

The Need to Go Beyond: Evaluating Antenatal Corticosteroid Trials With Long-Term Outcomes

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Abstract

A single course of antenatal corticosteroids (ACS) reduces the risk of severe neonatal morbidity and is associated with a strong trend towards a reduced risk of abnormal neurodevelopmental outcome. However, because 50% of women given ACS remain undelivered and continue to be at risk for preterm delivery, the question remains: would these women benefit from repeated courses of ACS, and, if so, how do repeated courses of ACS affect the fetus and long-term neurodevelopmental outcome? The serious consequences of this effect on the developing brain justify the need for long-term outcome studies (beyond two years of age) before repeat courses of ACS become standard care in the management of pregnant women who are at risk of preterm delivery throughout pregnancy.

Résumé

Un seul traitement aux corticostéroïdes prénatals (CSP) abaisse le risque de morbidité néonatale grave et est associé à une forte tendance à la baisse du risque de connaître une issue neurodéveloppementale anormale. Cependant, puisque 50 % des femmes bénéficiant d'un traitement aux CSP n'en sont encore pas rendues à l'accouchement et continuent donc de courir un risque d'accouchement préterme, nous sommes en droit de nous poser la question suivante : ces femmes tireraient-elles profit de traitements répétés aux CSP et, le cas échéant, quels seraient les effets de ces traitements répétés aux CSP sur le fœtus et les issues neurodéveloppementales à long terme? Les conséquences potentiellement graves de cet effet sur le cerveau en développement justifient la nécessité de procéder à des études sur les issues à long terme (au-delà de l'âge de deux ans) avant de normaliser le recours à des traitements répétés aux CSP, dans le cadre de la prise en charge des femmes enceintes qui courent un risque d'accouchement préterme tout au long de la grossesse.

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INTRODUCTION

The incidence of preterm birth has been steadily rising in many industrialized countries since the early 1980s. Most recently, the preterm birth rate has been reported to be 6.8% in Canada and 12.1% in the United States.^{1,2} Infants born preterm are at increased risk of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia, and other neonatal morbidities, which in turn increase the risk of abnormal neurodevelopmental outcome later in life.^{3,4}

In 1972, Liggins and Howie published the results of the first randomized controlled trial (RCT) evaluating the effects of a single course of antenatal corticosteroids (ACS).⁵ In women who had been in spontaneous preterm labour, ACS reduced the risk of RDS and early neonatal mortality. A 2006 Cochrane review of 21 RCTs, involving more than 4269 infants, reports a reduced risk of neonatal death, RDS, and IVH with a single course of ACS, and a strong trend towards a reduced risk of abnormal neurodevelopmental outcome on long-term follow-up of the children.⁶ Since the early 1990s, it has been generally recommended that women receive a single course of ACS if they are at 24 to 34 weeks' gestation and at increased risk of preterm birth.^{7,8} However, because 50% of women given a course of ACS remain undelivered 7 to 14 days later,⁹ it has been suggested that women, who remain undelivered after a single course of ACS may benefit from receiving additional courses of ACS.¹⁰

Risks of Antenatal Corticosteroids to the Fetus and Infant

Several RCTs have been conducted in animals to evaluate the effects of ACS in increasing doses. Although there is progressive improvement in postnatal lung function, there is a higher risk of adverse effects, and the risk increases with repeated exposure to ACS.¹¹⁻¹⁷ Corticosteroids were found

Table 1. Randomized controlled trials of repeat (weekly/biweekly) courses of antenatal corticosteroids

Study	Country of origin	Original sample size	Recruited (N)
Guinn ²⁴	USA	1000	502
NICHD ²⁵	USA	2400	495
TEAMS	UK	4000	154
ACTORDS ²⁶	Australia	980	982
MACS ²⁷	Canada	1900	1858

to have effects on the growth and development of the central nervous system as well as on overall growth. Investigators who have focused on brain development have noted a decrease in the growth of all brain structure, especially the hippocampus.^{18–20}

A well-organized interplay of several hormones supports the developing brain in utero. Too much or too little of any hormone can cause deviation in development and can lead to abnormal function, depending on the timing of exposure during development of the brain. Within the developing brain, the limbic system, and in particular the hippocampus, is sensitive to both endogenous and exogenous glucocorticoids. The hippocampus has a myriad of functions that support cognition, memory, and behaviour. For the human, a large percentage of maturation of the hypothalamic-pituitary-adrenal axis takes place in utero.²¹ In addition, during weeks 24 to 32 of gestation, the developing fetal brain undergoes significant changes related to neuronal migration and organization.²² A growing body of evidence suggests that ACS can influence the trajectory of neurodevelopment and that exposure to ACS during this period may adversely program the developing brain. Therefore, maternal ACS can theoretically have an impact on the developing brain, particularly the hippocampus, during critical periods of development.²³

Clinical Antenatal Corticosteroid Trials

Over recent years, several large RCTs have been initiated to study the effects of repeat (weekly/biweekly) courses of ACS (Table 1). Both the Guinn²⁴ and the NICHD²⁵ RCT found no significant reduction in the risk of stillbirth, neonatal death, or serious neonatal morbidity. The Australian trial (ACTORDS)²⁶ found a reduction in RDS. The Multiple Courses of Antenatal Corticosteroids for Preterm Birth (MACS) trial²⁷ has just completed recruitment and is expected to release its findings in the fall of 2007. Only two trials (ACTORDS and MACS) have a planned 18- to 24-month neurodevelopmental outcome phase.

Long-Term Effects of Corticosteroids

Several RCTs have studied the long-term effects of a single course of ACS on children. The 2006 Cochrane review of these RCTs found a strong trend towards a reduced risk of long-term neurological abnormality.⁶ The Dutch trial and the original New Zealand trial continued to follow children to 20 and 30 years of age and found no adverse long-term effects (psychological function, health-related quality of life, health risk factors) following one course of ACS.^{28–30}

Information about the effect of repeat courses of ACS on the long-term outcomes for children is currently limited to observational studies (Table 2); the 12-month follow-up of the ACTORDS trial has been published as an abstract.³⁵ The findings of these studies are conflicting: there is some evidence of benefit, some evidence of harm, and some evidence indicating no effect from repeat exposure to ACS. The observational studies are subject to selection bias, and the effects found may be due to the differences in the populations studied rather than to differences in the number of courses of ACS.

The Need for Long-Term Follow-Up

The primary goals of perinatal care are to decrease infant mortality, enhance health-related quality of life, and improve neurodevelopmental outcomes in infants following high-risk pregnancies. Neurodevelopmental outcome is increasingly becoming the benchmark for the efficacy of medical interventions in infants born preterm.³⁶ Outcome is also becoming the benchmark for the effectiveness of interventions in some obstetrical trials.³⁷ Although long-term follow-up is difficult to conduct, it is necessary to identify the positive and the negative effects a standard of care has on the brain that might not be obvious in the first years of life. This is especially true of antenatal corticosteroids. Animal studies have demonstrated potential negative influences on certain brain structures that have a major effect on functioning as the child grows older and needs to use these structures in school and daily activities. Assessments of children at 18 to 24 months of age will be

Table 2. Observational studies of repeat courses of antenatal corticosteroids (ACS) on long-term outcomes

Study	Gestational age at birth	Total number	Length of follow-up	Repeat ACS (betamethasone)	Findings
French et al. ³¹	23–32 weeks	477	3 years	Exposure to 0 to ≥ 3 courses of ACS	No significant effect of repeat courses of ACS on cerebral palsy or neurodevelopmental disability, or on growth parameters
Thorp et al. ³²	< 34 weeks	299	7 years	Weekly courses of ACS	No effect of repeat courses of ACS on intelligence, achievement, behaviour, or head circumference
French et al. ³³	20–32 weeks	541	6 years	Exposure to 0 to ≥ 3 courses of ACS	Repeat courses of ACS were associated with a lower risk of cerebral palsy (2.6% [1 course] and 2.9% [2 courses] vs. 5.7% [no courses]; an increased risk of aggressive/destructive behaviour (29% [2 courses], 28% [≥ 3 courses] vs. 9% [1 course]), an increase in distractible and hyperkinetic behaviour, but no effect on cognition
Kumar et al. ³⁴	24–34 weeks	126	2–2½ years	Exposure to 1 to ≥ 3 courses of ACS	No significant effect of repeat courses of ACS on abnormal neurodevelopmental outcome (10% [< 2 courses] vs. 14% [≥ 2 courses])

reassuring for the absence of major neurodevelopmental morbidities such as severe cerebral palsy, neurosensory deficits (blindness, deafness), and severe neurocognitive deficits (severe mental retardation). However, early cognitive assessments have been shown not to be as predictive in the absence of concomitant deficits, and caution is urged in this regard for decisions regarding a treatment or management approach.³⁸ Assessment of the older child is required to determine more accurately the consequences of repeat courses of ACS on cognitive skills, behaviour, memory, visual and spatial capacity, and other more complex functions.

Two trials, MACS and ACTORDS, have recognized this need, and will see the children at five years and six to eight years of age respectively with the goal of assessing the more subtle neurocognitive skills that are important for future functioning. Long-term assessments of the children in the current trials need to be carried out to ensure that this treatment approach has not led to an altered incidence of the commonly seen difficulties (“hidden disabilities”) that significantly affect school functioning.³⁹

CONCLUSION

Many approaches to care in both obstetrics and neonatology have become standard practice without adequate evidence to support them. Once a policy of clinical management has been accepted and implemented, it is very difficult to undertake research designed to determine the safety and effectiveness of the practice. Practice changes only after harm has been noted.

If found to be beneficial in reducing serious neonatal morbidity, repeat courses of ACS will find their way into standard care in much less time than the twenty years that were required for single course ACS. Serious

neurodevelopmental morbidity may not be a concern. However, the animal studies of the effects on brain growth and development are of concern and bear close monitoring and assessment. If there is evidence that this treatment approach has not led to a significantly and clinically altered incidence of the hidden disabilities, only then should it be endorsed as standard care for the pregnant woman who is at increased risk of preterm delivery.

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COMMENTARY

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