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Antenatal and postnatal corticosteroids: A swinging pendulum

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Antenatal corticosteroid therapy prior to preterm birth remains one of the most important interventions for improving survival and reducing morbidity in preterm babies, and is a rare example of a treatment that not only saves babies' lives and but also reduces health care costs [1]. While initially given to prevent respiratory distress syndrome, antenatal corticosteroids (ACS) induce maturation across a range of fetal tissues and thus have been shown to reduce many of the other major morbidities associated with preterm birth [2]. Postnatally, corticosteroids remain a key adjunctive therapy for treatment of severe neonatal lung disease and have been used in prevention of bronchopulmonary dysplasia (BPD), a form of chronic neonatal pulmonary insufficiency associated with long-term respiratory and neurological sequelae [3].

Since the introduction of corticosteroids as both fetal and neonatal therapy, uptake and use in the perinatal period has changed dramatically over the decades. Following observations of corticosteroid-induced pulmonary maturation in fetal rabbits [4] and then in lambs [5], the first clinical trial of antenatal betamethasone for preterm birth was commenced in Auckland in 1969 and enrolled 1142 women through to 1974. As cogently illustrated in the Cochrane logo [6], the Auckland Steroid Trial produced estimates of treatment effect almost identical to that seen in subsequent meta-analyses, including in the most recent review of over 25 trials across four decades [2,7]. Although initially met with scepticism, the results of this and other important trials eventually led the National Institutes of Health (NIH) to recommend routine use of ACS for preterm birth in 1994 [1]. Not only did this see a dramatic increase in the use of this therapy but many jurisdictions also rapidly embraced use of repeat doses of antenatal corticosteroids, despite lack of evidence of efficacy or safety. This practice had already begun in New Zealand and Australia [8], and parts of the United Kingdom [9] based on a *post hoc* subgroup analysis of data from the Auckland Steroid Trial that showed that preterm babies born more than seven days after corticosteroid exposure appeared to have an increased incidence of respiratory distress syndrome [7]. This finding was not confirmed in subsequent analyses or other trials, illustrating the need for caution when interpreting subgroup analyses [10].

With the emergence of the developmental origins of disease paradigm in the 1990s [11] and the recognition that fetal over-exposure to maternal corticosteroids may play a role in mediating lifetime risk of metabolic disease [12], in 2000, the NIH discouraged use of repeat ACS pending further data from clinical trials [13]. That evidence emerged over the subsequent decade, and showed that the absolute benefit of repeat dose(s) of ACS for neonatal respiratory morbidity was similar to that of an initial course, with additional reduction in other serious morbidity [14,15]. Despite reassuring outcome data from adult subjects in the Auckland Steroid Trial [16–19], and absence of any adverse neurocognitive or cardiometabolic effects at 6–8 years in children exposed to repeat antenatal betamethasone [20–22], with potential additional benefits in fetal growth restriction [23,24], clinical practice regarding ACS, especially repeat administration, has remained conservative. In Australia and New Zealand, where use of repeat ACS was once almost universal, a quarter of obstetricians still report that they never use this therapy [25]. However, 52% report using antenatal corticosteroids at 35–36 weeks' gestation and 79% report using them prior to term elective section, despite safety concerns and lack of high-quality long-term outcome data for these indications [25].

There have been similar pendulum swings in use of postnatal corticosteroids (PCS) since their introduction in the 1980s to combat ventilator-induced lung injury and evolving BPD. With evidence of efficacy from several small trials [26,27], PCS therapy was widely adopted into neonatal practice, initially for treatment of ventilator-dependent lung disease and subsequently for prophylaxis of BPD, again in the absence of long-term safety data. When those data eventually emerged, it became apparent that the short-term respiratory benefits of postnatal corticosteroids may be off-set by increased risk of neurological impairment, especially motor difficulties [28,29], although earlier studies in non-human primates had already identified the potential for adverse effects on brain development [30,31]. By the 2000s, the tide of opinion had turned and neonatologists started to avoid PCS, except in babies with prolonged ventilator dependence, such that important trials of targeted low-dose therapy were unable to complete recruitment [32].

Within a little more than a decade, contemporary practice has come

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full circle with trialists again focusing on alternative ways to harness the benefits of PCS for BPD prevention and increasing neonatal survival, while minimising harms. This has been driven by international trends of increasing BPD rates, when other neonatal morbidities are decreasing [33], and recognition that neurological outcome represents a complex trade-off between exposure and underlying risks [34]. Similarly, obstetric practice has seen renewed emphasis on extending ACS use to late preterm and term birth (elective caesarean, infants of diabetics), even though treatment for the highest risk infants – single courses ≤24 weeks' gestation and repeat dose(s) < 32 weeks' – is often underutilised. One might consider that history is repeating itself, with introduction of therapy prior to adequate assessment of long-term outcomes and potential trade-offs.

The main glucocorticoid drugs used in perinatal practice - betamethasone and dexamethasone - were introduced more than 60 years ago, and there have been few changes to antenatal dosage, formulation or timing since the first clinical trials. Recent ovine studies suggest that lower doses may be equally effective while minimising fetal exposure [35,36]. In humans, genetic polymorphisms in steroid pathways appear to influence ACS efficacy, suggesting that individual optimisation of dose may be possible [37]. Moreover, alternative glucocorticoid receptor ligands, known as selective glucocorticoid receptor modulators, with varying degrees of transactivation (targeted gene expression) are now available and are entering phase two trials in adults [38]. Theses agents have the potential to provide novel therapeutic options for preterm birth and neonatal lung disease, but are yet to be studied in the fetus and neonate.

Given the cost of large multicentre trials and the importance of following children at least to school-age in order to fully assess the impact of perinatal corticosteroid interventions, a key challenge for future research will be to decide whether alternative pharmacological strategies offer the potential for a benefit to risk profile than is substantially better than is already available with current regimens. Thorough assessment in adequately powered trials is essential as apparently small changes in drug regimen may have clinically significant effects. For example, changing from 12- to 24-hourly dosing of betamethasone was associated with a higher rate of necrotising enterocolitis [39], and use of dexamethasone rather than betamethasone in extremely preterm infants may decrease rates of neurosensory impairment, although final results from the A*STEROID trial are awaited [40,41].

Traditionally, ACS have been thought to target lung immaturity while PCS target lung inflammation. However, these processes coincide during the perinatal period, especially with preterm birth. For example, intrauterine inflammation plays a key role in onset of preterm labour and preterm premature rupture of membranes, while postnatal arrest of pulmonary maturation remains central to the development of BPD, along with lung injury and inflammation [42]. There is increasing evidence that antenatally, corticosteroids modulate the effects of intrauterine inflammation on lung and brain development [43,44], though timing may be important [45]. Further, ACS have been shown to reduce lung injury following resuscitation at birth [46]. Conversely, in the early postnatal period, corticosteroids may have a role not just in reducing inflammation but also in supporting ongoing lung development [47,48]. Similarly, both ACS and PCS facilitate cardiovascular transition by promoting closure of the ductus arteriosus [14,49].

Thus, ACS and PCS may be better thought of as complimentary perinatal therapies targeting different aspects of the transition from prenatal to postnatal life in the preterm fetus. Normally at term, activation of the fetal adrenal gland plays a key role in coordinating this transition. Rising circulating cortisol concentrations promote widespread differentiation of tissues [50], preparing the fetus for extrauterine life, and further increases in cortisol during labor and birth support postnatal transition [51]. This late gestation fetal cortisol surge also contributes to several feed-forward loops that ultimately lead to myometrial prostaglandin synthesis and onset of labour, thereby achieving synchrony between fetal maturation and parturition [52]. In preterm birth, these processes are disrupted and the fetus and preterm neonate may be affected not only by pathological processes associated with inflammation but also immaturity of the adrenal gland. ACS and PCS therapies may both have a role in addressing these perturbations.

The aim of this special edition is to consider collectively current issues in the use of ACS and PCS, in the hope that insights from one therapy may inform the other. We are delighted to have contributions from leading international experts in the field, who have provided state-of-the-art reviews regarding corticosteroid biology and mechanisms [53] optimisation of ACS therapy [54], obstetric controversies in ACS [55]; ACS use after 34 weeks' gestation [56]; early prophylactic PCS with hydrocortisone [57,58]; and inhaled, nebulized and intratracheal PCS [59]. Chapter 8 summaries current knowledge gaps and research priorities [60].

Regardless of whether they are administered before or after birth, optimal use of corticosteroids across the perinatal period requires careful consideration of data from basic science and randomized trials, and clinical judgement as to the appropriate balance of short and long-term benefits and risks. We hope that this edition will assist readers in achieving this goal.

References

[1] National Institutes of Health. Effect of corticosteroids for fetal maturation on perinatal outcomes. Consens Statement 1994;12(2):1–24.

[2] Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2017;3:CD004454.

[3] Gough A, Spence D, Linden M, Halliday HL, McGarvey LPA. General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia: a systematic review. Chest 2012;141(6):1554–67.

[4] Buckingham S, McNary WF, Sommers SC, Rothschild J. Is lung an analog of Moog's developing intestine? Phosphatases and pulmonary alveolar differentiation in fetal rabbits. Fed Proc 1968;27:328.

[5] Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 1969;45(4):515–23.

[6] Reynolds L, Tansey E, editors. Prenatal corticosteroids for reducing morbidity and mortality after preterm birth. London: The Wellcome Trust Centre for the History of Medicine; 2005.

[7] Howie RN, Liggins GC. Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in pre-term infants. In: Andersen A, Beard R, Brundell J, Dunn P, editors. Pre-term labour: proceedings of the fifth study group of the Royal College of Obstetricians and Gynaecologists. London: Royal College of Obstetricians and Gynaecologists; 1977. p. 281–9.

[8] Quinlivan JA, Evans SF, Dunlop SA, Beazley LD, Newnham JP. Use of corticosteroids by Australian obstetricians–a survey of clinical practice. Aust N Z J Obstet Gynaecol 1998;38(1):1–7.

[9] Brocklehurst P, Gates S, McKenzie-McHarg K, Alfirevic Z, Chamberlain G. Are we prescribing multiple courses of antenatal corticosteroids? A survey of practice in the UK. Br J Obstet Gynaecol 1999;106(9):977–9.

[10] Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006;3:CD004454https://doi.org/10.1002/14651858.CD004454.pub2.

[11] Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341(8850):938–41.

[12] Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CR. Glucocorticoid exposure in utero: new model for adult hypertension. Lancet 1993;341(8841):339–41.

[13] National Institutes of Health. Antenatal corticosteroids revisited: repeat courses. NIH Consens Statement 2000;17(2):1–18.

[14] McKinlay CJD, Crowther CA, Middleton P, Harding JE. Repeat antenatal glucocorticoids for women at risk of preterm birth: a Cochrane systematic review. Am J Obstet Gynecol 2012;206(3):187–94.

[15] Crowther CA, Middleton PF, Voysey M, Askie L, Zhang S, Martlow TK, et al. Effects of repeat prenatal corticosteroids given to women at risk of preterm birth: an individual participant data meta-analysis. PLoS Med 2019;16(4):e1002771.

[16] Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. BMJ 2005;331(7518):665.

[17] Dalziel SR, Fenwick S, Cundy T, Parag V, Beck TJ, Rodgers A, et al. Peak bone mass after exposure to antenatal betamethasone and prematurity: follow-up of a randomized controlled trial. J Bone Miner Res 2006;21(8):1175–86.

[18] Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet 2005;365(9474):1856–62.

[19] Dalziel SR, Rea HH, Walker NK, Parag V, Mantell C, Rodgers A, et al. Long term effects of antenatal betamethasone on lung function: 30 year follow up of a

randomised controlled trial. Thorax 2006;61(8):678–83.
[20] Crowther CA, Anderson PJ, McKinlay CJ, Harding JE, Ashwood PJ, Haslam RR, et al. Mid-childhood outcomes of repeat antenatal corticosteroids: a randomized controlled trial. Pediatrics 2016;138(4):e20160947.
[21] McKinlay CJD, Cutfield WS, Battin MR, Dalziel SR, Crowther CA, Harding JE. Cardiovascular risk factors in children after repeat antenatal glucocorticoids: an RCT. Pediatrics 2015;135(2):e405–15.
[22] McKinlay CJD, Cutfield WS, Battin MR, Dalziel SR, Crowther CA, Harding JE. Mid-childhood bone mass after exposure to repeat doses of antenatal glucocorticoids: a randomized trial. Pediatrics 2017. https://doi.org/10.1542/peds.2016-4250.
[23] Cartwright RD, Crowther CA, Anderson PJ, Harding JE, Doyle LW, McKinlay CJD. Association of fetal growth restriction with neurocognitive function after repeated antenatal betamethasone treatment vs placebo: secondary analysis of the ACTORDS randomized clinical trial. JAMA Netw Open 2019;2(2):e187636.
[24] Cartwright RD, Harding JE, Crowther CA, Cutfield WS, Battin MR, Dalziel SR, et al. Repeat antenatal betamethasone and cardiometabolic outcomes. Pediatrics 2018;142(1):e20180522.
[25] Tuohy JF, Harding JE, Crowther CA, Bloomfield FH. Reported adherence to current antenatal corticosteroid guidelines in Australia and New Zealand. Aust N Z J Obstet Gynaecol 2018. https://doi.org/10.1111/ajo.12890.
[26] Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. N Engl J Med 1989;320(23):1505–10.
[27] Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. Lancet 1983;1(8338):1356–8.
[28] Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics 1998;101(5):E7.
[29] O'Shea TM, Kothadia JM, Klinepeter KL, Goldstein DJ, Jackson BG, Weaver 3rd RG, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics 1999;104(1 Pt 1):15–21.
[30] Uno H, Eisele S, Sakai A, Shelton S, Baker E, DeJesus O, et al. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 1994;28(4):336–48.
[31] Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I. Hippocampus. Brain Res Dev Brain Res 1990;53(2):157–67.
[32] Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. Pediatrics 2006;117(1):75–83.
[33] Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. J Am Med Assoc 2015;314(10):1039–51.
[34] Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia. J Pediatr 2014;165(6):1258–60.
[35] Schmidt AF, Kemp MW, Rittenschober-Bohm J, Kannan PS, Usuda H, Saito M, et al. Low-dose betamethasone-acetate for fetal lung maturation in preterm sheep. Am J Obstet Gynecol 2018;218(1). 132.e1-.e9.
[36] Kemp MW, Saito M, Usuda H, Watanabe S, Sato S, Hanita T, et al. The efficacy of antenatal steroid therapy is dependent on the duration of low-concentration fetal exposure: evidence from a sheep model of pregnancy. Am J Obstet Gynecol 2018;219(3). 301.e1-.e16.
[37] Haas DM, Lai D, Sharma S, Then J, Kho A, Flockhart DA, et al. Steroid pathway genes and neonatal respiratory distress after betamethasone use in anticipated preterm birth. Reprod Sci 2016;23(5):680–6.
[38] Sundahl N, Bridelance J, Libert C, De Bosscher K, Beck IM. Selective glucocorticoid receptor modulation: new directions with non-steroidal scaffolds. Pharmacol Ther 2015;152:28–41.
[39] Khandelwal M, Chang E, Hansen C, Hunter K, Milcarek B. Betamethasone dosing interval: 12 or 24 hours apart? A randomized, noninferiority open trial. Am J Obstet Gynecol 2012;206(3). 201.e1-.e11.
[40] Crowther CA, Harding JE, Middleton PF, Andersen CC, Ashwood P, Robinson JS. Australasian randomised trial to evaluate the role of maternal intramuscular dexamethasone versus betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability (A*STEROID): study protocol. BMC Pregnancy Childbirth 2013;13:104.
[41] Crowther CA, Middleton PF, Andersen CC, Ashwood P, Doyle LW, Robinson JS, et al. Dexamethasone or betamethasone prior to preterm birth to increase survival free of childhood neurosensory disability: the A*STEROID Trial. J Paediatr Child Health 2017;53(S2):22.
[42] Jobe AH. Glucocorticoids, inflammation and the perinatal lung. Semin Neonatol 2001;6:331–42.
[43] Kent A, Lomas F, Hurrion E, Dahlstrom JE. Antenatal steroids may reduce adverse neurological outcome following chorioamnionitis: neurodevelopmental outcome and chorioamnionitis in premature infants. J Paediatr Child Health 2005;41(4):186–90.
[44] Yoo HS, Chang YS, Kim JK, Ahn SY, Kim ES, Sung DK, et al. Antenatal betamethasone attenuates intrauterine infection-aggravated hyperoxia-induced lung injury in neonatal rats. Pediatr Res 2013;73(6):726–33.
[45] Kuypers E, Jellema RK, Ophelders DR, Dudink J, Nikiforou M, Wolfs TG, et al. Effects of intra-amniotic lipopolysaccharide and maternal betamethasone on brain inflammation in fetal sheep. PLoS One 2013;8(12):e81644.
[46] Hillman NH, Pillow JJ, Ball MK, Polglase GR, Kallapur SG, Jobe AH. Antenatal and postnatal corticosteroid and resuscitation induced lung injury in preterm sheep. Respir Res 2009;10:124.
[47] Kothe TB, Royse E, Kemp MW, Schmidt A, Salomone F, Saito M, et al. Effects of budesonide and surfactant in preterm fetal sheep. Am J Physiol Lung Cell Mol Physiol 2018;315(2). L193–l201.
[48] Yang CF, Jeng MJ, Soong WJ, Lee YS, Tsao PC, Tang RB. Acute pathophysiological effects of intratracheal instillation of budesonide and exogenous surfactant in a neonatal surfactant-depleted piglet model. Pediatr Neonatol 2010;51(4):219–26.
[49] Shaffer ML, Baud O, Lacaze-Masmonteil T, Peltoniemi OM, Bonsante F, Watterberg KL. Effect of prophylaxis for early adrenal insufficiency using low-dose hydrocortisone in very preterm infants: an individual patient data meta-analysis. J Pediatr 2019;207. 136-142.e5.
[50] McKinlay CJ, Dalziel SR, Harding JE. Antenatal glucocorticoids: where are we after forty years? J Dev Orig Health Dis 2015;6(2):127–42.
[51] Fowden AL, Li J, Forhead AJ. Glucocorticoids and the preparation for life after birth: are there long-term consequences of the life insurance? Proc Nutr Soc 1998;57(1):113–22.
[52] Challis JR, Sloboda DM, Alfaidy N, Lye SJ, Gibb W, Patel FA, et al. Prostaglandins and mechanisms of preterm birth. Reproduction 2002;124(1):1–17.
[53] Hooper S, Cole T. The science of steroids. Seminars in Fetal & Neonatal Medicine; 2019.
[54] Kemp MW, Schmidt AF, Jobe AH. Optimizing antenatal corticosteroid therapy. Semin Fetal Neonatal Med 2019. https://doi.org/10.1016/j.siny.2019.05.003.
[55] Shanks AL, Grasch JL, Quinney SK, Haas DM. Controversies in antenatal corticosteroids seminars in fetal & neonatal medicine. 2019.
[56] Groom KM. Antenatal corticosteroids after 34 Weeks gestation: do we have the evidence? Semin Fetal Neonatal Med 2019. https://doi.org/10.1016/j.siny.2019.03.001.
[57] Cheong JLY, Doyle L. Long-term effects of postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia: balancing the risks and benefits. Semin Fetal Neonatal Med 2019. https://doi.org/10.1016/j.siny.2019.03.002.
[58] Baud O, Watterberg K. Prophylactic postnatal corticosteroids: early hydrocortisone. Semin Fetal Neonatal Med 2019. https://doi.org/10.1016/j.siny.2019.04.007.
[59] Rüegger CM, Bassler D. Alternatives to systemic postnatal corticosteroids: inhaled, nebulized and intratracheal. Semin Fetal Neonatal Med 2019. https://doi.org/10.1016/j.siny.2019.04.006.
[60] Manley B, McKinlay. *Semin Fetal Neonatal Med.* 2019.