CHAPTER 14

Programming Effects of Excess Glucocorticoid Exposure in Late Gestation

Timothy J.M. Moss* and Deborah M. Sloboda

Abstract

Glucocorticoids are powerful hormones that play a crucial role in normal maturation of fetal organs in preparation for life outside the womb. However, exposure of the fetus to elevated levels of glucocorticoids, or exposure at inappropriate times, subtly disturbs normal fetal development. Experimental studies have demonstrated that late gestational exposure to excess glucocorticoids causes programming of a number of organ systems.

Introduction

In the late 1960s and early 1970s a series of experiments conducted by Sir Graeme 'Mont' Liggins in New Zealand led to the use of maternal glucocorticoid treatment for the prevention of respiratory distress syndrome in preterm babies.[1] He had shown that preterm lambs born after infusion of the synthetic glucocorticoid, dexamethasone, were able to breathe effectively, despite delivery at an age at which immaturity of their lungs would normally make this impossible.[2] By harnessing the potent maturational effects of glucocorticoids, the therapy devised by Mont Liggins has improved or saved the lives of thousands of preterm infants.

In recent years it has become evident that exposure of the fetus to inappropriately high levels of either endogenous or exogenous glucocorticoids can cause programming, whereby the long term health of an individual is affected by subtle developmental alterations that cause permanent changes to the body's tissues, organs and systems.[3] Furthermore, elevated fetal exposure to glucocorticoids is a common characteristic of a variety of interventions with programming effects, such as maternal under nutrition.[4,5] In this chapter we highlight the major programming effects of excess glucocorticoid exposure in late gestation, rather than exposure early in gestation or throughout its entirety. We focus on programming effects of the clinical use of glucocorticoids, as demonstrated by human studies, and on our own investigations in sheep, using glucocorticoid treatments designed to mimic those used clinically (see Table 1).

Normal Glucocorticoid Levels in Late Gestation

Normally, glucocorticoid production by the fetal adrenal gland is high in early gestation and becomes reduced during mid-late gestation.[6,7] Maintenance of these normal low levels of glucocorticoids is essential for normal fetal growth and development. The fetus is usually 'protected' from exposure to circulating maternal cortisol by the presence of the enzyme 11βhydroxysteroid dehydrogenase type 2 (11βHSD2) in the placenta, which converts active cortisol to inactive cortisone.

*Corresponding Author: Timothy J.M. Moss—School of Women's and Infants' Health, University of Western Australia, Box m094, 35 Stirling Highway, Crawley, Western Australia 6009, Australia. Email: tmoss@cyllene.uwa.edu.au

Early Life Origins of Health and Disease, edited by E. Marelyn Wintour and Julie A. Owens.

Table 1. Timing of late gestational glucocorticoid treatment used in our sheep experiment

Treatment Group	Gestational Age 104 Days	111 Days	118 Days	124 Days
Control	Saline	Saline	Saline	Saline
Single treatment	Betamethasone	Saline	Saline	Saline
Repeated treatment	Betamethasone	Betamethasone	Betamethasone	Betamethasone

Maternal or ultrasound-guided fetal intramuscular betamethasone injections (0.5 mg/kg maternal or fetal bodyweight, respectively) are given at gestational ages of 65-85% of full term. Antenatal corticosteroid treatment is recommended for women at risk of preterm delivery between 24-34 weeks' gestation (60-85% of full term).[79] In recent years, the use of repeated courses of antenatal corticosteroid treatment was common.[80]

In many mammalian species circulating fetal cortisol (the principal glucocorticoid in most mammals, including humans) levels rise exponentially in the days leading up to birth (Fig. 1)[8] as a result of increased activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis. These rising glucocorticoid levels not only contribute to the initiation of parturition but also cause a switch in many cells from division to differentiation, thus slowing fetal growth and causing maturation of a variety of organs in order to prepare the late gestation fetus for extrauterine life. An extensive list of cellular functions affected by glucocorticoids in utero is provided in an excellent review of the programming effects of various endocrine factors.[9]

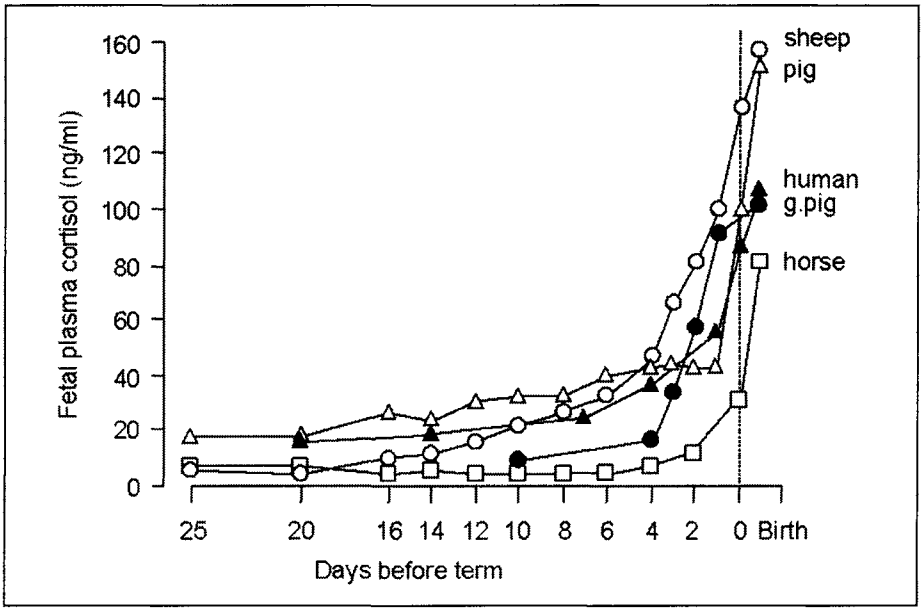

Figure 1. Endogenous glucocorticoid levels in late gestation for various mammalian species. Reprinted with permission from The Nutritional Society. Fowden AL, Li J, Forhead AJ. Glucocorticoids and the preparation for life after birth: are there long-term consequences of the life insurance? The Procedings of The Nutritional Society, 1998; 57:113-122. ©1998 The Nutritional Society.

Excess Glucocorticoids and Direct Effects on Fetal Growth

The normal late gestational slowing of fetal growth in sheep can be abolished by adrenalectomy, and premature increases in cortisol by exogenous infusion causes the fetal growth rate to slow early.[10] Thus, in many species, intrauterine growth restriction (IUGR) is a direct consequence of late gestation exposure of the fetus to excess glucocorticoids.

Administration of the synthetic glucocorticoid, betamethasone, to pregnant sheep, in doses and at times that mimics clinical use in pregnant women, causes IUGR.[11] While single courses of antenatal glucocorticoids used in obstetric practice do not cause IUGR,[12] repeated treatment given to women at continual risk of preterm birth can have adverse effects on fetal growth.[13,14] Determination of the effects of repeated glucocorticoid treatments, the use of which arose mainly from an incomplete understanding of long term efficacy of the therapy and the supposition that 'more is better,[15] are currently the subject of randomised controlled trials.

In contrast to the direct fetal growth restricting effects of maternal betamethasone we have observed, direct ultrasound-guided fetal injections of betamethasone do not cause IUGR.[11,16] We believe the growth restricting effect of maternal betamethasone is due to the prolonged duration of fetal exposure to betamethasone that occurs after maternal injection.[17] Consistent with this, previous studies in which fetuses received intravenous cortisol infusions demonstrated that fetal growth begins to slow only after approximately a day of exposure.[10]

Excess Glucocorticoids and Programming

Early studies by David Barker, which showed associations between low birthweight and subsequent 'adult-onset' diseases, suggest that the direct growth restricting effects of late gestation glucocorticoid exposure might be accompanied by later programmed physiological perturbations. This indeed seems to be the case[3,9] and it is evident that fetal exposure to glucocorticoids is a common, and critical, consequence of a number of experimental interventions that affect fetal programming.[4,5,18] However, like any other programming stimulus, the effects of exposure to excess glucocorticoids are dependent on the timing of the insult and the sex of the fetus. The programming effects of excess glucocorticoid exposure in late gestation are summarised below.

Late Gestational Glucocorticoids and Programming of Metabolism

In recent years the health of millions throughout the world has been threatened by an upsurge in the incidence of 'the metabolic syndrome' or 'Syndrome X', the constituents of which include type 2 diabetes (glucose intolerance/insulin resistance), hyperlipidemia, hypertension and obesity.[19] Since Prof. David Barker's initial investigations, demonstrating an association between birthweight and the incidence of type 2 diabetes,[20] it has become well established that an individual's intrauterine environment influences their risk of developing the metabolic syndrome and that fetal exposure to glucocorticoids is the likely mediator of this effect.[21]

Using a protocol designed to mimic clinical use of glucocorticoids for women at risk of preterm birth, we have shown that single or repeated maternal betamethasone injections, given to pregnant sheep during the final third of pregnancy, cause alterations in postnatal glucose metabolism of their offspring.[16] In this same study we showed that direct fetal injections had similar effects on postnatal glucose metabolism; prenatal betamethasone exposure resulted in elevated insulin responses to intravenous glucose administration, suggesting these sheep were insulin resistant. The different effects on fetal growth of maternal or fetal betamethasone injection (outlined above) allowed us to demonstrate that effects on postnatal glucose metabolism of late gestation glucocorticoid exposure occur independently of effects on fetal growth.[16]

Our studies in sheep are consistent with investigations conducted using rats, which have begun to illustrate the likely molecular mediators of the programming effects of late gestation glucocorticoids on postnatal metabolism. Administration of the synthetic glucocorticoid, dexamethasone, to rats late in pregnancy resulted in fetal growth restriction and adult offspring that

were hyperglycaemic at rest with elevated insulin responses to glucose challenge.[22] These rats had increased hepatic expression of glucocorticoid receptor (GR) and phosphoenopyruvate carboxykinase (PEPCK), the rate limiting enzyme in gluconeogenesis, which would be expected to result in increased hepatic glucose production. These effects of late gestation glucocorticoid exposure were not observed when dexamethasone was administered earlier in pregnancy.[22]

Other mechanisms that may underlie the association between late gestation glucocorticoid exposure and altered postnatal metabolism are incompletely understood. Effects of excess glucocorticoids on postnatal insulin sensitivity of peripheral tissues are complex.[23] A critical role for glucocorticoids in fetal pancreatic development is established, and fetal pancreatic insulin content is related to fetal glucocorticoid levels,[24] but there has been no thorough investigation of the effects of excess glucocorticoids in late gestation on pancreatic development. Our initial observations indicate that normal late gestational fetal pancreatic islet remodelling is altered in fetal sheep as a result of repeated maternal betamethasone injections in late gestation (unpublished).

Intergenerational programming of dexamethasone-induced growth restriction, elevated hepatic PEPCK activity and abnormal glucose homeostasis have recently been demonstrated in rats.[25] Male and female offspring of pregnant rats treated with dexamethasone during late pregnancy themselves had male offspring that were of low birthweight, with elevated hepatic PEPCK activity and abnormal glucose homeostasis, without exposure to dexamethasone during gestation. These second generation effects were not present in third generation offspring. The fact that intergenerational programming occurred in male offspring of either males or females whose mothers were treated with dexamethasone demonstrates that this phenomenon cannot be attributed to the intrauterine environment. Rather, these findings raise the intriguing possibility of epigenetic effects of late gestational dexamethasone exposure, and the persistence of genomic 'imprinting' in subsequent generations.[25]

To date, there are no published data from studies of human subjects relating to the effects on glucose metabolism of antenatal corticosteroid treatment.

Late Gestational Glucocorticoids and Programming of the Hypothalamic-Pituitary-Adrenal Axis

Normal physiology is dependent on adequate function of the HPA axis, which is responsible for regulating synthesis and release of a variety of corticosteroid hormones. Cortisol is the principle corticosteroid (in mammals other than rodents) produced by the adrenal cortex; it regulates metabolic, immune and behavioural processes, and the body's response to stressful stimuli. Cortisol acts through glucocorticoid and mineralocorticoid receptors (GR and MR, respectively), which are present in many organs. Permanent alterations in GR and/or MR gene expression have been observed in a variety of organs after manipulation of fetal glucocorticoid exposure[26] and such changes are likely to underlie some of the programming effects on HPA axis function of late gestational glucocorticoid exposure.

Administration of dexamethasone to pregnant rhesus monkeys, late in pregnancy, results in elevated basal and stress-induced circulating cortisol concentrations in juvenile offspring.[27] Rats born after maternal dexamethasone treatment throughout the last third of gestation have elevated circulating corticosteroid concentrations in adulthood, accompanied by hypertension.[28] These same rat offspring had lower GR mRNA expression levels in discrete hippocampal regions responsible for HPA axis feedback regulation, but not in brain nuclei associated with central cardiovascular control,[28] therefore the physiological programming effects of late gestation glucocorticoids in these animals appear to result from GR-mediated alterations in HPA axis regulation. In contrast, HPA axis programming does not appear to underlie postnatal hypertension induced by dexamethasone treatment in early pregnancy in sheep.[29] A short period of maternal dexamethasone treatment in late gestation did not alter early postnatal corticosteroid levels in young rats but hypothalamic CRH/AVP content was altered, which may increase HPA axis responsiveness.[30] Evidence from experiments using guinea pigs indicates that programming effects of late gestational glucocorticoid exposure on the HPA axis are age-[31]

and sex-dependent.[32,33] HPA axis function in young adult female guinea pigs, born after repeated maternal dexamethasone treatments in late pregnancy, depended on the stage of their reproductive cycle, reflecting the influence of female sex hormones.[33]

Our own longitudinal studies using sheep, and others' experiments using guinea pigs, have demonstrated that the capacity of late gestational glucocorticoid exposure to alter HPA responsiveness is dependent on postnatal age. We have demonstrated that responsiveness of the HPA axis to stimulation by corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) is elevated in one-year-old lambs after gestational exposure to maternal or fetal injection of betamethasone.[34] Later in postnatal life, adrenal responsiveness is reduced in sheep exposed in late gestation to single or repeated maternal betamethasone injections.[35] Male guinea pigs born after repeated maternal dexamethasone injections, studied as young adults, had reduced HPA axis function compared to control.[33] Older adult males, exposed to identical prenatal treatments, displayed more normal HPA axis function, despite abnormalities in hippocampal MR expression. These older male guinea pigs, born after repeated maternal dexamethasone treatments, had higher blood pressure than controls,[31] an effect not observed in younger animals.[33] These longitudinal experiments demonstrate that the effects of late gestational glucocorticoid exposure on postnatal HPA axis responsiveness are dynamic.

Published accounts of the effects of antenatal corticosteroid treatment on postnatal HPA axis function are limited to studies of neonates, which indicate that stress-induced activation of the HPA axis may be impaired, despite infants' ability to maintain normal cortisol concentrations under basal conditions.[36] Whether or not abnormalities persist throughout postnatal life remains to be determined.

Late Gestational Glucocorticoids and Programming of Blood Pressure

Administration of dexamethasone to rats throughout the final third of gestation results in offspring that are growth restricted in utero, hypertensive as adults, and have abnormal HPA function.[28] Betamethasone treatment of pregnant rats throughout this same period reduced birth weight but did not alter postnatal blood pressure.[37] There are numerous potential explanations for the discrepant findings from these two studies.[37] Other experiments using rats, in which dexamethasone treatment was restricted to shorter periods during the final third of pregnancy, have demonstrated an association between postnatal hypertension and reduced nephron endowment; but only when dexamethasone treatment occurred between 70-85% of gestation, and not at earlier or later times.[38] As mentioned above, repeated maternal dexamethasone treatments during late pregnancy (which do not significantly alter birthweight) result in hypertension in mature, but not younger adult, male offspring[31,33] but the underlying cause is unknown.

In sheep, single or repeated, maternal or fetal, betamethasone injections in late gestation do not cause hypertension in adult offspring,[39] in contrast to the established and well-characterised effects of glucocorticoid administration early in prenatal life, which causes hypertension in sheep.[40,41] Postnatal hypertension resulting from early gestational dexamethasone exposure is associated with a reduction in nephron number,[42] similar to observations from studies of rats, outlined above.[38] The gestational timing of corticosteroid treatment resulting in postnatal hypertension in rats and sheep is quite different; however, in terms of renal development, dexamethasone treatment is given at similar times, prior to commencement of nephrogenesis.[42,43] Our investigations in sheep, a species with a similar gestational nephrogenic profile to humans,[44] indicate that late gestational betamethasone exposure in sheep does not reduce nephron number (unpublished observations); this suggests that antenatal corticosteroid treatment in humans is unlikely to alter nephron number.

The entire spectrum of possible effects of antenatal corticosteroid treatment on postnatal blood pressure in humans has been observed. Systolic blood pressure was lower in a group of 20 year olds born after 1 course of antenatal corticosteroids than in controls;[45] higher systolic and diastolic pressures were observed in 14 year old children born after 1 course of antenatal corticosteroid treatment;[46] no effect of antenatal corticosteroid treatment was observed on follow

up of 6-year-olds whose mothers were enrolled in Liggins's original randomised controlled trial.[47] Such differences between studies could theoretically be due to changes associated with age but this seems unlikely. Certainly, any reported effects of antenatal corticosteroid treatment on postnatal blood pressure are small.[45,46]

Late Gestation Glucocorticoids and Programming of Immune Function

Function of the immune system is influenced by basal glucocorticoid levels and by HPA axis responsiveness,[48] raising the possibility that alterations in postnatal HPA axis function induced by exposure to excess glucocorticoids in late gestation might alter susceptibility to postnatal inflammatory/immune disease.

Investigations in rats and pigs have demonstrated that prenatal stress results in postnatal immunosuppression.[49-51] These effects are likely mediated by prenatal exposure to glucocorticoids but alterations in postnatal HPA axis function do not necessarily account for altered postnatal immune function in these studies,[50,51] suggesting that prenatal stress has direct programming effects on development of the immune system.

Only a few experimental studies have examined effects on postnatal immune function, beyond the immediate neonatal period, of glucocorticoid exposure in late gestation. Mice aged 5 months, born after prolonged maternal dexamethasone treatment during the final half of gestation, had impaired immunological function, associated with low thyroxine levels and anatomically abnormal thymus, adrenal and thyroid glands.[52] Immunosuppression was also observed in juvenile monkeys born at term, 1 month after 2 days of maternal dexamethasone administration.[53]

A few studies of human neonates, born after antenatal corticosteroid therapy, indicate that immediate postnatal immune function is impaired. Total numbers of circulating white cells are decreased by antenatal corticosteroids, with particular effects on T cells.[54] T cell proliferation is impaired in infants born after antenatal corticosteroids but natural killer cell activity is increased.[55] These effects do not result in an increased (or decreased) incidence of infection in neonates born after a single course of antenatal corticosteroids[12] but data suggest that the incidence of infection in childhood may be increased by the therapy.[56] Multiple courses of antenatal corticosteroids increase the risk of early onset sepsis and sepsis-related neonatal death.[57] The long term effects in humans of single or repeated courses of antenatal corticosteroids remain to be determined.

Late Gestational Glucocorticoids and Programming of the Brain and Behaviour

Late gestation excess glucocorticoid exposure reduces fetal brain growth (Fig. 2)[58-60] and we have shown recently that such glucocorticoid-induced reductions in brain weight persist until adulthood.[39] The brain regions and cell types that are affected by late gestational glucocorticoids are unknown but reductions in fetal brain myelination in sheep[61-63] and reductions in cytoskeletal microtubule associated proteins and the synapse associated protein, synaptophysin, in fetal baboons[64] have been observed. Neuronal number in the brains of fetal and juvenile primates is reduced after late gestational dexamethasone treatment(s), apparently due to neuronal degeneration.[27,65] The hippocampus is likely the most affected brain region because it has a high density of glucocorticoid receptors.[66]

Reductions in brain weight of experimental animals exposed to late gestational glucocorticoids are consistent with observations of human infants, showing dose-dependent reductions in neonatal head circumference after antenatal corticosteroids.[14,13] Magnetic resonance imaging of a small group of infants born after repeated antenatal corticosteroid treatments showed that cortical folding and surface area are reduced, suggesting delayed brain maturation.[67]

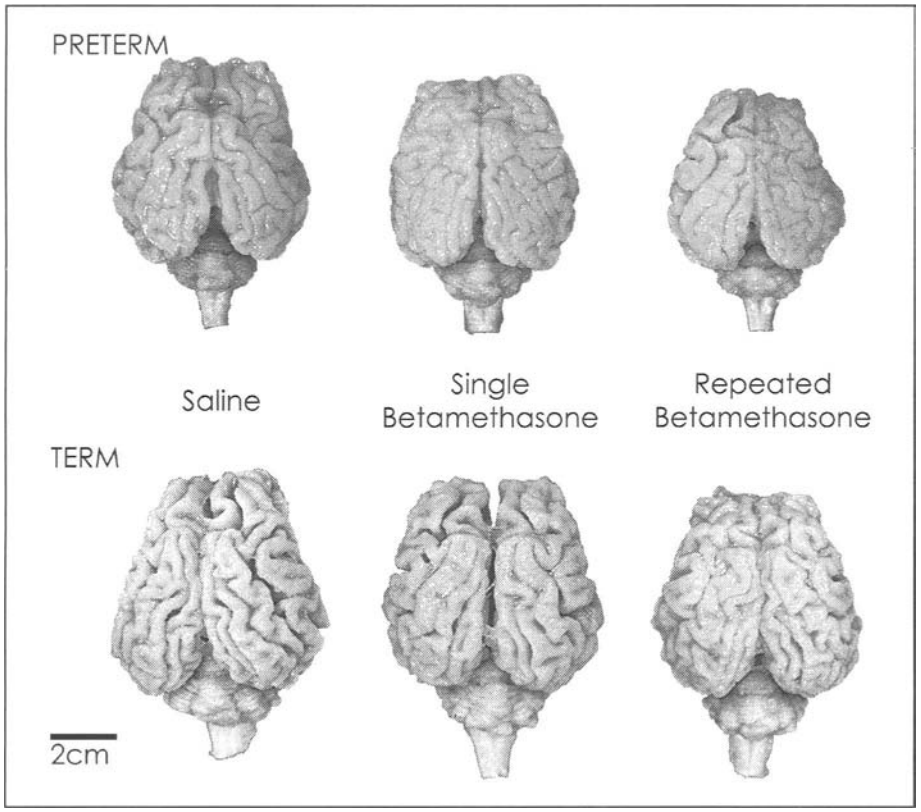

Figure 2. Effects of single or repeated injections of betamethasone in late gestation on fetal brain growth. Reprinted with permission from Huang WL, Beazley LD, Quinlivan JA et al. Effect of corticosteroids on brain growth in fetal sheep. Onstetrics and Gynecology 1999; 94:213-218. ©1999 The American College of Obstetricians and Gynecologists.

The effects on postnatal behaviour of late gestational glucocorticoid exposure have been the subject of only a few studies. Subtle behavioural effects of prenatal betamethasone or dexamethasone exposure have been observed in mice but there were no major adverse consequences.[68] This is consistent with data from humans showing that there are no adverse long-term neurological or cognitive effects of a single course of antenatal corticosteroids.[69-71] However, evidence of psychomotor delay[72] and hyperactivity[73] in children have been associated with repeated courses of antenatal corticosteroids.

There are a number of adverse cognitive or behavioural outcomes associated with reduced head size, including low cognitive ability,[74] and low developmental and intelligence quotients[75] in childhood. Small head circumference at birth is associated with an increased risk of developing schizophrenia;[76] characteristics of which include reductions in brain weight and hippocampal volume,[77] and altered function of the hypothalamic-pituitary-adrenal axis.[78] Such changes are consequences of antenatal corticosteroid treatments in sheep or primates[11,34,65] and together these data raise the possibility that antenatal corticosteroid treatments could contribute to the development of schizophrenia and related disorders; to our knowledge, this possibility has never been investigated.

Conclusion

The ubiquitous effects of late gestational glucocorticoid exposure on fetal development have programming consequences for many physiological functions. The extent to which maternal stress during late pregnancy and antenatal corticosteroid therapy contribute to postnatal health and wellbeing will be elucidated by ongoing and future investigations. Future experimental studies will be necessary to determine the mechanisms responsible for the programming effects of late gestational glucocorticoid exposure, and to investigate potential strategies for preventing or ameliorating adverse effects.

References

1. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972; 50:515-525.
2. Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 1969; 45:515-523.
3. Seckl JR. Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. Mol Cell Endocrinol 2001; 185:61-71.
4. Clark PM. Programming of the hypothalamo-pituitary-adrenal axis and the fetal origins of adult disease hypothesis. Eur J Pediatr 1998; 157(Suppl 1):S7-10.
5. Langley-Evans SC. Fetal programming of cardiovascular function through exposure to maternal undernutrition. Proc Nutr Soc 2001; 60:505-513.
6. Glickman JA, Challis JR. The changing response pattern of sheep fetal adrenal cells throughout the course of gestation. Endocrinology 1980; 106:1371-1379.
7. Wintour EM, Brown EH, Denton DA et al. The ontogeny and regulation of corticosteroid secretion by the ovine foetal adrenal. Acta Endocrinologica 1975; 79:301-316.
8. 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; 57:113-122.
9. Fowden AL, Forhead AJ. Endocrine mechanisms of intrauterine programming. Reproduction 2004; 127:515-526.
10. Fowden AL, Szemere J, Hughes P et al. The effects of cortisol on the growth rate of the sheep fetus during late gestation. J Endocrinol 1996; 151:97-105.
11. Newnham JP, Evans SF, Godfrey M et al. Maternal, but not fetal, administration of corticosteroids restricts fetal growth. J Matern Fetal Med 1999; 8:81-87.
12. Crowley P. Prophylactic corticosteriods for preterm birth. Cochrane Library 2004; 4.
13. French NP, Hagan R, Evans SF et al. Repeated antenatal corticosteroids: Size at birth and subsequent development. Am J Obstet Gynecol 1999; 180:114-121.
14. Thorp JA, Jones PG, Knox E et al. Does antenatal corticosteroid therapy affect birth weight and head circumference? Obstet Gynecol 2002; 99:101-108.
15. Antenatal corticosteroids revisited: Repeat courses - National Institutes of Health Consensus Development Conference Statement, August 17-18, 2000. (Obstet Gynecol 2001; 98:144-150).
16. Moss TJ, Sloboda DM, Gurrin LC et al. Programming effects in sheep of prenatal growth restriction and glucocorticoid exposure. Am J Physiol Regul Integr Comp Physiol 2001; 281:R960-970.
17. Moss TJ, Doherty DA, Nitsos I et al. Pharmacokinetics of betamethasone after maternal or fetal intramuscular administration. Am J Obstet Gynecol 2003; 189:1751-1757.
18. Seckl JR. Glucocorticoids, feto-placental 11 beta-hydroxysteroid dehydrogenase type 2, and the early life origins of adult disease. Steroids 1997; 62:89-94.
19. Zimmet P, Alberti KGMM, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001; 414:782-787.
20. Hales CN, Barker DJ, Clark PM et al. Fetal and infant growth and impaired glucose tolerance at age 64. BMJ 1991; 303:1019-1022.
21. Bertram CE, Hanson MA. Prenatal programming of postnatal endocrine responses by glucocorticoids. Reproduction 2002; 124:459-467.
22. Nyirenda MJ, Lindsay RS, Kenyon CJ et al. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. J Clin Invest 1998; 101:2174-2181.
23. Cleasby ME, Kelly PAT, Walker BR et al. Programming of rat muscle and fat metabolism by in utero overexposure to glucocorticoids. Endocrinology 2003; 144:999-1007.
24. Blondeau B, Lesage J, Czernichow P et al. Glucocorticoids impair fetal beta-cell development in rats. Am J Physiol Endocrinol Metab 2001; 281:E592-599.
25. Drake AJ, Walker BR, Seckl JR. Intergenerational consequences of fetal programming by in utero exposure to glucocorticoids in rats. Am J Physiol Regul Integr Comp Physiol 2004:00106-02004.

26. Cleasby ME, Livingstone DE, Nyirenda MJ et al. Is programming of glucocorticoid receptor expression by prenatal dexamethasone in the rat secondary to metabolic derangement in adulthood? Eur J Endocrinol 2003; 148:129-138.
27. Uno H, Eisele S, Sakai A et al. Neurotoxicity of glucocorticoids in the primate brain. Horm Behav 1994; 28:336-348.
28. Levitt NS, Lindsay RS, Holmes MC et al. Dexamethasone in the last week of pregnancy attenuates hippocampal glucocorticoid receptor gene expression and elevates blood pressure in the adult offspring in the rat. Neuroendocrinology 1996; 64:412-418.
29. Dodic M, Peers A, Moritz K et al. No evidence for HPA reset in adult sheep with high blood pressure due to short prenatal exposure to dexamethasone. Am J Physiol Regul Integr Comp Physiol 2002; 282:R343-350.
30. Bakker JM, Schmidt ED, Kroes H et al. Effects of short-term dexamethasone treatment during pregnancy on the development of the immune system and the hypothalamo-pituitary adrenal axis in the rat. J Neuroimmunol 1995; 63:183-191.
31. Banjanin S, Kapoor A, Matthews SG. Prenatal glucocorticoid exposure alters hypothalamic-pituitary-adrenal function and blood pressure in mature male guinea pigs. J Physiol (Lond) 2004; 558:305-318.
32. Dean F, Matthews SG. Maternal dexamethasone treatment in late gestation alters glucocorticoid and mineralocorticoid receptor mRNA in the fetal guinea pig brain. Brain Research 1999; 846:253-259.
33. Liu L, Li A, Matthews SG. Maternal glucocorticoid treatment programs HPA regulation in adult offspring: Sex-specific effects. Am J Physiol Endocrinol Metab 2001; 280:E729-739.
34. Sloboda DM, Moss TJ, Gurrin LC et al. The effect of prenatal betamethasone administration on postnatal ovine hypothalamic-pituitary-adrenal function. J Endocrinol 2002; 172:71-81.
35. Sloboda DM, Moss TJM, Nitsos I et al. Antenatal glucocorticoid treatment in sheep results in adrenal supression in adulthood. J Soc Gynecol Investig 2003; 10:233A.
36. Davis EP, Townsend EL, Gunnar MR et al. Effects of prenatal betamethasone exposure on regulation of stress physiology in healthy premature infants. Psychoneuroendocrinology 2004; 29:1028-1036.
37. McDonald T, Franko K, Brown J et al. Betamethasone in the last week of pregnancy causes fetal growth retardation but not adult hypertension in rats. J Soc Gynecol Investig 2003; 10:469-473.
38. Ortiz LA, Quan A, Weinberg A et al. Effect of prenatal dexamethasone on rat renal development. Kidney Int 2001; 59:1663-1669.
39. Moss TJM, Doherty DA, Nitsos I et al. Effects into adulthood of single or repeated antenatal corticosteroids in sheep. Am J Obstet Gynecol 2205; 192:146-152.
40. Dodic M, May CN, Wintour EM et al. An early prenatal exposure to excess glucocorticoid leads to hypertensive offspring in sheep. Clin Sci (Lond) 1998; 94:149-155.
41. Dodic M, Peers A, Coghlan JP et al. Altered cardiovascular haemodynamics and baroreceptor-heart rate reflex in adult sheep after prenatal exposure to dexamethasone. Clin Sci (Lond) 1999; 97:103-109.
42. Wintour EM, Moritz KM, Johnson K et al. Reduced nephron number in adult sheep, hypertensive as a result of prenatal glucocorticoid treatment. J Physiol 2003; 549:929-935.
43. Bertram JF, Young RJ, Spencer K et al. Quantitative analysis of the developing rat kidney: Absolute and relative volumes and growth curves. Anat Rec 2000; 258:128-135.
44. Moritz KM, Wintour EM. Functional development of the meso- and metanephros. Pediatr Nephrol 1999; 13:171-178.
45. Dessens AB, Haas HS, Koppe JG. Twenty-year follow-up of antenatal corticosteroid treatment. Pediatrics 2000; 105:E77.
46. Doyle LW, Ford GW, Davis NM et al. Antenatal corticosteroid therapy and blood pressure at 14 years of age in preterm children. Clin Sci (Lond) 2000; 98:137-142.
47. Dalziel SR, Liang A, Parag V et al. Blood pressure at 6 years of age after prenatal exposure to betamethasone: Follow-up results of a randomized, controlled trial. Pediatrics 2004; 114:e373-377.
48. Wilckens T, De Rijk R. Glucocorticoids and immune function: Unknown dimensions and new frontiers. Immunology Today 1997; 18:418-424.
49. Sobrian SK, Vaughn VT, Bloch EF et al. Influence of prenatal maternal stress on the immunocompetence of the offspring. Pharmacol Biochem Behav 1992; 43:537-547.
50. Kay G, Tarcic N, Poltyrev T et al. Prenatal stress depresses immune function in rats. Physiol Behav 1998; 63:397-402.
51. Tuchscherer M, Kanitz E, Otten W et al. Effects of prenatal stress on cellular and humoral immune responses in neonatal pigs. Vet Immunol Immunopathol 2002; 86:195-203.
52. Eishi Y, Hirokawa K, Hatakeyama S. Long-lasting impairment of immune and endocrine systems of offspring induced by injection of dexamethasone into pregnant mice. Clin Immunol Immunopathol 1983; 26:335-349.
53. Coe CL, Lubach GR. Prenatal influences on neuroimmune set points in infancy. Ann NY Acad Sci 2000; 917:468-477.

54. Chabra S, Cottrill C, Rayens MK et al. Lymphocyte subsets in cord blood of preterm infants: Effect of antenatal steroids. Biol Neonate 1998; 74:200-207.
55. Kavelaars A, van der Pompe G, Bakker JM et al. Altered immune function in human newborns after prenatal administration of betamethasone: Enhanced natural killer cell activity and decreased T cell proliferation in cord blood. Pediatr Res 1999; 45:306-312.
56. Smolders-de Haas H, Neuvel J, Schmand B et al. Physical development and medica history of children who were treated antenatally with corticosteroid to prevent respiratory distress syndrome: A 10- to 12- year follow- up. Pediatrics 1990; 86:65-70.
57. Vermillion ST, Soper DE, Newman RB. Neonatal sepsis and death after multiple courses of antenatal betamethasone therapy. Am J Obstet Gynecol 2000; 183:810-814.
58. Johnson JWC, Mitzner W, Beck JC et al. Long-term effects of betamethasone on fetal development. Am J Obstet Gynecol 1981; 141:1053-1064.
59. Huang WL, Beazley LD, Quinlivan JA et al. Effect of corticosteroids on brain growth in fetal sheep. Obstet Gynecol 1999; 94:213-218.
60. Scheepens A, Van De Waarenburg M, Van Den Hove D et al. A single course of prenatal betamethasone in the rat alters postnatal brain cell proliferation but not apoptosis. J Physiol 2003; 552:163-175.
61. Dunlop SA, Archer MA, Quinlivan JA et al. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. J Matern Fetal Med 1997; 6:309-313.
62. Huang WL, Harper CG, Evans SF et al. Repeated prenatal corticosteroid administration delays myelination of the corpus callosum in fetal sheep. Int J Dev Neurosci 2001; 19:415-425.
63. Quinlivan JA, Dunlop SA, Newnham JP et al. Repeated, but not single, maternal administration of corticosteriods delays myelination in the brain of fetal sheep. Prenat Neonat Med 1999; 4:47-55.
64. Antonow-Schlorke I, Schwab M, Li C et al. Glucocorticoid exposure at the dose used clinically alters cytoskeletal proteins and presynaptic terminals in the fetal baboon brain. J Physiol 2003; 547:117-123.
65. Uno H, Lohmiller L, Thieme C et al. Brain damage induced by prenatal exposure to dexamethasone in fetal rhesus macaques. I Hippocampus Brain Res Dev Brain Res 1990; 53:157-167.
66. Matthews SG. Antenatal glucocorticoids and the developing brain: Mechanisms of action. Semin Neonatol 2001; 6:309-317.
67. Modi N, Lewis H, Al-Naqeeb N et al. The effects of repeated antenatal glucocorticoid therapy on the developing brain. Pediatr Res 2001; 50:581-585.
68. Rayburn W, Christensen H, Gonzalez C. A placebo-controlled comparison between betamethasone and dexamethasone for fetal maturation: Differences in neurobehavioral development in mice offspring. Am J Obstet Gynecol 1997; 176:842-851.
69. Doyle L, Ford G, Rickards A et al. Antenatal corticosteroids and outcome at 14 years of age in children with birth weight less than 1501 grams. Pediatrics 2000; 106:e2.
70. Dessens A, Smolders-de Has H, Koppe J. Twenty year follow-up of antenatal corticosteroid treatment. Pediatrics 2000; 105:e77.
71. Matthews SG. Antenatal glucocorticoids and programming of the developing CNS. Pediatr Res 2000; 47:291-300.
72. Esplin M, Fausett M, Smith S et al. Multiple courses of antenatal steroids are asociated with a delay in long-term psychomotor development in children with birth weights < 1500 grams. Am J Obstet Gynecol 2000; 182:S24.
73. French N, Hagan R, Evans S et al. Repeated antenatal corticosteroids:Effects on cerebral palsy and childhood behaviour. Am J Obstet Gynecol 2004; 190:588-595.
74. Stathis S, O'Callaghan M, Harvey J et al. Head circumference in ELBW babies is associated with learning difficulties and cognition but not ADHD in the school-aged child. Dev Med Child Neurol 1999; 41:375-380.
75. Brandt I, Sticker E, Lentze M. Catch-up growth of head circumference of very low birthweight, samll for gestational age preterm infants and mental development to adulthood. J Pediatr 2003; 142:463-468.
76. MacNeil T, Cantor-Graae E, Ismail B. Obstetric complications and congential malformation in schizophrenia. Brain Res Rev 2000; 31:166-178.
77. Harrison P. The neuropathology of schizophrenia. A critical review of the data and their interpretation. Brain 1999; 122:593-624.
78. Cotter D, Pariante C. Stress and the progression of the developmental hypothesis of schizophrenia. Br J Psychiarty 2002; 181:363-365.
79. Effect of corticosteroids for fetal maturation on perinatal outcomes. Am J Obstet Gynecol 1995; 173:246-252.
80. Goldenberg RL, Wright LL. Repeated courses of antenatal corticosteroids. Obstet Gynecol 2001; 97:316-317.