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Steroids and Injury to the Developing Brain:

Net Harm or Net Benefit?

Shadi N. Malaeb, MD^{a,*} and Barbara S. Stonestreet, MD²

^aDepartment of Pediatrics, St. Christopher's Hospital for Children, Drexel University College of Medicine, 245 North 15th Street, NewCollege Building, Room7410, Mail Stop 1029, Philadelphia, PA 19102, USA

^bDepartment of Pediatrics, Women & Infants Hospital of Rhode Island, The Alpert Medical School of Brown University, 101 Dudley Street, Providence, RI 02905, USA

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INTRODUCTION

Glucocorticoids, commonly referred to as *steroids*, are widely used in neonatal/perinatal medicine. They are prescribed to pregnant women at risk for premature birth, and sometimes to infants with significant airway or lung disease, refractory hypotension, or septic shock. Preterm infants are at high risk for brain injury, morbidity, and mortality. Steroids are thought to attenuate some of these risks.^{1,2} However, steroid regimens used vary widely, from a single short course of antenatal steroids given to the mother early in the third trimester, to repeated or prolonged courses of steroids given over weeks to the premature infant. As more data have accumulated regarding the long-term outcomes of infants exposed to steroids, concern has been increasing about neurodevelopmental impairment after exposure to steroids in certain settings. This article summarizes some of the experimental and clinical findings, and explores the complex nature of the relationship between steroids and brain injury, with a focus on the premature brain.

OVERVIEW OF BRAIN DEVELOPMENT

Normal brain development requires a well-orchestrated ontogeny of cellular proliferation, migration, differentiation, angiogenesis, synaptogenesis, myelination, and apoptosis.³ Neurogenesis remains active well into adulthood in the subventricular zone and hippocampal dentate gyrus.⁴ Neuronal progenitor cells migrate from their sites of origin and become mature integrated neurons. Early-stage neuronal progenitor cells maintain an active cell cycle and can either divide or die via apoptosis. As progenitor cells mature, they exit the cell cycle and commit to differentiate.⁵ A large number of migrating neurons populate a transient

*Corresponding author. Shadi.Malaeb@drexelmed.edu.

subcortical layer known as the *subplate zone*. Other neurons enter the cortical plate and integrate into neuronal circuits. Synaptic connectivity is essential to maintain survival for cortical neurons. Most subplate neurons involute through apoptosis toward late gestation and in infancy. Oligodendrocyte progenitor cells follow neuronal tracts and mature to form myelin. Cerebral vascular endothelial cells, pericytes, and astrocytes promote angiogenesis to form neurovascular units that will support neurons and form the blood–brain barrier.^{6,7} The ontogeny of the developing nervous system is under tight regulation by intrinsic, paracrine, endocrine, and external modulators. Perturbations in any of these factors could result in long-term consequences that affect the structure and function of the developing central nervous system (CNS).³

NEUROTROPHIC EFFECTS OF STEROIDS

Steroids are essential for maturation and survival of several cell types in the CNS. Adrenalectomy in adult rats results in massive cell death in the dentate gyrus and decreases the number of dendritic branch points.^{8,9} Corticosterone replacement after adrenalectomy reverses these processes.⁹ Corticosterone administration accelerates neuronal migration of cerebellar granule cells and enhances cerebellar Purkinje cell growth in the offspring. This treatment also accelerates the emergence of perinucleolar rosettes forming accessory nucleolar bodies of Cajal.¹⁰ The emergence of this structure signifies increases in transcriptional activity present during the late stages of neuronal maturation.¹¹ Corticosterone application early in development also accelerates the differentiation of membrane electrical properties in embryonic chick neurons.¹² In addition, glucocorticoids activate brain-derived neurotrophic factor receptor (Trk) tyrosine kinases and induce the expression of thyroid hormone–dependent transcription factor Kruppel-like factor 9 gene.^{13–15} These events are implicated in the plasticity of hippocampal neurons and postnatal development.^{13–15} Short-term corticosterone exposure increases synaptogenesis in the developing cortex. Reducing endogenous glucocorticoid activity decreases spine process turnover, and corticosterone reverses this process.^{16,17} Therefore, corticosterone seems to accelerate neuronal maturation. Glucocorticoids also induce oligodendrocyte precursor differentiation¹⁸ and increase oligodendroglial marker expression during myelinogenesis.^{19–21} In summary, steroids exert important trophic effects on cell survival, differentiation, maturation, and synaptogenesis (Box 1).

NEUROPROTECTION BY STEROIDS

Steroids protect the brain acutely from neuroinflammatory damage.²² Glucocorticoids also attenuate excitotoxic white matter injury by protecting oligodendrocytes from alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)–induced excitotoxicity through upregulating erythropoietin signaling.²³ Prenatal glucocorticoid administration enhances pericyte coverage, inhibits angiogenesis, and results in trimming of the germinal matrix neovasculature, thereby reducing the propensity for germinal matrix hemorrhage.²⁴

ANTENATAL STEROIDS ACCELERATE ONTOGENIC CHANGES IN THE DEVELOPING CNS

Ontogenic decreases in blood–brain barrier permeability have been reported in ovine fetuses from 60% of gestation up to maturity in the adult.²⁵ Treatment of pregnant ewes with a glucocorticoid regimen similar to those used in the clinical setting was associated with decreases in blood–brain barrier permeability in fetal sheep at 60% and 80% of gestation.^{26,27} Ontogenic decreases in brain water content have also been reported in fetal sheep between 60% and 90% of gestation.²⁸ Maternal treatment with dexamethasone resulted in decreases in regional brain water content in fetal sheep at 60% of gestation.²⁸ At the molecular level, Na⁺/K⁺-ATPase pump α 1-subunit expression is lower at 60% than at 90% of gestation, and dexamethasone treatment of pregnant ewes at 60% of gestation increased the expression of this protein.²⁹ Therefore, antenatal steroid treatment of pregnant ewes using regimens similar to those used in the clinical setting accelerates some aspects of brain development in the immature sheep fetus.

DEVELOPMENTAL STAGE AT TIME OF EXPOSURE AND DURATION OF EXPOSURE MODULATE STEROID EFFECTS ON THE CNS

The effects of glucocorticoids on the developing CNS are a function of both the stage of development at the time of exposure and the duration of exposure. The developmental stage reflects the systemic physiology and the nature of different cellular populations within the brain, both of which are affected by postmenstrual and chronologic ages. For example, cerebral water content in the fetal brain decreased after treatment of pregnant ewes with dexamethasone at 60% of gestation, but not at 80% or 90%.²⁸ Similarly, aquaporin protein expression was decreased in lambs and adult sheep brains after dexamethasone treatment, but not in the fetal brain after exposure of the ewes to dexamethasone.³⁰ Maternal treatment with glucocorticoids was also associated with decreases in blood–brain barrier permeability in fetal sheep at 60% and 80% of gestation, but not at 90%, and not in lambs after postnatal glucocorticoids.^{27,31} Dexamethasone also reduced the affinity of the *N*-methyl-*D*-aspartate (NMDA) receptor to its ligand in lambs, but not in the fetal or adult sheep brain.³² Maternal exposure to dexamethasone at 70% of gestation, but not at 90%, resulted in significant decreases in total and nonneuronal apoptosis in the fetal cerebral cortex.³³

The effect of the duration of exposure to glucocorticoids was examined by comparing fetuses of ewes exposed to a single course of dexamethasone or placebo injections every 12 hours for 48 hours between 104 and 107 days of gestation versus fetuses of ewes receiving the same treatment once a week for 5 weeks between 76 and 107 days of gestation. Full-term gestation in sheep is 147 days. Maternal dexamethasone treatment at 70% of gestation was associated with decreases in water content in the fetal brain after multiple, but not after a single course of steroids.³⁴ Likewise, multiple courses of steroids, but not single courses, also increased myosin isoform expression in the fetal carotid arteries.³⁵ In contrast, apoptosis in the fetal cerebral cortex was decreased at 70% of gestation after exposure to single, but not after multiple courses of dexamethasone.³³ Even more concerning is the finding that Na⁺/K⁺-ATPase enzyme activity, as an index of neuronal membrane integrity in

the fetal brain, was reduced after multiple courses of dexamethasone, but not after single courses.³⁶ Perhaps the most intriguing aspect of modulation of the steroid effects on the brain with reference to the duration of exposure stems from observations suggesting that chronic glucocorticoid exposure facilitates paradoxical proinflammatory responses to injury in the brain,^{22,37} which is in direct contrast to classical anti-inflammatory responses expected after acute glucocorticoid exposure.³⁸

Taken together, these findings suggest that the developmental stage at the time of exposure and the duration of exposure each have important contributions to the ultimate glucocorticoid effects on the developing CNS. Comprehension of the pharmacodynamics of steroids in the developing CNS is also necessary to understand the multifaceted effects of glucocorticoids on the brain, and these are addressed in the following sections (Box 2).

PHARMACODYNAMICS OF NATURAL VERSUS SYNTHETIC GLUCOCORTICOIDS IN THE BRAIN

Glucocorticoids are synthesized by the fetal adrenal cortex, mostly by maternal progesterone that crosses the placenta.³⁹ The natural glucocorticoid in humans is cortisol and in rodents is corticosterone. Human fetal serum cortisol levels decrease from 8 ng/mL at 15 weeks to 4 ng/mL by 20 weeks. In the absence of labor and under the regulation of placental corticotropin-releasing hormone and fetal adrenocorticotrophin, a steep increase occurs in cortisol levels: to 20 ng/mL by 36 weeks of gestation and 45 ng/mL near term.⁴⁰ Glucocorticoids are approximately 75% bound to corticosteroid-binding globulins in the circulation. Both natural and synthetic steroids readily penetrate the blood–brain barrier to reach the parenchyma. However, synthetic steroids such as dexamethasone are actively pumped out of the brain by the multidrug resistance protein 1A (mrd1A) P-glycoprotein, which is highly expressed at the blood–brain barrier.⁴¹ Hence, dexamethasone is retained less efficiently than natural glucocorticoids in brain regions possessing a functional blood–brain barrier, and more efficiently when the blood–brain barrier is injured. Dexamethasone is also effectively retained in regions devoid of a blood–brain barrier, such as the circumventricular organs, where glucocorticoids suppress the hypothalamic-pituitary-adrenal (HPA) axis. Once in the parenchyma, steroids diffuse readily across cell membranes.

Natural and related steroids such as hydrocortisone are inactivated by an intracellular glucocorticoid-metabolizing enzyme, 11b-hydroxysteroid dehydrogenase type 2 (HSD2),⁴² which converts them into inactive 11-keto derivatives.⁴² HSD2 significantly attenuates the actions of natural glucocorticoids on the brain.^{43,44} HSD2 expression decreases with advancing gestation from fetal to newborn, and up to adulthood, concomitantly as endogenous glucocorticoid production increases. Consequently, a larger portion of endogenous cortisol or exogenous hydrocortisone that enters the brain at more mature postmenstrual ages will remain active to bind more receptors and augment their biologic actions.^{45,46} On the other hand, synthetic glucocorticoids are resistant to inactivation by HSD2. The same property, which prevents their placental deactivation, exaggerates their biologic actions in the brain, even though very little is retained because of elimination by the multiple drug resistance mrd1A protein expressed at the blood–brain barrier.

GLUCOCORTICOID RECEPTORS IN THE BRAIN

Two types of glucocorticoid receptors are present in the CNS.^{47,48} The type 1 receptor is a mineralocorticoid receptor (MR), which has high affinity for cortisol and corticosterone, with aldosterone and hydrocortisone as agonists, and spironolactone as an antagonist. It binds poorly to dexamethasone and betamethasone. The type 2 receptor is a *glucocorticoid receptor* (GR), which has a high affinity for dexamethasone but 10 times lower affinity for corticosterone, with methylprednisolone and betamethasone as agonists, and mifepristone (RU 38486) as an antagonist. MRs are unique in that they are highly expressed exclusively in the hippocampus and limbic brain regions, whereas GRs are expressed ubiquitously across all brain regions. The main receptor activated at physiologic cortisol levels is the MR in the hippocampus, with little to no GR activation. The MR nuclear response elements are thought to mediate neurotrophism.^{47,49} At higher cortisol levels, GRs throughout the brain become activated along with the activated MRs in the limbic brain. In contrast, when pure GR agonists such as dexamethasone or betamethasone are administered, GR activation primarily occurs throughout the CNS with little or no MR activation. Prolonged dexamethasone administration suppresses the HPA axis and depletes systemic and local cortisol levels within brain tissue. Hence, prolonged administration of pure GR agonists, as opposed to mixed MR/GR agonists, paradoxically attenuates MR activation in the hippocampus and other brain structures responsible for learning and memory.^{22,37,47} Local cortisol depletion, along with limited the ability of dexamethasone to be retained because of MDR1A P-glycoprotein elimination, leads to a paradoxically enhanced microglial reactivity and sustained neuroinflammation after brain injury with prolonged exposure to the supposedly “anti-inflammatory” synthetic glucocorticoid. This process results in neurodegeneration, demyelination, synaptic dysfunction, and a loss of cortisol-mediated positive trophism. Administration of a GR antagonist, such as RU 38486 or corticosterone replacement, counteracts the cortisol-depleting effects of prolonged dexamethasone exposure on the hippocampus.^{50,51} Hence, the balance between MR/GR stimulation is a major determinant of the effects of glucocorticoids on the brain.

HAZARDS OF GR OCCUPANCY

Accentuated and prolonged GR occupancy underlies an array of injurious effects of glucocorticoids on the brain. Stimulation of cultured embryonic rat neural stem cells with dexamethasone or with high concentrations of corticosterone, but not low concentrations, reduces cell proliferation.⁵² These effects were inhibited by specific GR, but not MR blockade. Chronic corticosterone administration reduces neurogenesis in the adult rat dental gyrus.⁵⁰ This inhibitory effect can be reversed by treatment with the GR antagonist mifepristone.^{50,53,54} Proliferation of cells in the dentate gyrus also was reduced in fetuses of pregnant monkeys receiving dexamethasone both early and late in gestation.⁵⁵ Premature human neonates whose mothers were treated with synthetic glucocorticoids and died shortly after delivery exhibited lower hippocampal neuronal densities than neonates who were not exposed to glucocorticoids.⁵⁶ These findings suggest that accentuated GR stimulation mediates glucocorticoid-related cell cycle inhibition in the developing brain.⁵² Excess maternal glucocorticoid administration also retarded migration of postmitotic neurons in the fetal cerebral cortex in rats.⁵⁷ Offspring of pregnant rats exposed to high-dose maternal

corticosterone showed long-lasting neurobehavioral impairment.⁵⁸ Betamethasone administration to pregnant sheep reduced the number of oligodendrocytes and axons in the corpus callosum, and delayed myelination in the fetal brain.^{59–61} The inhibitory effects of synthetic steroids on myelination in the sheep were dependent on the stage of development, and decreased with advancing gestational age.^{60,62} Repeated administration of dexamethasone during the first week of life to rat pups resulted in prominent apoptosis, particularly in proliferating cells, and depleted the hippocampal neural precursor cell pool, resulting in sustained reductions in the volume of the dentate gyrus.⁶³ Therefore, accentuated GR occupancy could have adverse effect on neurons and glia in the developing brain (Box 3).

GLUCOCORTICOIDS AND RECOVERY AFTER BRAIN INJURY

Cerebral hypoxia-ischemia and reperfusion induces waves of free-radical injury, excitotoxicity, neuroinflammation, and delayed cell death.⁶⁴ Induction of neural stem cell proliferation often occurs after brain injury and during the subsequent recovery and remodeling phases.^{4,65} Survival of early progenitor cells requires trophism by MR occupancy, whereas their proliferation is hindered by heightened GR occupancy. In fact, maternal pretreatment with antenatal dexamethasone did not attenuate ischemic brain injury in the ovine fetus.⁶⁶ The effects of glucocorticoids on hypoxic-ischemic brain injury were elegantly summarized in a recent review by Bennet and colleagues.⁶⁷

UNIFYING HYPOTHESIS

The emerging picture of glucocorticoid effects on the developing brain derived from mounting experimental evidence is that of an inverse-U-shaped curve, because both insufficient glucocorticoid exposure and accentuated or prolonged exposure exert an array of deleterious effects mediated by either low MR occupancy or by high GR occupancy (Fig. 1). Conditions associated with excessive GR relative to MR occupancy include: (1) administration of high doses or prolonged courses of hydrocortisone; (2) administration of dexamethasone at an advanced postmenstrual age, when endogenous cortisol production had increased and HSD2 protection decreased, which could exaggerate an already heightened GR occupancy by cortisol; (3) administration of prolonged courses of dexamethasone that can suppress the HPA axis and deplete local brain tissue cortisol, thereby reducing MR occupancy; (4) administration of dexamethasone during conditions that impair elimination by the multidrug resistance pump at the blood-brain barrier, such as during cerebral hypoxia/ischemia; and (5) early administration of a pure GR agonist dexamethasone when endogenous cortisol levels for effective MR occupancy are deficient. The consequent overall effects of steroids on the brain are dependent on the developmental stage, duration of exposure, and the presence or absence of other disease processes in the brain and/or body before or after the time of exposure. The effect of steroids on the brain is also dependent on the dose and type of glucocorticoid used. This concept has been proposed by many investigators, including De Kloet and colleagues,⁴⁷ Diamond and colleagues,⁶⁸ McEwen,⁶⁹ and Sousa and Almeida.⁴⁹ These concepts could provide a basis for clarifying the disparate effects of glucocorticoids observed in clinical trials, and guiding future clinical strategies to

maximize the beneficial effects of steroids while minimizing the detrimental effects of glucocorticoid therapy.

CLINICAL PERSPECTIVES

Antenatal Steroids

The ability of a single antenatal course of glucocorticoids to accelerate fetal lung maturation has been extensively documented by clinical trials.^{70,71} The 2 most frequently used glucocorticoids are betamethasone and dexamethasone. Betamethasone has slightly greater beneficial pulmonary effects compared with dexamethasone.⁷² Antenatal administration of glucocorticoids reduces the incidence and severity of respiratory distress syndrome and decreases the incidence of intraventricular hemorrhage, necrotizing enterocolitis, and risk of mortality.^{70,71} Antenatal treatment with glucocorticoids is also associated with a trend toward a lower incidence of cerebral palsy and less neurodevelopmental delays in childhood (relative risk, 0.49; 95% CI, 0.24–1.00).⁷⁰ However, when the same course of antenatal steroids was repeated weekly, head circumference at birth was smaller compared with that of infants whose mothers had received a placebo.⁷³ Children exposed to multiple courses of betamethasone tended to have higher incidences of cerebral palsy⁷⁴ and attention problems in later childhood.⁷⁵ In addition, multiple courses of antenatal dexamethasone were associated with an increased risk of periventricular leukomalacia and neurodevelopmental impairment at 2 years of age.⁷⁶ These findings suggest that glucocorticoids can have beneficial effects when given over short intervals, whereas prolonged GR occupancy potentially results in CNS injury and impaired development.

POSTNATAL STEROIDS: EARLY ADMINISTRATION

In several clinical trials, both hydrocortisone and dexamethasone have been administered to premature infants early in the first week of life,¹ based on the assumption by some investigators that sick premature infants could have relative adrenal insufficiency.^{77–79} The existence of this condition remains controversial, and appreciation of the net benefit from this approach has been guarded at best. These studies have suggested occasional improvement and better neurologic outcomes after hydrocortisone treatment than after dexamethasone treatment, especially in infants exposed to chorioamnionitis.^{80–82} However, glucocorticoid administration during the first week of life has also been associated with an increased incidence of intraventricular hemorrhage and gastrointestinal perforation.^{80,83} Infants treated with dexamethasone early after birth also have been reported to have smaller head circumferences and lower weights at 36 weeks' postmenstrual age; higher incidences of cerebral palsy; and developmental delays later in life compared with placebo-treated infants.^{84,85} In contrast, the risk for cerebral palsy was not increased in premature infants treated with hydrocortisone in the first week of life.^{1,86} Nonetheless, these complications outweigh the neurotrophic benefits of MR occupancy by hydrocortisone, and have limited the use of glucocorticoids shortly after birth.

POSTNATAL STEROIDS: ADMINISTRATION AFTER THE FIRST WEEK OF LIFE

Glucocorticoids have also been used after the first week of life in several regimens to treat sick premature infants with pulmonary insufficiency and/or hypotensive shock.^{2,87,88}

Delayed administration of dexamethasone is associated with glycosuria, hypertension, and gastrointestinal bleeding, but not with perforation.² Moreover, an increased incidence of severe retinopathy of prematurity and abnormal neurologic examinations is seen on follow-up, warranting further scrutiny.^{2,88}

POSTNATAL STEROIDS: MODERATELY EARLY VERSUS DELAYED ADMINISTRATION

A systematic review of clinical trials further compared developmental outcomes of premature infants after receiving dexamethasone courses beyond the first week of life, and focused on the timing of treatment onset.⁸⁹ Studies were stratified into trials with a moderately early onset between 1 and 2 weeks of life or delayed onset of treatment beginning after 3 weeks of life. In the trials with the moderately early treatment onset, an inverse relationship was found between the dose of dexamethasone and risk of the combined outcome of mortality and/or cerebral palsy, and of a motor developmental index less than -2 standard deviations below the mean. The negative regression correlation coefficient suggests a decreased risk for neurodevelopmental impairment with dexamethasone if treatment is started moderately early (ie, between 7 and 14 days of life). However, an increased risk for hypertension, hyperglycemia, gastrointestinal bleeding, hypertrophic cardiomyopathy, and infection was seen.⁸⁷ In contrast, delaying the initiation of therapy beyond 21 days of age was associated with a trend toward incremental increases in the risk of the combined outcome of mortality and/or cerebral palsy with increasing dexamethasone doses. Similarly, a recent large multicenter prospective cohort study of very premature infants born with birth weights less than 1000 g receiving dexamethasone starting late at 5.1 ± 2.1 weeks of life showed that an increase of each 1-mg/kg dose was associated with a 40% increase in the risk for cerebral palsy and a 2-point reduction on the mental developmental index. Treatment after 33 weeks' postmenstrual age was associated with even greater harm.⁹⁰

In summary, these studies support the contention that the age at onset of treatment could influence the effects of steroids on the developing CNS in infants. The relationships among the dose and duration of treatment with systemic steroids and their effects on neurologic outcomes, potential beneficial effects on pulmonary outcomes, and/or systemic side effects are complex and need further investigation in large-scale randomized controlled clinical trials.⁸⁹

POSTNATAL STEROIDS: PROLONGED TREATMENT

In one controlled trial, prolonged courses of dexamethasone were given to preterm infants born at birth weights of 1250 g or less and gestational ages of 30 weeks or less who were dependent on mechanical ventilation and oxygen at 2 weeks of age.⁹¹ The starting dosage of

0.5 mg/kg/day was tapered over 42 days. Follow-up at 15 months of age showed normal neurologic examinations and Bayley developmental index scores greater than 83 in 7 of the 9 infants after dexamethasone, but in only 2 of 5 after placebo treatment, favoring beneficial effects for dexamethasone ($P<.05$). However, another randomized controlled trial administered a 42-day tapering course of dexamethasone to more mature preterm infants born with birth weights of 1500 g or less beginning between 15 and 25 days of age, with an initial dosage of 0.25 mg/kg/day.⁹² Follow-up at 12 months of age found more abnormal neurologic findings and instances of cerebral palsy (25% vs 7%; adjusted odds ratio, 5.3; 95% CI, 1.3–21.4) in the dexamethasone-treated infants compared with those treated with placebo. Taken together, these findings suggest that the critical developmental window for optimal benefits from postnatal treatment with glucocorticoids in sick premature infants is before 32 weeks' postmenstrual age and beginning within the second week of life (Box 4).^{90–92}

HYDROCORTISONE AND THE PREMATURE INFANT

Hydrocortisone is often prescribed for sick premature infants after the first week of life as an alternative to dexamethasone and betamethasone, with the goal of improving pulmonary outcomes and preserving neurologic function. Hydrocortisone therapy has been reported to improve severe capillary leak lung syndrome in ventilated preterm infants.⁹³ Extremely low-birth-weight infants receiving hydrocortisone after the second week of life had similar extubation rates and improved somatic growth compared with those receiving betamethasone.⁹⁴ Preservation of regional brain volumes at term-equivalent age was observed after treating ventilator-dependent infants with low-dose hydrocortisone for a week, suggesting the potential safety of hydrocortisone.^{95–97} The effectiveness of low-dose hydrocortisone in suppressing the evolution of bronchopulmonary dysplasia (BPD) and the safety of higher doses must be confirmed in clinical trials.⁸⁶

EFFECT MODIFICATION BY RISK OF BPD

Premature infants requiring continued respiratory support beyond 36 weeks' postmenstrual age are at high risk for developing cerebral palsy.⁹⁸ Glucocorticoids can reduce the risk of chronic lung disease. Therefore, it is reasonable to assume that steroid therapy can have indirect benefits for infants at high risk for developing BPD, by mitigating their risk of brain damage via attenuating the severity of their chronic lung disease. Occasionally, the benefits of reducing the severity of BPD could outweigh the risks of neurologic impairment resulting from the untoward effects of steroid therapy. On the other hand, the use of steroids in infants at low risk for developing BPD could unnecessarily expose infants to the adverse side effects of steroids. A meta-regression analysis conducted by Doyle and colleagues⁹⁹ found that for every 10% increase in the rate of chronic lung disease, a 2.3% decrease occurred in the risk of cerebral palsy (95% CI, 0.3%–4.3%) as a result of steroid therapy. A significant steroid-related benefit was observed only when the incidence of chronic lung disease exceeded 65%. Therefore, the challenge is to identify infants at high risk for BPD early in their course and administer a dose of glucocorticoid that can attenuate the progression of BPD (Box 5).

PREDICTING RISK OF BPD

A recent large prospective cohort study of newborns of extremely low gestational age found 3 distinct patterns of respiratory disease in the first 2 postnatal weeks (see Fig. 2).¹⁰⁰ The incidence of chronic lung disease was 67% in infants with early and persistent pulmonary dysfunction. Other studies have observed that a low cortisol level in the first week of life predicts a slightly higher probability of chronic lung disease or death at 36 weeks' postmenstrual age, particularly in infants with elevated illness scores.^{101–103} Hydrocortisone treatment increased survival without BPD in infants with basal serum cortisol values less than a median of 140 nmol/L.¹⁰⁴ When considering these findings together, one could speculate that postnatal glucocorticoid therapy may be beneficial when administered shortly after the first week of life to premature infants with early and persistent pulmonary dysfunction (Box 6).

SUMMARY

The relationship between glucocorticoids and neurodevelopmental impairment is complex. A thorough understanding of the underlying physiology of the positive and negative effects of glucocorticoids on the developing brain based on the concept of the inverse-U-shaped hypothesis is essential when deciding whether to treat a sick premature infant with glucocorticoids. Clearly, steroids play a major role in supporting brain development. Most probably, some infants could benefit from antenatal and postnatal administration of steroids. Ideally, the decision to treat should ensure the maximum respiratory benefit from steroids at the lowest neurologic risk, and at the same time avoid any serious systemic complications. This article suggests the following: (1) glucocorticoid therapy should be restricted to premature infants born before 30 weeks' gestation in whom findings suggest a high risk (>65%) for developing BPD, (2) the first course of postnatal steroids should be considered at approximately day 14 of life, and (3) the nature and dose of steroids used should be consistent with doses shown in clinical studies to be effective in improving survival and pulmonary outcomes. This approach must be validated in controlled trials. Of particular interest are 2 ongoing multicenter randomized placebo-controlled trials^{105,106} investigating the use of moderately early hydrocortisone to prevent BPD in preterm infants. The results of these studies may provide a better understanding of the efficacy and safety of this approach.

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KEY POINTS

- Steroid effects on the brain mimic an inverse-U-shaped curve, because deleterious effects result from both glucocorticoid insufficiency and/or excess glucocorticoid tissue exposure.
- The effects of glucocorticoids on the developing central nervous system are a function of both the stage of development and duration of exposure.
- The beneficial effects of glucocorticoids are optimal when given to sick premature infants in a critical window before 32 weeks' postmenstrual age.
- Glucocorticoids have net beneficial effects when given shortly after the first week of life to premature infants at high risk for severe chronic lung disease.
- The challenge is to identify infants at high risk for bronchopulmonary dysplasia (BPD) early in their course and to administer a dose that attenuates the progression of BPD.

Box 1**Neurotrophic effects of glucocorticoids**

- Enhance survival of early-stage neuroblasts
- Accelerate neuronal cell migration and maturation
- Facilitate synaptogenesis, pruning, and plasticity
- Induce oligodendrocyte precursor differentiation

Box 2**Determinants of the effect of glucocorticoids on the developing CNS**

- Stage of brain development at the time of exposure
- Duration of exposure
- Pharmacodynamic properties of the steroid
- Dosage used

Box 3**Effects of MR and GR occupancy on the developing brain**

- MR occupancy mediates neurotrophism by steroids.
- Accentuated or prolonged GR occupancy underlies an array of injurious effects of glucocorticoids on the brain.

Box 4**Critical developmental window for optimal benefits from postnatal glucocorticoid administration**

- Less than 32 weeks' postmenstrual age in sick premature infants
- Beginning in the second week of life

Box 5**Clinical challenges**

- Identify infants at high risk for BPD early in their course
- Administer a dose of glucocorticoid that impacts BPD progression while at the same time minimizes glucocorticoid-related brain injury

Box 6**Most beneficial time frame for administration of postnatal glucocorticoid therapy**

- Administered shortly after first week of life to premature infants born before 30 weeks of gestation
- To infants with signs of early and persistent pulmonary dysfunction, particularly if clinical or serologic signs of relative adrenal insufficiency are evident

Fig. 1.

Inverse-U-shaped hypothesis as a guide for risk/benefit analysis of glucocorticoid administration in experimental and clinical scenarios. Note that during the first few days of life, although a degree of MR occupancy by hydrocortisone may be neurotrophic in premature infants, systemic side effects of very early administration of hydrocortisone outweigh the potential benefits. See text for details.

Fig. 2.

Speculative predictive analysis for risk of death or cerebral palsy after postnatal glucocorticoid therapy according to pattern of respiratory disease in premature infants. Patterns of respiratory disease during the first 2 postnatal weeks among newborns with extremely low gestational age show that the incidence of chronic lung disease was 67% in infants with early and persistent pulmonary dysfunction. Doyle et al⁹⁹ observed significant steroid-related benefit only when the incidence of chronic lung disease exceeded 65%. These data suggest that the risk of cerebral palsy may be reduced if postnatal glucocorticoids are given to sick premature infants with early and persistent pulmonary dysfunction whose risk for developing BPD may exceed 65%, particularly if they also have low basal levels of cortisol. This predictive analysis must be validated in randomized clinical trials. CLD, chronic lung disease; EPPD, early and persistent pulmonary dysfunction; FiO₂, fraction of inspired oxygen; PD, pulmonary dysfunction. (*Adapted from* Laughon M, Allred EN, Bose C, et al. Patterns of respiratory disease during the first 2 postnatal weeks in extremely premature infants. *Pediatrics* 2009;123(4):1124–31; with permission.)