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Antenatal and postnatal corticosteroids: Knowledge gaps and research priorities

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We have had the pleasure to co-edit this series, in which leading experts from around the world in the science, clinical research, and clinical application of antenatal (ACS) and postnatal corticosteroids (PCS) to improve outcomes for preterm infants have summarized the best evidence for the use of these important therapies, and discussed the most important knowledge gaps and research priorities that it is the perinatal community's challenge to resolve.

The administration of ACS to women at risk of very preterm birth has been one of the most effective interventions to improve the outcomes of preterm infants [1]. Indeed, this intervention has contributed significantly to the dramatically improved survival rates for preterm infants observed over the last five decades [2], and international guidelines recommend ACS administration to women at high risk of very preterm birth [3–6]. However, despite the high-level evidence from randomized trials for the effectiveness of ACS, there remain many controversies.

To provide context for subsequent discussions, in Chapter 1 Cole et al. have summarized the 'science of steroids', including the biological actions of steroid hormones in the fetus and in preterm infants. They note that the detailed mechanisms of action of steroids in the fetus, where they are involved in the regulation of large numbers of target genes, are not well understood and require further investigation. They also call for the development of novel selective partial glucocorticoid receptor agonists that could provide new therapies to treat the respiratory complications of preterm birth whilst avoiding deleterious effects in other organ systems.

In Chapters 2–4, Kemp et al., Shanks et al., and Groom note that ACS are increasingly used for indications other than the risk of very preterm birth, including before 24 weeks' gestation, in anticipation of *late* preterm birth, and before elective cesarean section at term. Although the phenomenon of "clinical creep" has undoubtedly contributed, there is increasing evidence from randomized trials of efficacy for these clinical indications. However, a paucity of short- and longer-term safety data warrants caution. Groom notes the effect sizes of benefit from ACS at late preterm and term gestational ages are smaller than for more immature births, and should be countered against potential harms. For example, ACS use prior to late preterm birth may be associated with an increase in the incidence of neonatal hypoglycemia [7], and any effect of ACS on neonatal glycemic control after planned cesarean section or for infants of diabetic mothers is unknown. This is very important in light of accumulating evidence of the adverse effects of neonatal hypoglycemia in later childhood [8], and routine postnatal blood glucose monitoring in these scenarios may be warranted. Shanks et al. further explore contemporary controversies around ACS use, including the choice of steroid, use at periviable gestations and issues surrounding repeated dosing of ACS for mothers who remain at risk of preterm birth. They advocate for individualized, or "personalised", dosing of ACS, and the need for biomarkers of response to ACS to guide dosing.

More broadly, it is not known whether ACS doses, even those used in line with best evidence guidelines, are the lowest effective doses. Kemp et al. call for an updated pharmacological profile of ACS drugs and integrated model of dosing, including accounting for fetal size, and for the study of alternative treatment regimens with the aim of minimizing fetal exposure to ACS while optimizing maturation. Large clinical trials are required to confirm efficacy and safety of new treatment approaches. With, of course, long-term follow-up of the mothers and, especially, infants. Kemp et al. also call for improved prediction models of risk of preterm birth to optimise timing of ACS therapy, and, along with Shanks et al., development of biomarkers of response to therapy.

The smallest, sickest preterm infants are born extremely preterm, before 28 weeks' gestation. With modern intensive care in developed countries, 85% of extremely preterm infants survive, but 50% or more develop bronchopulmonary dysplasia (BPD) – the chronic lung disease of prematurity [9]. BPD is associated with increased infant mortality and adverse neurodevelopmental outcomes [10]. Many infants with BPD develop early chronic obstructive pulmonary disease as adults [11,12]. Despite recent advances in neonatal intensive care, BPD rates

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remain static with some evidence of *worsening* lung function in surviving children [13], and prevention of BPD is a major research priority [14]. In Chapters 5–7, Cheong and Doyle, Watterberg and Baud, and Rüegger and Bassler discuss the evidence for PCS use to improve outcomes for preterm infants, including promising new administration techniques.

Cheong and Doyle describe the PCS conundrum facing neonatal clinicians: systemic (intravenous or enteral) PCS, given either "early" (before 8 days of age) or "late" (after 7 days) to extremely preterm infants with evolving BPD, have proven efficacy for reducing exposure to mechanical ventilation, and the combined outcome of death or BPD [15,16]. However, systemic dexamethasone given early and routinely to extremely preterm infants is associated with a higher rate of neurosensory disability and cerebral palsy in survivors [15]. The risk of adverse neurodevelopment is highest if dexamethasone is given to preterm infants at low risk of BPD. Judicious use of systemic PCS, in only those infants deemed high-risk of BPD, is recommended [17] – hence much research has focused on prediction models for BPD and its severity, such as that developed by the National Institutes of Child Health and Development (NICHD) [18].

Watterberg and Baud present the evidence for and against lower-dose systemic hydrocortisone as an alternative to dexamethasone for "early" PCS treatment. Early, lower-dose hydrocortisone significantly increases survival without BPD (by about 8%) compared to placebo [19]. This very important benefit is tempered by an observed increase in late-onset sepsis in the most immature infants, but the higher rate of sepsis has no effect on mortality. Watterberg and Baud make a strong case for the use of early lower-dose hydrocortisone in extremely preterm infants, but many neonatal clinicians remain wary of routine systemic administration of PCS, the largest study of early lower-dose hydrocortisone was stopped early [20], and long-term benefit has not been demonstrated [19]. Further research to improve patient selection for this promising therapy is called for.

Concerns about long-term outcomes after systemic PCS, coupled with the need for a safer, prophylactic, therapy against BPD that could be administered to all extremely preterm infants, or tailored for high-risk subgroups of extremely preterm infants, have led to the search for alternative PCS administration routes. Rüegger and Bassler discuss the current evidence for inhaled PCS and intra-tracheal PCS mixed with surfactant. Direct pulmonary administration could be ideal, as this could maximise effects in the lung, and potentially lower the minimal effective dose and time to onset of action, whilst minimizing systemic absorption and corticosteroid side-effects. Inhaled budesonide, delivered via a metered dose inhaler which can be technically challenging in very small infants, has a borderline effect on the combined outcome of death or BPD, but was associated with *increased* mortality in the largest randomized trial [21]. Future research focusing on the design of aerosol delivery systems to more effectively deliver the drug to the distal airway of preterm infants, hence improving efficacy and lowering the cumulative dose, will be important.

Intra-tracheal budesonide mixed with surfactant is promising, with the largest completed trial in mechanically ventilated, very low birth weight infants finding a large effect size (despite a modest sample size) for the primary combined outcome of death or BPD [22]. The intervention in this trial used bovine surfactant and a budesonide dose of 0.25 mg/kg. Replication of these results with porcine surfactant is required, and it is not known whether the dose of budesonide used is the lowest effective dose, although pre-clinical studies are reassuring [23–26]. The results of larger and more generalizable RCTs are awaited: it will be important to include extremely preterm infants receiving non-invasive respiratory support and/or less invasive surfactant administration techniques in such trials. Of course, long-term neurodevelopmental and respiratory outcomes of this newer PCS administration technique will be critical, as will studies of systemic absorption of PCS delivered intra-tracheally, correlated with any corticosteroid side-effects.

Table 1
Research priorities for antenatal and postnatal corticosteroids.

Develop novel selective partial glucocorticoid receptor agonists that could provide new, targeted therapies to treat the respiratory complications of preterm birth.
Following the results of trials in progress, a meta-analysis of antenatal betamethasone vs. dexamethasone for preterm birth to determine which drug is associated with better short- and longer-term outcomes, and then undertake studies of optimal dosing of the chosen drug.
Develop biomarkers of fetal response to ACS to optimise outcomes through personalised therapy.
Follow-up of infants in trials of ACS for late preterm birth through to school age.
Large, high-quality trial(s) of ACS for planned cesarean section at term, with follow-up to school age.
Confirm if ACS increase the risk of neonatal hypoglycemia in late preterm and term infants, including the mechanisms of any effect.
Follow-up of extremely preterm infants in trials of early, lower-dose systemic hydrocortisone through to school age, in order to better weigh the benefits and risks of this therapy.
Determine the short and long-term efficacy and safety of intratracheal budesonide-surfactant in extremely preterm infants, including infants receiving non-invasive respiratory support and/or less-invasive surfactant administration techniques, and using natural porcine surfactant.

In Table 1, we list our top research priorities for ACS and PCS therapy, adapted from those suggested by the expert authors of the previous Chapters. These priorities were arrived at after consideration of the potential benefit to infants, and the potential to change international clinical practice. ACS and PCS have saved many lives, but, as always, it is our duty to optimise these therapies to ensure the best outcomes for mothers and babies.

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