# Effect of Corticosteroids on Brain Growth in Fetal Sheep

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***Objective*: To compare the effects of single and repeated courses of corticosteroids on brain growth in fetal sheep.**

***Methods*: Pregnant sheep were given intramuscular betamethasone (0.5 mg/kg) at 104 days' gestation followed at 111, 118, and 124 days by equivalent volumes of sterile normal saline ($n = 12$) or betamethasone ($n = 12$). Controls received equivalent volumes of sterile normal saline at all four intervals ($n = 12$). Lambs were delivered at 125 (preterm) or 145 (term) days. After perfusion, we measured weights (grams) for whole brain, cerebrum, cerebellum, and brain stem, volumes (milliliters) for whole brain and cerebrum, and maximum cerebral anterior-posterior length, width, and depth (centimeters).**

***Results*: In the single-injection group at preterm, there were no significant differences ($P = .070$) in whole-brain weight between the corticosteroid-treated animals (38.0 ± 1.81 g) and controls (42.5 ± 1.65 g). Cerebral length and depth were significantly reduced in the corticosteroid group ($P < .05$); other measures were not significantly different. At term, whole-brain weight was significantly lower (47.5 ± 1.70 g; $P = .022$) compared with controls (53.4 ± 1.73 g). All other measures were significantly reduced ($P < .05$) except cerebral and brain-stem weights and cerebral length. In the group that received repeated injections at preterm, whole-brain weight was significantly reduced (35.5 ± 1.65 g; $P = .005$) compared with controls (42.5 ± 1.65 g). All other measures were significantly reduced ($P < .05$) except cerebellar and brain-stem weights. At term, whole-brain weight was also significantly reduced (42.4 ± 1.52 g; $P = .001$) compared with controls (53.4 ± 1.73 g) as were all other measures ($P < .05$).**

***Conclusion*: Administration of single and repeated courses of corticosteroids to pregnant sheep retarded fetal brain growth. (Obstet Gynecol 1999;94:213–8. © 1999 by The American College of Obstetricians and Gynecologists.)**

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Since the 1970s, corticosteroids have been used with great success to reduce mortality and morbidity in preterm infants.[1] Randomized trials found no neurologic or cognitive effects in children who were treated prenatally with single courses of corticosteroids and followed up between 3, 6, and 12 years of age.[2–4] Administrating a single course of corticosteroids is now standard practice. In 1995, the US National Institutes of Health recommended that all infants at risk of preterm delivery receive single courses of corticosteroids to improve the survival rates.[5]

There has been a trend to increase the number of treatments given to pregnant women at risk of preterm delivery, particularly in situations when risk persists or recurs after initial courses. A recent survey of obstetric practice in Australia found that 85% of clinicians would use repeated injections of corticosteroids in such cases, and half would do so weekly.[6] That practice has arisen without safety data; however, a randomized, controlled trial in humans on the effects of repeated courses of corticosteroids has recently started in Australia at multiple centers and is coordinated by the University of Adelaide (Australian Collaborative Trial of Repeated Doses of Steroids; personal communication, Dr. Caroline Crowther). Other trials in the United States and the United Kingdom are under development.

A number of animal studies documented detrimental effects of repeated corticosteroid doses on short- and long-term brain development.[7–11] Many of those studies were considered of questionable clinical relevance[5] because they used small laboratory mammals (rats, mice, and rabbits) in which corticosteroid treatment occupied a large portion of their short gestation and rapid postnatal development periods. Variations in route of administration—namely, maternal or direct injection into



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fetuses or newborn pups—are now known to alter outcome.[12]

Previous data from our laboratory indicated that repeated corticosteroids delay myelination of the ovine optic nerve,[13] urgently suggesting that we extend our observations to other white-matter tracts. We compared the effects of clinically appropriate single- and repeated-corticosteroid doses on brain growth in sheep, chosen because of their extensive use as experimental models for human pregnancy.[14] The sheep brain is relatively mature at birth, similar to the human brain,[15] and thus is appropriate for examining effects of corticosteroids on brain growth. We chose maternal injection because it is currently standard clinical practice.

## *Materials and Methods*

The effects of corticosteroids on organ weights were reported on animals in this study.[16] Ewes were date-mated, then singleton pregnancy was confirmed in each case by ultrasound examination at 85 days' gestation. All ewes were injected intramuscularly at 100 days' gestation with 150 mg medroxyprogesterone acetate (Depo Provera; Upjohn, Rydalmere, Australia) to minimize risks of preterm births.

Pregnant ewes were ear-tagged at mating; then, a random number sequence was used to assign them to one of the three experimental groups and to preterm (day 125) or term (day 145) delivery. In the single corticosteroid group ($n = 12$), ewes received an intramuscular injection of betamethasone (Celestone Chronodose, 0.5 mg/kg; Schering Plough, Baulkham Hill, Australia) on day 104 of gestation followed by three injections of an equivalent volume of sterile normal saline on days 111, 118, and 124 of gestation. In the repeated corticosteroid group ($n = 12$), betamethasone was given intramuscularly at all four time points. Control ewes ($n = 12$) received intramuscularly an equivalent volume of sterile normal saline at the same time points as the single- and repeated-corticosteroid groups. All injections were carried out by a single operator (JAQ) and the group allocation was masked to the other investigators.

Cesarean delivery was done on pregnant ewes after premedication with intramuscular ketamine (12 mL, 100 mg/mL) and spinal anesthesia (4 mL, 2% lidocaine). Newborn lambs were weighed before terminal anesthesia with intravenous ketamine (1 to 2 mL, 100 mg/mL) and perfusion by ascending aorta with saline, followed by Karnovsky's fixative in cacodylate buffer (0.1 mol/L 300 mosm, pH 7.4).

Fetal brains were removed and whole-brain weights and volumes measured. The maximum cerebral anterior-posterior length, width, and depth were measured with vernier callipers. The cerebellum with brain stem attached was removed as one piece by cutting through the base of the inferior colliculus. The two structures were then separated and weighed individually. The weights and volumes of the cerebra were measured.

The sample of six animals per group was chosen to determine, with 80% power, a difference of 6 g in brain weight, assuming the standard deviation for the control animals to be 3 g, adjusting the type 1 error rate for multiple comparisons. Analysis of variance was used to compare each of the control and single- and repeated-corticosteroid groups. Maternal body weight, lamb gender, and gestational age were included in the analysis as covariates because they also affect the outcome. The Tukey-Kramer multiple-comparison adjustment was used to calculate the significance levels. $P < .05$ was considered statistically significant.

The project was approved by the Animal Ethics and Experimentation Committee of The University of Western Australia and compiled with the Australian National Health and Medical Research Council's Code of Practice for the Use and Care of Animals for Experimentation.

**Table 1.** Maternal Body Weights and Lamb Birth Weights

| Gestational age (d) | Treatment | Maternal body weight (kg)* | Lamb birth weight (kg)* |
|---|---|---|---|
| Preterm 125 d | Control ($n = 6$) | 51.9 (4.22) | 3.2 (0.22) |
| | Single steroid ($n = 6$) | 50.3 (5.64) | 3.0 (0.35) |
| | Repeated steroid ($n = 6$) | 52.9 (6.97) | 2.6 (0.20) |
| Term 145 d | Control ($n = 6$) | 55.5 (3.29) | 5.9 (0.33) |
| | Single steroid ($n = 6$) | 49.6 (3.26) | 5.5 (0.24) |
| | Repeated steroid ($n = 6$) | 52.3 (4.20) | 4.0 (0.52) |

* Data are presented as mean (standard deviation).

## *Results*

Table 1 provides the data of maternal body weights, lamb birth weights, and gestational ages. As we reported, lamb weights were significantly reduced.[16] There were no significant differences in baseline variables of maternal weight or gestational age. Tables 2 and 3 summarize brain growth data for the preterm and term animals in the control and single- and repeated-corticosteroid groups, respectively.

In the single corticosteroid group, after delivery at 125 days' preterm gestation, whole-brain weights were not significantly different compared with controls (Table 2). There were no significant differences between the

**Table 2.** Preterm and Term Data for the Single-Corticosteroid Group

| Measurement | Preterm | | | Term | | |
|---|---|---|---|---|---|---|
| | Control ($n = 6$)* | Single steroid ($n = 6$)* | Control/Single $P$ value† | Control ($n = 6$)* | Single steroid ($n = 6$)* | Control/Single $P$ value† |
| Whole-brain weight (g) | 42.5 (1.65) | 38.0 (1.81) | .070 | 53.4 (1.73) | 47.5 (1.70) | .022† |
| Whole-brain volume (mL) | 37.7 (1.56) | 34.0 (1.71) | .107 | 48.5 (1.63) | 43.6 (1.61) | .040† |
| Cerebral weight (g) | 37.8 (1.43) | 34.0 (1.57) | .072 | 45.6 (1.50) | 41.3 (1.48) | .055 |
| Cerebral volume (mL) | 34.3 (1.32) | 30.8 (1.45) | .076 | 42.9 (1.38) | 38.7 (1.36) | .040† |
| Cerebellar weight (g) | 3.1 (0.22) | 2.8 (0.24) | .494 | 5.0 (0.23) | 4.2 (0.22) | .015† |
| Brain-stem weight (g) | 1.4 (0.07) | 1.3 (0.08) | .185 | 2.3 (0.07) | 2.1 (0.07) | .075 |
| Maximum cerebral A-P length (cm) | 5.3 (0.08) | 5.0 (0.09) | .021† | 5.3 (0.09) | 5.2 (0.08) | .298 |
| Maximum cerebral width (cm) | 4.9 (0.07) | 4.8 (0.08) | .300 | 5.1 (0.08) | 4.9 (0.08) | .027† |
| Maximum cerebral depth (cm) | 2.9 (0.06) | 2.5 (0.07) | .001† | 3.3 (0.06) | 3.0 (0.06) | .008† |

A-P = anterior-posterior.
* Data are presented as mean (standard deviation).
† Tukey-Kramer test; $P < .05$ is considered statistically significant.

single-corticosteroid group and controls in whole-brain volume, cerebral weight and volume, cerebellar and brain-stem weights, and maximum cerebral depth. Maximum cerebral anterior-posterior lengths and depths were significantly reduced compared with controls.

At term, the single-corticosteroid group showed significant reductions compared with controls in whole-brain weight and volume, cerebral volume, cerebellar weight, and maximum cerebral width and depth (Table 2). The remaining measures, cerebral and brain-stem weights and maximum cerebral anterior-posterior lengths, showed no significant differences.

Repeated corticosteroids had more profound effects on brain growth than single doses. After preterm delivery, the repeated-corticosteroid group showed significant reductions in weights and volumes of whole brains and cerebra, and maximum cerebral anterior-posterior lengths, widths, and depths (Table 3). The cerebellar and brain-stem weights did not show significant reductions. Figures 1 and 2 (upper rows) present examples of brains and cerebella, respectively, from preterm control, and single- and repeated-corticosteroid animals, showing the smaller sizes in the repeated-corticosteroid group.

At term, the repeated-corticosteroid treated group showed significant reductions in all measurements (Table 3). Figures 1 and 2 (bottom rows) show representative examples of brains and cerebella in the term control and single- and repeated-corticosteroid animals showing smaller sizes and disrupted vermal cerebellar surfaces resulting from corticosteroid treatment.

## *Discussion*

Single and repeated doses of corticosteroids retarded brain growth in fetal sheep; repeated doses had more profound effects, particularly at term.

The clinical dose of betamethasone (Table 4)[17–21] results in a 75% occupancy of corticosteroid receptors in the lung; higher or more frequent doses have little additional benefit.[5] The dosage for the current study

**Table 3.** Preterm and Term Data for Repeated-Corticosteroid Group

| Measurement | Preterm | | | Term | | |
|---|---|---|---|---|---|---|
| | Control ($n = 6$)* | Repeated steroid ($n = 6$)* | Control/Repeated $P$ value† | Control ($n = 6$)* | Repeated steroid ($n = 6$)* | Control/Repeated $P$ value† |
| Whole-brain weight (g) | 42.5 (1.65) | 35.5 (1.65) | .005† | 53.4 (1.73) | 42.4 (1.52) | .001† |
| Whole-brain volume (mL) | 37.7 (1.56) | 31.6 (1.56) | .008† | 48.5 (1.63) | 38.7 (1.45) | .001† |
| Cerebral weight (g) | 37.8 (1.43) | 31.6 (1.44) | .004† | 45.6 (1.50) | 36.8 (1.33) | .001† |
| Cerebral volume (mL) | 34.3 (1.32) | 28.7 (1.32) | .005† | 42.9 (1.38) | 34.5 (1.23) | .001† |
| Cerebellar weight (g) | 3.1 (0.22) | 2.5 (0.22) | .058 | 5.0 (0.23) | 3.6 (0.20) | .001† |
| Brain-stem weight (g) | 1.4 (0.07) | 1.2 (0.07) | .076 | 2.3 (0.07) | 1.8 (0.06) | .001† |
| Maximum cerebral A-P length (cm) | 5.3 (0.08) | 4.8 (0.08) | .001† | 5.3 (0.09) | 4.9 (0.08) | .002† |
| Maximum cerebral width (cm) | 4.9 (0.07) | 4.7 (0.07) | .024† | 5.1 (0.08) | 4.8 (0.07) | .001† |
| Maximum cerebral depth (cm) | 2.9 (0.06) | 2.6 (0.06) | .001† | 3.3 (0.06) | 2.9 (0.06) | .001† |

A-P = anterior-posterior.
* Data are presented as mean (standard deviation).
† Tukey-Kramer test; $P < .05$ is considered statistically significant.

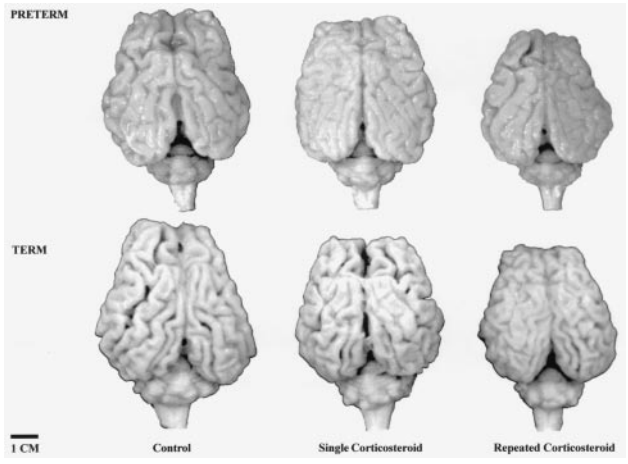


**Figure 1.** Dorsal view of representative brains from control and single- and repeated-corticosteroid groups for preterm and term animals.

was similar to that used clinically (Table 4) and conformed to previous studies in sheep in which fetal lung maturation was shown.[21] Measurement of fetal plasma betamethasone concentrations in humans and sheep found similar courses in peak values and rates of clearance (Table 4). Corticosteroids resulted in adrenal suppression in humans and sheep (Table 4). Humans and sheep respond similarly to corticosteroids in terms of lung maturation and adrenal suppression; the challenge is to find similarities in neurodevelopmental outcome.

There is much evidence from small laboratory mammals that shows exogenous corticosteroids retard brain development with a concomitant mosaic of biochemical,[7] structural,[8] and behavioral[22] deficits. Small laboratory mammals are considered inappropriate for examining outcomes of repeated-corticosteroid administration in a clinical setting, but their use has indicated a fundamental retardation of brain growth. For example, prenatal treatment administered maternally during the last week of pregnancy in rats consistently decreased brain weights in animals at preterm or term,[23] or within the first 2 to 4 weeks of life.[24] Examination at approximately 2 months postnatally found a catch-up in brain weight after a characteristic initial delay.[11] Treatment by direct injection into mouse and rat pups between 2 and 7 days postnatally resulted in reduced brain weights at 1 month[7] and at over 1 year.[22]

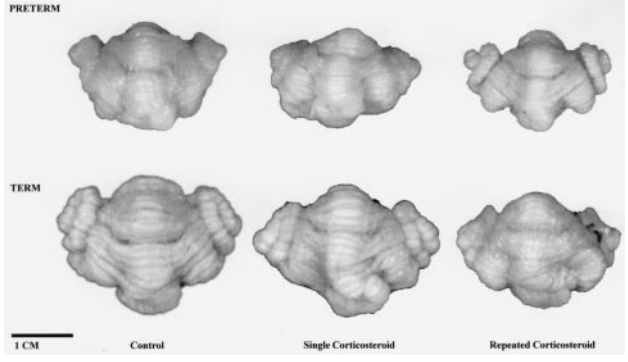


**Figure 2.** Posterior view of the cerebellum from control and single- and repeated-corticosteroid groups for preterm and term animals.

There are few studies in larger, more clinically relevant experimental animals on effects of maternally administered exogenous corticosteroids on brain growth. Exposure of rhesus monkey fetuses to corticosteroids on days 132 and 133, and examination by day 135 (term = 165) found a trend towards lower brain weights, although reductions were not significant.[10] Hippocampal pyramidal cell numbers were reduced and neuronal and synaptic damage was evident. The interval between administration and delivery was too short to expect significant brain-weight reductions. Significant reductions in brain weight were found in rhesus monkeys after daily maternal injection between days 120 and 133 and delivery at term.[9] The only study that examined brain weights in sheep involved direct fetal administration of corticosteroids. Continuous infusion of catheterized animals for 60 hours from day 128 and delivery at 130 days showed a significant reduction in brain weight.[25] None of those large animal studies used an injection protocol that conformed to clinical practice.

The present study's protocol closely reflects treatment in human pregnancy (Table 4). Several of our measurements showed that single and repeated doses of corticosteroids slowed brain growth in sheep by term. The National Institutes of Health consensus on single corticosteroid treatment showed no long-term deleterious neurological or cognitive effects in humans.[5] If sheep are accurate models for humans, we suggest that effects of single courses of corticosteroids on sheep will be recovered in the long term. Studies addressing that issue are currently under way.

We have yet to determine whether effects of repeated corticosteroids on brain growth in our study are relevant to humans. A recent study in infants born at less than 33 weeks and observed to 3 years of age found that repeated corticosteroid doses significantly reduced birth weights and head circumferences by as much as 9% and 4%, respectively.[26] Behavioral problems increased with increasing corticosteroid treatment, assessed by externalizing behavior on the Child Behavior Checklist and the Distractibility scale on the Parenting Stress Index (French NP, Hagan R, Evans SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids (CS): Behaviour outcomes in a regional population of very preterm (VP, < 33w) infants [abstract]. Pediatr Res

**Table 4.** Dosages, Maternal and Fetal Plasma Betamethasone Levels, and Fetal Adrenal Suppression in Sheep and Humans

| | Corticosteroid administration | |
|---|---|---|
| | Sheep | Humans |
| Dosage | 0.5 mg/kg* (maternal body weight) of intramuscular betamethasone as single course | 2 doses of 12 mg§ intramuscular betamethasone given 24 hours apart as a single course |
| Maternal plasma level of betamethasone | No data | 1 h: peak at 75 μg cortisol equivalents/100 mL<br>6 h: half-life<br>2 d: little activity after second dose‖ |
| Fetal plasma level of betamethasone | 3 h: peak at 22.7 μg cortisol equivalents/100 mL<br>6 h: half-life<br>11.1 h: not detectable† | First dose<br>1–2 h: peak at 14.3 μg cortisol equivalents/100 mL<br>12 h: half-life<br>24 h: not detectable<br>Mean value: 15 μg cortisol equivalents/100 mL (0–24 h)<br>Second dose<br>Mean value: 12 μg cortisol equivalents/100 mL (24–48 h)<br>62–72 h: not detectable‖ |
| Fetal adrenal suppression | Postnatal plasma cortisol levels after 40-min ventilation<br>Control: 2.3 μg/dL<br>Experimental animals<br>2 d: 1.2 μg/dL<br>4 d: 1.55 μg/dL<br>7 d: 2.0 μg/dL‡ | Normal: 8.4 μg/dL cortisol<br>First dose<br>6–16 h: 3.7 μg/dL cortisol<br>17–20 h: 5.8 μg/dL cortisol<br>Second dose<br>1 h: 3.8 μg/dL cortisol<br>7 d: 8.4 μg/dL cortisol¶ |

* The 0.5-mg/kg dose was to ensure fetal response.[21] Given a mean ewe weight of 50 kg, the total dosage was 25 mg.
† Fetuses were catheterized chronically. Fetal blood samples were obtained at various times after maternal injections.[18]
‡ Betamethasone was given to fetuses 2, 4, or 7 days before delivery at 128 days' gestation.[17]
§ In humans, for a maternal body weight of 70 kg, a single course was 0.34 mg/kg.
‖ Samples of maternal venous blood were collected before and at various times after treatment. Mixed cord bloods were collected when delivery occurred within 4 days after first dose.[19]
¶ Samples were collected as described in Ballard et al.[19,20]

1998;43:214). Further studies need to establish the relative risks and benefits of clinical antenatal corticosteroid use.

At the mechanistic level, glucocorticoids are powerful regulators of differentiation and maturation; therefore, administration of exogenous corticosteroids can alter brain development.[27] For example, in rats hydrocortisone depresses the activity of thymidine kinase activity,[28] an enzyme that regulates the rate of DNA synthesis and the production of nucleotides. A reduction in thymidine kinase activity would result in decreased cell division and delays in brain growth. Glucocorticoids regulate maturation of oligodendrocytes,[29] which produce myelin in the central nervous system, and they regulate production of key components of myelin, such as cerebrosides, proteolipid protein, and myelin basic protein.[30] It was shown that corticosteroids arrest myelination of the optic nerve.[8,13] Reductions in cell division and myelination of fiber tracts would contribute to decreased brain weights reported here and in other studies.[7,9]

## *References*


1. Crowley P. Antenatal corticosteroid therapy: A meta-analysis of the randomised trials, 1972 to 1994. Am J Obstet Gynecol 1995;173:322–35.
2. Collaborative group on antenatal steroid therapy. Effects of antenatal dexamethasone administration in the infant: Long term follow-up. J Pediatr 1984;104:259–67.
3. MacArthur BA, Howie RN, Dezoete JA. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. Pediatrics 1982;70:99–105.
4. Smolders-de-Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: A 10- to 12-year follow-up. Pediatrics 1990;86:65–70.
5. NIH Consensus Development Panel on the Effects of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. JAMA 1995;273:413–8.
6. 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;38:1–7.
7. Cotterrell M, Balazs R, Johnson AL. Effects of corticosteroids on the biochemical maturation of rat brain: Postnatal cell formation. J Neurochem 1972;19:2151–67.
8. Gumbinas M, Oda M, Huttenlocher P. The effects of corticosteroids on myelination of the developing rat brain. Biol Neonate 1973;22:355–66.
9. Johnson JW, Mitzner W, Beck JC, London WT, Sly DL, Lee PA, et al. Long-term effects of betamethasone on fetal development. Am J Obstet Gynecol 1981;141:1053–64.
10. Uno H, Lohmiller L, Thieme C, Kemnitz JW, Engle MJ, Roecker EB, et al. Brain damage induced by prenatal exposure to dexametha-

sone in fetal rhesus macaques. I. Hippocampus. Brain Res Dev Brain Res 1990;53:157–67.
11. Slotkin TA, Lappi SE, McCook EC, Tayyeb MI, Eylers JP, Seidler FJ. Glucocorticoids and the development of neuronal function: Effects of prenatal dexamethasone exposure on central noradrenergic activity. Biol Neonate 1992;61:326–36.
12. Newnham JP, Evans SF, Godfrey M, Huang WL, Ikegami M, Jobe A. Maternal, but not fetal, administration of corticosteroids restricts fetal growth. J Matern Fetal Med (in press).
13. Dunlop SA, Archer MA, Quinlivan JA, Beazley LD, Newnham JP. Repeated prenatal corticosteroids delay myelination in the ovine central nervous system. J Matern Fetal Med 1997;6:309–13.
14. Ruiz U, Piasecki GJ, Balogh K, Polansky BJ, Jackson BT. An experimental model for fetal pulmonary hypertension. A preliminary report. Am J Surg 1972;123:468–71.
15. McIntosh GH, Baghurst KI, Potter BJ, Hetzel BS. Foetal brain development in the sheep. Neuropathol Appl Neurobiol 1979;5: 103–14.
16. Quinlivan JA, Archer MA, Dunlop SA, Evans SF, Beazley LD, Newnham JP. Fetal growth retardation, particularly within lymphoid organs, following repeated maternal injections of betamethasone in sheep. J Obstet Gynecol Res 1998;24:1–9.
17. Ikegami M, Polk DH, Jobe AH. Effect of interval from fetal corticosteroid treatment to delivery on postnatal lung function of preterm lambs. J Appl Physiol 1996;80:591–7.
18. Berry LM, Polk DH, Ikegami M, Jobe AH, Padbury JF, Ervin MG. Preterm newborn lamb renal and cardiovascular responses after fetal or maternal antenatal betamethasone. Am J Physiol 1997;272: R1972–9.
19. Ballard PL, Granberg P, Ballard RA. Glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy to prevent respiratory distress syndrome. J Clin Invest 1975;56:1548–54.
20. Ballard PL, Gluckman PD, Liggins GC, Kaplan SL, Grumbach MM. Steroid and growth hormone levels in premature infants after prenatal betamethasone therapy to prevent respiratory distress syndrome. Pediatr Res 1980;14:122–7.
21. Ervin MG, Berry LM, Ikegami M, Jobe AH, Padbury JF, Polk DH. Single dose fetal glucocorticoid administration stabilizes postnatal glomerular filtration rate and alters endocrine function in premature lambs. Pediatr Res 1996;40:645–51.
22. Benesova O, Pavlik A. Perinatal treatment with glucocorticoids and the risk of maldevelopment of the brain. Neuropharmacology 1989;28:89–97.
23. Carlos RQ, Seidler FJ, Slotkin TA. Fetal dexamethasone exposure alters macromolecular characteristics of rat brain development: A critical period for regionally selective alterations? Teratology 1992; 46:45–59.
24. Romano MC, Gioia IA, Bernasconi MV. Prednisone effects on postnatal brain development of rats following maternal therapy. Pediatr Res 1977;11:1042–5.
25. Stein HM, Oyama K, Martinez A, Chappell A, Blount L, Padbury JF. Effects of corticosteroids in preterm sheep on adaptation and sympathoadrenal mechanisms at birth. Am J Physiol 1993;264: E763–9.
26. French NP, Hagan R, Evan SF, Godfrey M, Newnham JP. Repeated antenatal corticosteroids: Size at birth and subsequent development. Am J Obstet Gynecol (in press).
27. Bohn MC. Glucocorticoid induced teratologies of the nervous system. In: Yanai J, ed. Neurobehavioural teratology. Amsterdam: Elsevier Science Inc. 1984:365–87.
28. Weichsel ME Jr. Glucocorticoid effect upon thymidine kinase in the developing cerebellum. Pediatr Res 1974;8:843–7.
29. Barres BA, Lazar MA, Raff MC. A novel role for thyroid hormone, glucocorticoids, and retinoic acid in timing oligodendrocyte development. Development 1994;120:1097–108.
30. Poduslo SE, Miller K, Pak CH. Induction of cerebroside synthesis in oligodendroglia. Neurochem Res 1990;15:739–42.

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