CURRENT TOPIC

Antenatal steroids and the developing brain

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Abstract

Randomised clinical trials show that two injections of corticosteroid into the mother before preterm delivery reduce respiratory distress syndrome, neonatal mortality, and intraventricular haemorrhage. However, repeated courses of antenatal steroid are not backed by such evidence of safety and efficacy. Animal studies have shown that maternal corticosteroid delays myelination and reduces the growth of all fetal brain areas particularly the hippocampus. Corticosteroids may reduce or enhance hypoxic-ischaemic injury to the developing brain depending on timing and dosage. Clinical trials of maternally administered corticosteroid show no evidence of increased disability on follow up but numbers are small. Postnatal trials of dexamethasone when brain maturity is still preterm show a significant increase in later disability in the dexamethasone treated groups. There is evidence from randomised trials, retrospective data, experiments on pregnant mice, and the chemical make up of the preparations that betamethasone may be safer and more protective of the immature brain than dexamethasone. Single course corticosteroid treatment before preterm delivery must still be recommended as a life saving and cost effective intervention, but clinicians may wish to change from using dexamethasone to betamethasone. In view of the animal and postnatal data, clinicians should be cautious with repeated courses of antenatal corticosteroids and repetition may be unnecessary for lung maturity.

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Maternal steroid treatment before preterm delivery is one of the best documented and most cost effective life saving treatments in perinatal medicine but, in certain circumstances, the price of accelerated lung maturity may be loss of brain cells and increased neurodevelopmental disability. The purpose of this review is to present the evidence from cell biology, animal models, and clinical trials, pointing out questions that still need answers and offering guidance to the clinician.

Perinatal physiology and evidence based medicine

During the 1960s, Liggins in Auckland developed the idea that the fetal brain played a central role in the onset of labour. He lesioned the hypothalamic-pituitary axis in the fetal lamb and observed that onset of labour was delayed, the fetal adrenal cortex was underdeveloped, and the fetal lungs would not inflate normally.[1 2] He then showed that administration of exogenous corticosteroid prevented these changes. Liggins went on to carry out a large randomised controlled trial which showed a reduction in respiratory distress syndrome and neonatal death after two intramuscular injections of 12 mg betamethasone 24 hours apart to mothers before preterm delivery.[3] Treating 23 mothers with corticosteroid before preterm delivery would prevent one neonatal death on average. The delay between publication of Liggins' trial (1972) and the general dissemination[4] of this life saving treatment (1990) was one of the driving forces behind the establishment of the Cochrane collaboration. A single course of prenatal corticosteroid is associated with a statistically significant reduction in intraventricular haemorrhage on ultrasound and a non-significant trend toward less neurodevelopmental disability.[5]

From one course to multiple courses of corticosteroids

The initial trials suggested that the beneficial effect of corticosteroids was absent if there was an interval of over seven days between treatment and delivery. This finding persuaded an increasing number of obstetricians to repeat the course of steroids after seven days if the pregnant women at risk of preterm delivery had not yet given birth. A recent survey of British obstetric departments showed that 98% are prescribing repeated courses of corticosteroids.[6] If a woman first threatens preterm labour, but then does not deliver, corticosteroid injection may be repeated three, four, or more times. It is not unknown for pregnant women with twins to receive six courses of corticosteroid as prophylaxis covering the period from 24 to 34 weeks gestation. This represents a much more prolonged exposure of the fetus to corticosteroids than that given by

Liggins and such repeated doses are not supported by the same kind of evidence of safety and efficacy.

Steroids and brain growth in animal models

There is considerable evidence from experimental animals that corticosteroids can have an adverse effect on the growth and development of the immature brain. Caution is necessary when extrapolating from animal models to human clinical medicine, but it is important to point out that the general sequence of brain growth shows no species differences between laboratory animals and humans.[7] Furthermore, a rat or mouse neurone has the same composition and electrical properties as a human neurone. Species differences relate to the complexity of the mature brain and the timing of the brain growth spurt in relation to birth. In humans, neuronal division, except for the cerebellum and dentate gyrus, is completed before the 24th week of gestation.[7] Subsequent cell division in the brain consists mainly of glia, especially oligodendroglial cells which will lay down myelin. In humans, the peak brain growth spurt occurs around term. In mice and rats, the brain growth spurt occurs after term but in monkeys and sheep it occurs before term. Thus a rat of 7 days of age is roughly equivalent to a full term infant in terms of growth, periventricular germinal matrix, neurochemical data, electroencephalographic pattern, and synapse formation.[8] A 1 day old rat would correspond to a human fetus at about 22–24 weeks.[7] In contrast, the peak brain growth spurt in the sheep[9] and monkey[10] occurs weeks before term. Myers[10] has shown that a hypoxic insult at 76% of gestation in the fetal rhesus monkey and 84% of gestation in the fetal sheep can produce white matter injury similar to that in the preterm infant.

Corticosteroids impair growth of the developing brain

Huang *et al*[11] showed that a single dose of betamethasone (0.5 mg/kg) to pregnant sheep at about 70% of gestation was followed by a reduction in brain weight of 10% at term. If a total of four doses of betamethasone were given at intervals of one week, the brain weight at term was reduced by 21%. Cerebrum, cerebellum, and brain stem were all reduced in weight. The same investigators examined the optic nerve and found that a single dose of corticosteroid did not reduce myelination, but four doses were followed by a reduction in fully myelinated axons from 51% to 24% if the lamb was delivered preterm.[12] If pregnancy was allowed to go to term, there were no differences in myelination in the optic nerve—that is, the effect was a delay in myelination. There was no effect on axonal numbers. Uno *et al*[13] gave dexamethasone in doses of 0.5, 5, or 10 mg/kg to pregnant rhesus macaques on day 132 (82% of term) and delivered the fetus at 135 days of gestation. Cell counting in the hippocampus showed decreased numbers of neurones in the CA regions and dentate gyrus. The loss of cells was increased by multiple doses in most of the areas. The hippocampal neurones contain a high density of corticosteroid receptors and may thus be particularly affected by pharmacological, as distinct from physiological, doses of corticosteroid. In general, neurones in the human brain have stopped dividing by the third trimester, but those in the dentate gyrus continue to divide long after full term and are thus vulnerable to adverse influences. One of the mechanisms by which corticosteroids reduce brain growth is by inhibiting growth factors and facilitating apoptosis.[14]

Corticosteroids can reduce or enhance hypoxic-ischaemic brain injury

There is considerable evidence that corticosteroids affect the ability of the brain to withstand hypoxia-ischaemia, but the results are inconsistent and contradictory. Kauffman *et al*[15] showed that maternal dexamethasone at 0.05, 0.2, and 0.8 mg/kg produced a dose dependent impairment of survival in 1 day old rat offspring in 5% O_2. Fetal rat hippocampal cultures showed that exposure to corticosterone enhanced both hypoxic and hypoglycaemic neuronal and astroglial injury.[16] In contrast, Tuor *et al*[17] have shown that 0.1 mg/kg dexamethasone reduced brain injury in the unilateral carotid occlusion and hypoxia model in 7 day old rats (roughly equivalent to term infants with respect to brain maturity) if given four hours before hypoxia whereas pretreatment at 48 hours or four days was ineffective. This effect was age dependent, as 28 day old rats were not protected. Flavin[18] used a fetal rat basal forebrain cell culture system subjected to a combined hypoxic and hypoglycaemic insult. He found that pretreatment with dexamethasone resulted in a dose dependent increase in cell damage whereas continuous application of dexamethasone before, during, and after the insult was protective.

Are there differences between corticosteroid preparations?

Both betamethasone and dexamethasone cross the placenta and are not inactivated to a major extent by placental enzymes. Both drugs have a fluoride substituted in the steroid, greatly increasing glucocorticoid potency and giving negligible mineralocorticoid effect. The only difference between the two molecules is the orientation of a methyl group on position 16. Although it is hard to believe that such a small difference between two molecules could have important consequences, the biological and clinical effects of photoisomerisation of the bilirubin molecule illustrate how a change in orientation can alter its biological effect.

Both betamethasone and dexamethasone are recommended for use before preterm delivery by the American National Institutes of Health.[19] Rayburn *et al*[20] compared the effect of a single dose of betamethasone 0.1 mg/kg, dexamethasone 0.1 mg/kg, or placebo at 74% of gestation in pregnant mice. When the offspring were mature, the betamethasone treated group showed enhancement of memory compared with the placebo group, but the dexamethasone treated group showed a decrement in memory.

Corticosteroids in human pregnancy and outcome in the infant

MacArthur *et al*[21] reported outcome at six years in 250 (82.2%) children who were in the original Auckland betamethasone trial. Betamethasone treated girls scored significantly better than control girls for school behaviour. There were no differences on the Peabody picture vocabulary test. The betamethasone treated group scored lower than the control group on Raven's progressive matrices and visual memory and visual closure. There were no differences in head circumference at 6 years of age. Considering the large number of developmental outcomes measured in this study, these results are compatible with little overall effect.

The US steroid group trial[22] found that, out of 200 children exposed to antenatal dexamethasone, nine were neurologically abnormal compared with 15 in the control group (odds ratio 0.61 (0.27–1.38)). In all, 6% of the placebo group had a Bayley motor index of below 68 whereas only 3.8% of the dexamethasone treated group had such a low motor score.

French *et al*[23] reported the outcome of 652 singleton liveborn infants delivered between 20 and 32 weeks gestation; 311 had received no corticosteroid, 123 had received one course (two doses of betamethasone), 20 had two courses, and 23 had received three or more. There was the expected higher mortality in the group that had not received betamethasone. One course of betamethasone was associated with a 0.42 cm reduction in head circumference at birth, two courses with a 0.74 cm reduction, and three or more courses with a 1.02 cm reduction. There were no significant differences in head circumferences at 3 years of age. Of the group that did not receive betamethasone, 7.8% had cerebral palsy at 3 years of age, whereas 5.1% of the infants who had received one course of betamethasone had cerebral palsy, and none of the infants who had received two or more courses of betamethasone developed cerebral palsy. Some 11.9% of the no betamethasone group and 12.1% of the group receiving a single course of betamethasone were disabled at 3 years of age, but only 6.7% of the infants receiving two or more courses were disabled.

Baud *et al*[24] reported outcome in a large retrospective multicentre regional cohort of 883 infants with gestational ages from 24 to 31 weeks who were admitted to level 3 neonatal units during a four year period. Mothers of 361 infants had received betamethasone, the mothers of 165 had received dexamethasone, and the mothers of 357 did not receive corticosteroid. The rates of cystic periventricular leucomalacia (PVL) were compared between the three groups using multivariate analysis adjusting for confounding factors such as sex, chorioamnionitis, infection, twin pregnancy, and other relevant factors. Some 8.4% of the no steroid group developed cystic PVL compared with 4.4% of the betamethasone treated group and 10.9% of the dexamethasone treated group. After adjustment, the odds ratio for cystic PVL was 0.5 (0.3–0.9) in the betamethasone treated group compared with the no steroid group, and 1.5 (0.8–2.9) for the dexamethasone treated group.

Outcome of postnatal corticosteroid treatment for preterm infants

Yeh *et al*[25] reported the two year outcome of a randomised trial of dexamethasone 0.5 mg/kg/day given to preterm infants with respiratory distress, starting before 12 hours of age and continuing for three weeks. The dexamethasone treated group had nearly twice the rate of neuromotor abnormalities (25 out of 63) as the control group (12 out of 70). O'Shea *et al*[26] reported one year neurological outcome on a randomised trial of postnatal dexamethasone for 42 days for preterm infants with chronic lung disease. Some 25% of the dexamethasone treated infants had cerebral palsy compared with 7% of the control infants.

Shinwell *et al*[27] reported the six year outcome of a large randomised trial of dexamethasone 0.5 mg/kg/day for only three days starting at 12 hours for preterm infants with respiratory distress syndrome. A total of 39 of 80 children treated with dexamethasone had cerebral palsy, with 35 having spastic diplegia or spastic quadriplegia, whereas only 12 of 79 control children had cerebral palsy. It should be pointed out that the dose received by the infant is 5–10 times higher with such postnatal treatment than is received by the fetus with conventional antenatal corticosteroid doses.

What advice can be offered to clinicians?

SHOULD OBSTETRICIANS CONTINUE TO GIVE SINGLE COURSES OF ANTENATAL CORTICOSTEROIDS BEFORE PREMATURE LABOUR?

Yes. There is no evidence from randomised trials that a single course of betamethasone increases the risk of brain injury or disability and there may be a protective effect. Because of the overwhelming evidence of reduced neonatal mortality, reduced intraventricular haemorrhage, and other morbidity, this intervention must continue to be recommended.[5]

SHOULD OBSTETRICIANS CURRENTLY USING DEXAMETHASONE SWITCH TO BETAMETHASONE?

Perhaps. The possibility that there may be a real difference between betamethasone and dexamethasone is suggested by several pieces of evidence.

(1) Separate meta-analyses of prenatal betamethasone and dexamethasone using the data in the Cochrane review[5] show that only betamethasone reduces neonatal mortality with statistical significance.
(2) Baud's own retrospective data[24] showed that antenatal betamethasone reduced PVL but dexamethasone did not.
(3) Rayburn's experiments with pregnant mice showed differences in memory and behaviour between betamethasone treated and dexamethasone treated groups of offspring.[20]
(4) Sulphiting agents in the dexamethasone preparation (but not in the betamethasone preparation) may be neurotoxic, especially in combination with peroxynitrite.[24]

In view of the insignificant reduction in neonatal mortality achieved with antenatal dexamethasone and the impressive evidence that postnatal dexamethasone increases the risk of neuromotor disability, one is left with the uneasy feeling that the considerable animal evidence of an adverse effect of dexamethasone on brain growth and development may apply to antenatal courses especially if repeated. It is clearly important to obtain school age follow up information from as many of the antenatal corticosteroid trials as possible, particularly those using dexamethasone. To our knowledge, only the US steroid group have published information on this.[22] It will be important to not only document neuromotor disability but to quantify cognitive and memory functions, because areas such as the hippocampus may have been affected. Although some will want to wait for more clinical data on single course antenatal dexamethasone before being convinced of its disadvantages, a switch from dexamethasone to betamethasone is hard to criticise.

SHOULD OBSTETRICIANS CONTINUE TO GIVE REPEATED DOSES OF CORTICOSTEROIDS?

Perhaps, but if the clinician proposes repeated courses, the pregnant woman needs to be informed that this treatment is not well supported by evidence. The data of French *et al*[23] suggest that there is no increased risk of neurodevelopmental disability from repeated courses of corticosteroids. However, the impressive animal evidence of retardation of brain growth with repeated courses of corticosteroids together with the consistently worse neurological outcome with postnatal dexamethasone should make clinicians cautious. McNamara and Bottoms[28] have recently published evidence that the incidence of respiratory distress does not increase when preterm delivery occurs more than seven days after steroid administration. If confirmed, this will remove the need for repeated courses of antenatal corticosteroids.

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