review and meta-analysis of 30 studies of medium-term (approximately 2 years) outcomes in >1.25 million children born during or after 2000 validated the differential results observed on the basis of gestational age at delivery. ACS-exposed children born extremely preterm had a markedly lower risk of neurodevelopmental impairment, whereas the late-preterm and term-born ACS-exposed children had a considerably higher risk of adverse neurocognitive and/or psychological outcomes when compared with unexposed children.⁵ When the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to rate the certainty of this finding in 6 domains (risk of bias, inconsistency, imprecision, indirectness, publication bias, and other considerations), the rating was low, partly explained by the observational nature of the included studies that were prone to confounding bias. Nevertheless, the low GRADE-rating cannot and should not be used to completely mitigate the emerging concerns about possible long-term adverse outcomes in late-preterm or term-born children exposed to ACS.
A single course of ACS in mothers at risk of preterm delivery within 7 days has been categorically shown to be a life-saving intervention and is consistent with best clinical practice. Over time it has even become an obstetrical quality metric. Indeed, as quality assurance and peer review programs have gained expanded authority, the fear of failure to administer ACS to an indicated patient has caused anxiety among clinicians. It is perhaps this defensive mentality that has increasingly led to excessive and suboptimal use of ACS. Despite the fact that >50% of women given ACS for presumed preterm delivery will not deliver within the optimal exposure window of 7 days, the practice has proliferated. This has not been deterred even by the fact that most recipients deliver after 35 weeks’ gestation and 44% to 50% deliver at term.

The failure to accurately predict impending preterm delivery was apparent from the Liggins and Howie study, in which approximately 1 in 3 women delivered >7 days after ACS administration. We have known for >50 years that timing is everything in regard to ACS efficacy, but the precision in our administration timing has not improved. By 2019, only 15% to 40% of women treated with ACS were treated within the optimal window of 7 days before delivery, leading to an approximate 50% reduction in expected benefit, irrespective of confounders. It has been estimated that for every 3 to 4 cases of premature births in which ACS were administered >7 days before delivery, the associated increase in neonatal mortality (when compared with those cases in which ACS administration was optimally timed) is roughly equivalent to the neonatal mortality associated with 1 case of failure to administer ACS.

The emerging data discussed in this document indicate that timing is everything not only in regard to efficacy but also in regard to safety of ACS. Although the full depth and breadth of the adverse neurodevelopmental effects of ACS in term-born children remain unknown, we do not consider it reasonable to continue to disregard the rapidly accumulating evidence of potential iatrogenic damage. We thus hope to stimulate action along 3 possible lines:

**Research prioritization**

Following the landmark study of Liggins and Howie (1972), the impact of ACS on fetal maturation and the effectiveness of this intervention in children born before 34 weeks’ gestation have been extensively studied. However, the 2020 Cochrane Database Systematic Review on ACS identified a need for more data in certain populations such as those with multiple pregnancies and pregnancies complicated by diabetes mellitus and hypertension.

Major knowledge gaps still exist, including the optimal dose, formulation, timing of administration, and indications. The empirical high-dose regimen used by Liggins and Howie, based on preclinical experiments in fetal sheep, has remained unchanged since 1972, without any optimization for human pregnancy.

Ensuring that ACS are administered within the optimal therapeutic window of 7 days before preterm delivery remains elusive. We have very few reliable decision support tools for timing the administration of ACS. Cervical length measurement and different biochemical markers (fetal fibronectin, cervical acetate, insulin-like growth factor-binding protein-1, placental alpha-macroglobulin-1) taken individually have poor positive predictive value, and there are still no validated methods of prediction. The combination of select clinical factors and biological markers into prediction models and tools, currently not generally accepted, may offer future research possibility.

We hope that the research gaps discussed above will prompt the Eunice Kennedy Shriver National Institute of Child Health and Human Development, other governmental research funders worldwide, and nongovernmental funding agencies to recognize the necessity to reprioritize research in the field of ACS and to consider launching specific requests for applications in this much-needed arena of research.

**Professional organizations’ practice guidelines**

We also urge our national societies and organizations—the American College of Obstetricians and Gynecologists (ACOG), Society for Maternal-Fetal Medicine (SMFM), and American Academy of Pediatrics—to update their guidelines for ACS.

**Joint recommendation, cooperative workshops, and consensus conferences**

Following the publication of the seminal trial by Liggins and Howie, it took 20 years for ACS to become generally accepted and regarded as standard of care. The first National Institutes of Health (NIH) Consensus Development Conference on ACS in 1994 was crucial in promoting the adoption of this practice. Initial reluctance was replaced by over-exuberance, and in 2000 the NIH Consensus Development Conference on ACS had to reconvene to put an end to the harmful practice of multiple, sometimes weekly courses of ACS. On the basis of the success of the above initiatives, reconvening a third Consensus Development Conference on ACS, bringing together a diverse, multispecialty, expert panel, should be considered. The 2020 Cochrane Database Systematic Review on ACS included 20 RCTs of pregnancies between 24- and 34-weeks’ gestation. All but 1 were conducted between 1972 and 2002. The relevance of these studies in high-resource countries may have changed. Such a conference may not only redefine and optimize, but also actualize the practice of ACS administration.

Until such acutely needed actions materialize, guidance on the prudent use of ACS can be found in the recent SMFM Special Statement of May 2022. Acknowledging the concerns about ACS exposure in term-born infants, SMFM proposed new quality metrics for hospitals. Quality improvement measures should focus on administration of ACS within the optimal window of efficacy instead of the universal administration of ACS to women with threatened preterm birth.

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This proposed primary quality metric incentivizes clinicians to think critically about the timing of this intervention. The proposed balancing quality metric is the rate of term birth among women given ACS, with a theoretical ideal rate of 0%. By observing these new metrics, we may be able to end the practice of “just in case” ACS administration, which ACOG has recommended against since 1994.

The SMFM—proposed primary quality metric is based, pragmatically, on the question—“Do you think this baby will be delivered within a week?” If the answer is affirmative, ACS may be needed. If not, perhaps ACS should be withheld with a “wait and see” approach based on close clinical monitoring, frequent reassessment, and individualization of treatment. Although it is accepted that the clinical context may change in hours or weeks, the decision to give ACS will be a thoughtful and considered action, rather than an indiscriminate reflex.

A reevaluation of current ACS practices is critically needed. We are rapidly reaching a point where most ACS-exposed fetuses are delivered at term and are unnecessarily exposed to a potentially harmful drug with lifelong consequences. Given the potential risks involved, we believe that we are ethically and morally bound to reconsider our approach.

REFERENCES