Review article for special issue of CJPP: Connecting maternal, fetal, and newborn physiology

Neonatal Stress and Resilience - Lasting Effects of Antenatal Corticosteroids

Alan H. Jobe, M.D., Ph.D.

Correspondence:

Alan H. Jobe, M.D., Ph.D.

Cincinnati Children's Hospital Medical Center

3333 Burnet Avenue, MLC 7029

Cincinnati, OH 45229-3039

This review summarizes a lecture for the 5th Canadian National Perinatal Meeting, Banff, Alberta Canada - February 14-17, 2018

Funding: No industry or grant funding.

Abstract

Antenatal corticosteroids (ACS) are standard of care for women at risk of preterm delivery between 24 -34 weeks gestation. Their use decreases preterm morbidities and mortality. However, ACS treatments mimic a stress response by increasing fetal steroid levels at early gestational ages when the fetus is normally protected from high glucocorticoid levels. Within the context of concept of the developmental origins of adult health and disease, ACS are effective stressors in fetal animal models that alter developmental programs and outcome in adult animals. Although few short-term adverse effects of ACS in infants and children are apparent, there are cohort studies demonstrating cognitive, metabolic and cardiovascular effects in humans beyond 30-years of age. ACS likely interact with other stresses – maternal diseases complicating prematurity, premature delivery and nutritional deficiencies -- to program outcomes that may not be known for many years. The risks of ACS will increase as indications for ACS increase to late gestation preterm infants and possibly C-section deliveries.

Key words: premature infants, neurodevelopment, antenatal injury, postnatal injury, programming.

The human fetus and preterm newborn are thought to be exceptionally vulnerable to the adverse effects of multiple toxins, maternal nutritional abnormalities and stresses that can alter development and adversely affect lifelong outcomes (Fig. 1). These adverse exposures include preconceptional nutrition that may alter fetal growth across generations. A particularly concerning multicomponent adverse stress is preterm delivery with all its associations with maternal diseases such as pre-eclampsia, growth restriction, and infection. Postnatal abnormalities associated with preterm delivery such as respiratory distress syndrome and intraventricular hemorrhage contribute to increased mortality after preterm birth. Slow postnatal growth often results in a postdelivery growth restriction despite intensive efforts to achieve good growth. Nevertheless, the majority of very preterm infants born at 24 to 30 weeks gestational age survive and become healthy adults, albeit with an increased incidence of neurodevelopmental deficits. This clinical experience is more optimistic than the results with animal models that demonstrate that a variety of single fetal or early life experiences can interfere with normal development. Empirically the human preterm seems to have substantial resilience, plasticity, and tolerance to compensate for the adversities surrounding preterm birth. The clinical management of abnormal pregnancies and premature infants appropriately focuses on optimizing short term survival, rather than with concerns about diseases such as heart attack or stroke in later life. Nevertheless, the concept of the developmental origins of adult health and disease cautions that there may be substantial risks from early life events for adverse outcomes in later life.

Antenatal corticosteroids (ANS) as a fetal/newborn stress

The normal fetus is exposed to very low levels of cortisol until just prior to delivery at term, because fetal cortisol production is very low, and the placenta prevents substantial amounts of maternal cortisol from entering the fetal circulation. Increased fetal cortisol levels induce organ maturation, and the cortisol increase just prior to normal labor promotes neonatal adaptation (Padbury et al. 1995). Any large increases in fetal cortisol prior to term presumably represent a fetal stress response that can program subsequent development. Within that context, the standard of care for women at risk of preterm delivery at 24-34 weeks gestational age is treatment with either of the potent fluorinated corticosteroids - betamethasone or dexamethasone (Roberts et al. 2017). These steroids readily cross the placenta to induce fetal organ maturation and decrease infant morbidity and mortality. These single treatments or repeated treatments if delivery has not occurred within 7 to 14 days and the fetus is still <34 weeks' gestational age should be a substantial stress signal to the fetus. Subsequently, multiple abnormal stimulations other than ACS inevitably occur in the care of the premature infant. The fetal steroid exposure may also program newborn and later life responses even if delivery was at term.

Some results from animal models

ANS treatments expose the fetus to the prototypic stress response that has been used extensively in experimental systems to demonstrate programming effects and to explore the mechanisms of those effects (Moisiadis and Matthews 2014). The experimental literature about fetal and early life corticosteroid exposures is vast, and primarily based on rodent models. A recent example from Steven Matthews' group in

Toronto is that 3 courses of maternal betamethasone treatment altered gene expression for 3 generations in guinea pigs (Moisiadis et al. 2017). Fetal sheep exposed to a two day maternal infusion of 0.28 mg/kg/d dexamethasone at 19% of gestation had increased blood pressure as newborns and to 7 years of age (Dodic et al. 2001). At 7 years of age cardiac output and stroke volume were increased by fetal steroid exposure, but the cardiac output was poorly responsive to dobutamine infusions relative to control animals (Dodic et al. 2001). While kidney weights were comparable for control and the 2-day fetal dexamethasone exposure groups at 7 years, glomerular number was decreased by 38% (Wintour et al. 2003). In contrast, a 2-day dexamethasone infusion at 41% of gestation had no effect on cardiovascular variables or glomerular number (Dodic et al. 2001). A clinical dose of betamethasone at about 55% of gestation glomerular filtration rate and again decreased nephron number in sheep, demonstrating that long term corticosteroid effects are sensitive to developmental timing of the exposures (Zhang et al. 2010). There is minimal information in humans about sensitive periods for ACS exposures on development, which is a concern as more immature periviable fetuses are being exposed to ACS.

Another intriguing result with fetal sheep is the report by Massmann et al. (Massmann et al. 2017) that combines ACS and postnatal obesity. Pregnant ewes were randomized to the clinical ACS treatment or placebo at 80 days and the lambs were allowed to deliver at term. The lambs were then randomized to normal or obese-generating diets for 3 months beginning at 9 months of age. At 1 year insulin responses to a glucose challenge were abnormal in normal weight females exposed to ACS but not

normal weight male sheep exposed to ACS. Obesity increased the abnormal insulin responses in females and uncovered abnormal responses in males exposed to ACS. The experiment demonstrated that the fetal ACS exposure was augmented by postnatal obesity, indicating that risks may increase as the number of exposures increase. Three year old male baboons (exposed to 3 repeated clinical courses of ACS) and delivered at term made more errors with touch screen training than controls, an effect not detected in the ACS exposed females (Rodriguez et al. 2011). Sex specific responses of programming have been frequently observed. Pericardial and hepatic fat were increased in 11-year-old baboons that had ACS exposure, findings indicative of increased cardiovascular disease risk (Kuo et al. 2018). Morisiadis and Matthews have identified programming of the hypothalamic/pituitary/adrenal axis as pathways altered by ACS (Moisiadis and Matthews 2014).

Clinical observations of outcomes from ACS

The randomized controlled trials (RCT) for single courses of ACS prior to 1993 demonstrated decreased RDS and mortality and other adverse outcomes for premature infants delivered prior to 34 weeks gestational age (Roberts et al. 2017). These multiorgan effects demonstrate that ACS have large and pleotropic effects on the human fetus and newborn. Follow-up of these individuals at 30 years demonstrated no long term adverse effects on growth, cardiovascular or metabolic health (Dalziel et al. 2005). However, these individuals had average birth weights of 2.3 Kg, and thus, they are not representative of the very preterm infants now surviving after an ACS exposure (Jobe and Goldenberg 2018). In the current era, the high survival rate of these very preterm

infants demonstrates their "resilience" to tolerate multiple adverse exposures. However, there are cohort studies that support that their resilience or plasticity may be decreased as a price for the short-term benefits of ACS exposure.

The majority of fetuses exposed to ACS will not deliver in the interval of 24 hours to 7 days or at <34 weeks gestational age considered to result in improved outcomes (Makhija et al. 2016). The ACS treatments thus are off-target and may cause only risk to the newborn. An example is the report that infants born at term to women evaluated for preterm labor that received ACS, tocolytics and antibiotics had lower cognition than a matched cohort of infants not exposed to the evaluation and initial treatments for preterm labor (Paules et al. 2017). The adverse off-target outcomes from the multicomponent treatment does not identify ACS as the cause of the lower cognition, but ACS were the most potent fetal exposure likely to alter fetal development. Another cohort study demonstrated that ACS were associated with an increased stress response as measured by an increase in cortisol at 8 years of age in females exposed as preterm fetuses to ACS and with term delivery compared to normal term delivered females (Alexander et al. 2012). Newborns exposed to ACS and delivered at <34 weeks had similar birth weights to a non-exposed group (Roberts et al. 2017). However, ACS before 34 weeks with delivery from 34 weeks to term resulted in decreased birth weights (Braun et al. 2015). These examples suggest that preterm fetal ACS can alter fetal growth, postnatal cognition and stress responses even when the individual delivered at term without exposure to the risks associated with preterm birth. Definitive studies would require randomization to the ACS exposure.

Other recent examples of ACS exposure and preterm birth in comparison with infants born preterm but not exposed to ACS suggest adverse programming effects with lifetime implications. Young adults exposed to ACS and born at about 29 weeks had increased aortic pulse velocity and decreased distensibility at 23-28 years of age relative to a no ACS group that also delivered preterm (Kelly et al. 2012). When analyzed for ACS exposure very premature infants with a mean birth weight of 0.84 kg and birth gestation of 27 weeks had more psychopathology at about 30 years of age that comparable infants not exposed to ACS (Savoy et al. 2016). These and other cohort studies must be interpreted with caution because pregnancies exposed to ACS may differ substantially from the no-ACS pregnancies, particularly when >90% of deliveries <34 weeks were exposed to ACS (Jobe and Goldenberg 2018).

The context for ACS

ACS treatments are potent modulators of development that likely have different effects at different times of exposure during fetal development. Any ACS effects very likely interact with other fetal exposures that result in premature delivery and subsequently with the postnatal experiences of the preterm infant (Fig. 2). ACS promote "resilience" from the perspective of decreased mortality and lower incidence of complications of prematurity. However, resilience to subsequent environmental exposures may be decreased by interfering with development and promoting (forcing) early organ maturation. A recent report demonstrates that early life experiences alters

DNA methylation and somatic variation in mice (Bedrosian et al. 2018). Fetal and premature infant stimuli are essential for normal development, but too little stimulation can result in sensory deprivation, and too much stimulation translates to stress, pain, and injury (Jobe 2014). There is no consensus as to the optimal amount of which type of stimulation will promote normal development. ACS are a major "stress" exposure that have benefits with few short-term risks but with virtually unknown life-course risks. The importance of risks increase when ACS are used for minimal benefit such as for late preterm pregnancies or elective Cesarean sections at term (Jobe and Goldenberg 2018).

Bibliography:

Alexander, N., Rosenlocher, F., Stalder, T., Linke, J., Distler, W., Morgner, J., and Kirschbaum, C. 2012. Impact of antenatal synthetic glucocorticoid exposure on endocrine stress reactivity in term-born children. J Clin Endocrinol Metab. **97**(10): 3538-3544. doi: 10.1210/jc.2012-1970.

Bedrosian, T.A., Quayle, C., Novaresi, N., and Gage, F.H. 2018. Early life experience drives structural variation of neural genomes in mice. Science, **359**(6382): 1395-1399. doi: 10.1126/science.aah3378.

Braun, T., Sloboda, D.M., Tutschek, B., Harder, T., Challis, J.R., Dudenhausen, J.W., Plagemann, A., and Henrich, W. 2015. Fetal and neonatal outcomes after term and preterm delivery following betamethasone administration. Int J Gynaecol Obstet. **130**(1): 64-69. doi: 10.1016/j.ijgo.2015.01.013.

Dalziel, S.R., Walker, N.K., Parag, V., Mantell, C., Rea, H.H., Rodgers, A., and Harding, J.E. 2005. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. Lancet, **365**(9474): 1856-1862. doi: 10.1016/S0140-6736(05)66617-2.

Dodic, M., Samuel, C., Moritz, K., Wintour, E.M., Morgan, J., Grigg, L., and Wong, J. 2001. Impaired cardiac functional reserve and left ventricular hypertrophy in adult sheep after prenatal dexamethasone exposure. Circ Res. **89**(7): 623-629.

Jobe, A.H. 2014. A risk of sensory deprivation in the neonatal intensive care unit. J Pediatr **164**(6): 1265-1267. doi: 10.1016/j.jpeds.2014.01.072.

Jobe, A.H., and Goldenberg, R.L. 2018. Antenatal Corticosteroids: An assessment of anticipated benefits and potential risks. Am J Obstet Gynecol. doi: 10.1016/j.ajog.2018.04.007.

Kelly, B.A., Lewandowski, A.J., Worton, S.A., Davis, E.F., Lazdam, M., Francis, J., Neubauer, S., Lucas, A., Singhal, A., and Leeson, P. 2012. Antenatal glucocorticoid exposure and long-term alterations in aortic function and glucose metabolism. Pediatrics, **129**(5): e1282-1290. doi: 10.1542/peds.2011-3175.

Kuo, A.H., Li, C., Mattern, V., Huber, H.F., Comuzzie, A., Cox, L., Schwab, M., Nathanielsz, P.W., and Clarke, G.D. 2018. Sex-dimorphic acceleration of pericardial, subcutaneous, and plasma lipid increase in offspring of poorly nourished baboons. Int J Obes. (Lond). doi: 10.1038/s41366-018-0008-2.

Makhija, N.K., Tronnes, A.A., Dunlap, B.S., Schulkin, J., and Lannon, S.M. 2016. Antenatal corticosteroid timing: accuracy after the introduction of a rescue course protocol. Am J Obstet Gynecol. **214**(1): 120 e121-126. doi: 10.1016/j.ajog.2015.08.018.

Massmann, G.A., Zhang, J., Seong, W.J., Kim, M., and Figueroa, J.P. 2017. Sex-dependent effects of antenatal glucocorticoids on insulin sensitivity in adult sheep: role of the adipose tissue renin angiotensin system. Am J Physiol Regul Integr Comp Physiol. **312**(6): R1029-R1038. doi: 10.1152/ajpregu.00181.2016.

Moisiadis, V.G., Constantinof, A., Kostaki, A., Szyf, M., and Matthews, S.G. 2017. Prenatal Glucocorticoid Exposure Modifies Endocrine Function and Behaviour for 3 Generations Following Maternal and Paternal Transmission. Sci Rep. **7**(1): 11814. doi: 10.1038/s41598-017-11635-w.

Moisiadis, V.G., and Matthews, S.G. 2014. Glucocorticoids and fetal programming part 1: Outcomes. Nat Rev Endocrinol. **10**(7): 391-402. doi: 10.1038/nrendo.2014.73.

Padbury, J.F., Polk, D.H., Ervin, M.G., Berry, L.M., Ikegami, M., and Jobe, A.H. 1995. Postnatal cardiovascular and metabolic responses to a single intramuscular dose of betamethasone in fetal sheep born prematurely by cesarean section. Pediatr Res. **38**(5): 709-715. doi: 10.1203/00006450-199511000-00013.

Paules, C., Pueyo, V., Marti, E., de Vilchez, S., Burd, I., Calvo, P., and Oros, D. 2017. Threatened preterm labor is a risk factor for impaired cognitive development in early childhood. Am J Obstet Gynecol. **216**(2): 157 e151-157 e157. doi: 10.1016/j.ajog.2016.10.022.

Roberts, D., Brown, J., Medley, N., and Dalziel, S.R. 2017. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev **3**: CD004454. doi: 10.1002/14651858.CD004454.pub3.

Rodriguez, J.S., Zurcher, N.R., Keenan, K.E., Bartlett, T.Q., Nathanielsz, P.W., and Nijland, M.J. 2011. Prenatal betamethasone exposure has sex specific effects in reversal learning and attention in juvenile baboons. Am J Obstet Gynecol. **204**(6): 545 e541-510. doi: 10.1016/j.ajog.2011.01.063.

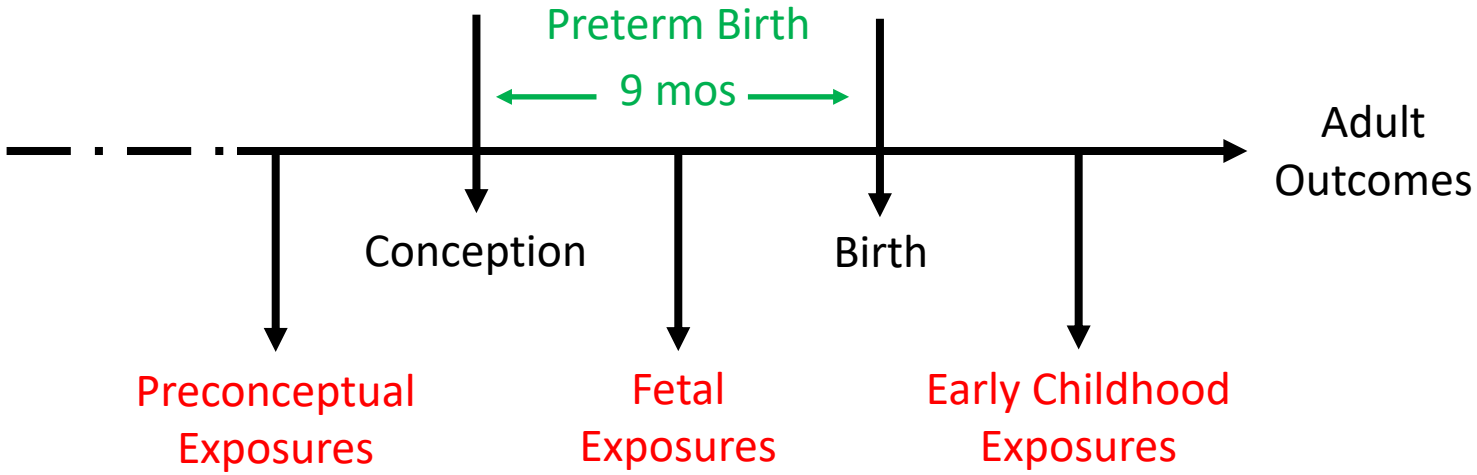
Savoy, C., Ferro, M.A., Schmidt, L.A., Saigal, S., and Van Lieshout, R.J. 2016. Prenatal betamethasone exposure and psychopathology risk in extremely low birth weight survivors in the third and fourth decades of life. Psychoneuroendocrinology, **74**: 278-285. doi: 10.1016/j.psyneuen.2016.09.021.

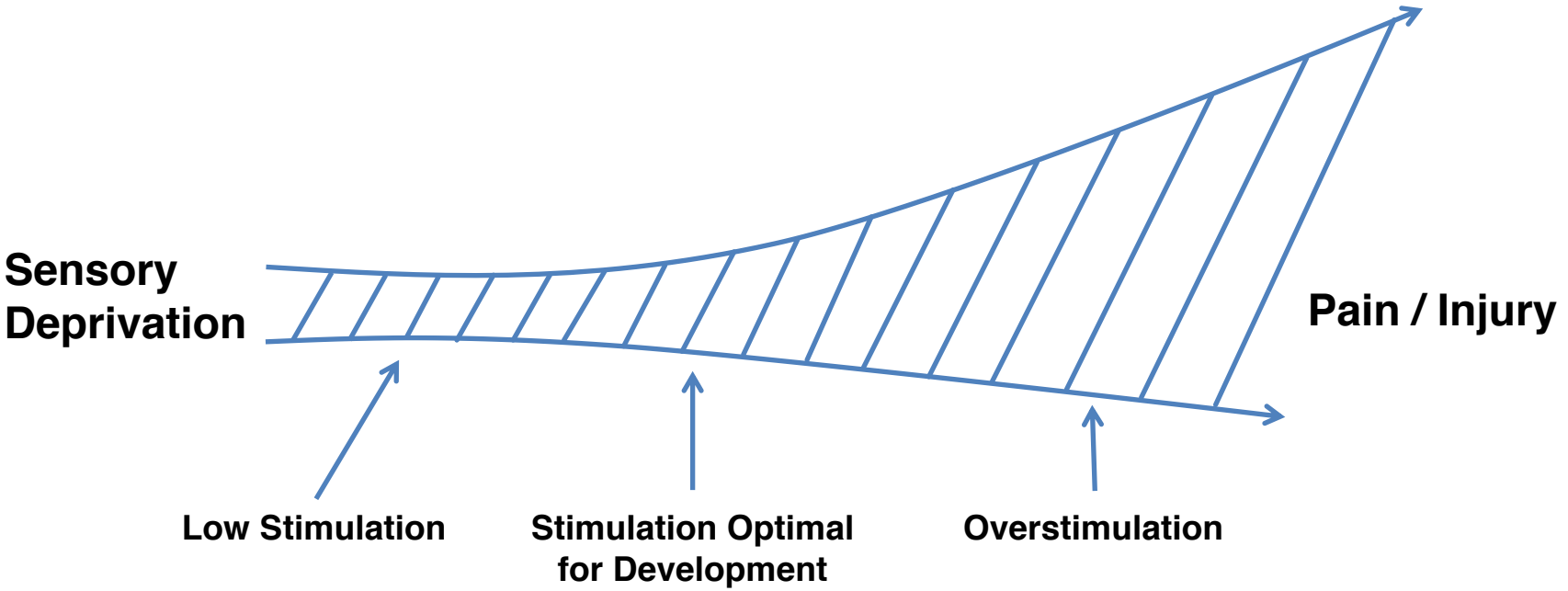
Wintour, E.M., Moritz, K.M., Johnson, K., Ricardo, S., Samuel, C.S., and Dodic, M. 2003. Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. J Physiol. **549**(Pt 3): 929-935. doi: 10.1113/jphysiol.2003.042408.

Zhang, J., Massmann, G.A., Rose, J.C., and Figueroa, J.P. 2010. Differential effects of clinical doses of antenatal betamethasone on nephron endowment and glomerular filtration rate in adult sheep. Reprod Sci. **17**(2): 186-195. doi: 10.1177/1933719109351098.

Figure caption:
Fig. 1
Legend: Developmental exposures from preconception to childhood can alter diseases in the adult. Every fetus and newborn will have multiple exposures that in combination will modulate phenotype.

Fig. 2
Legend: A schematic of sensory exposures to emphasize that an exposure may be essential for optimal development, but low or high exposure may be harmful.





Stimulations	Variables
Light	Gestational age
Sound	Fetal sex
Neuromotor	Maturational state
Tactile	Genetics
Antenatal corticosteroids	Prior and subsequent stimulations