Developmental Assessment of Prematurely Born Children Exposed to Antenatal Corticosteroids

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The beneficial effect of antenatal steroid administration on fetal lung maturation and on premature infant survival was first reported by Liggins and Howie in 1972 [1] and was subsequently confirmed by others [2–4]. Several studies have demonstrated a significant reduction in the incidence of intraventricular hemorrhage and periventricular leukomalacia in premature infants following antenatal exposure to exogenous steroids [5–7], and some authors have also observed a reduction in the incidence of bronchopulmonary dysplasia [8], necrotizing enterocolitis [9] and retinopathy of prematurity [10]. The National Institutes of Health Consensus Developmental Panel on the effect of corticosteroids for fetal maturation on perinatal outcome concluded in 1994 that the use of a single course of corticosteroids for fetal maturation is a rare sample of a technology that yields substantial cost savings in addition to improving health [11].

The presence of steroids is essential for the normal growth and development of the central nervous system [12]. *In vitro* studies have suggested that corticosteroids may promote resilient neuronal activity through their effect on various mediators, such as ciliary neurotrophic factor and basic fibroblast growth factor, and also on the availability of insulin-like growth factor-1 binding protein [13]. Being anti-inflammatory agents, steroids may also block the action of pro-inflammatory cytokines implicated in the evolvement of white matter cerebral lesions [14,15]. On the other hand, under normal circumstances, the brain is protected from a potentially harmful excess of steroids, and access of maternal cortisol and corticosterone to the fetus is low due to placental 11 β-hydroxysteroid dehydrogenase activity [12]. This enzyme, however, has a low affinity for synthetic glucocorticoids, which pass rapidly from mother to fetus [12].

Despite the improved neonatal outcome, concern has been raised regarding the long-term implications of exposure to antenatal steroids [16,17]. Animal studies have demonstrated that antenatal exogenous steroids administered at critical stages of development may alter later neuro-endocrine function and behavior pattern [12]. Ample evidence has accumulated regarding the inhibitory effect of antenatal exogenous steroids on fetal body growth and on the growth and development of the fetal brain [18–22]. The magnitude of the effect differed according to the animal species studied and the number of doses given [12]. However, most animal studies demonstrated a larger inhibitory effect following multiple antenatal exposures than that following a single exposure [23].

During the last decade it became common practice to administer repetitive courses of steroids to women who remain at risk for premature delivery 7 days after the initial course [21,24]. The trend was consequent to the widely held belief, based on unsubstantiated initial results, that there is a decreased benefit from antenatal steroids 7 days after treatment [24]. While a few human studies have provided evidence that exposure to repetitive courses of steroids results in improved neonatal pulmonary function, others failed to observe similar beneficial effects and documented an inhibitory effect on birth weight and head circumference and an increased incidence of neonatal sepsis and mortality [21–23,25,26]. In view of the above data, recent publications have cautioned against the antenatal administration of multiple courses of corticosteroids, advocating the use of only one or two courses [17,24]. Consideration of the appropriate timing and dosage of exogenous steroid administration is incomplete without evaluating the long-term effect on human outcome. While quite abundant data have accumulated over the years regarding the long-term effect of a single course of antenatal steroids, follow-up studies of multiple course treatment are limited in number.

Long-term studies following a single course of antenatal steroids

The first cohort of premature infants exposed to antenatal exogenous steroids [1] was evaluated at the seventh year of age by MacArthur and colleagues [27]. Cognitive and psychosocial development and school progress were evaluated in 250 children, among whom 139 were born to mothers who had received betamethasone prior to delivery. There were no significant differences between the exposed and the control groups in the majority of measures, except for one cognitive sub-test (Raven's colored progressive matrices) where the control group scored better. The mean birth weight of the children was above 2,000 g and their mean gestational age was more than 34 weeks. Only 22 children had a birth weight below 1,500 g. The authors thus concluded that antenatal betamethasone administration was safe and has no adverse long-term effects.

In another study [28], 406 surviving American children (mean birth weight 1.9 kg, mean gestational age 31 weeks), whose mothers enrolled in a double-blind, randomized trial in 1976 to evaluate the efficacy of antenatal dexamethasone administration for the prevention of respiratory distress syndrome, were assessed within the first 3 years of life. No detectable growth, physical, motor or

developmental deficiencies could be attributed to antenatal exposure to the drug [28]. Similar results were obtained in the Netherlands when aspects of children's intellectual and motor development, school achievement and social-emotional functioning were investigated at 10–12 years of age (their mean birth weight was 1.75 kg and mean gestational age 31 weeks) [29]. There was also no effect of antenatal betamethasone exposure on physical development including lung function, although children exposed to betamethasone experienced more hospital admissions during the first years of life [30]. When the same cohort was evaluated at 20–22 years of age, groups did not differ in medical or psychological variables, including gender development, sexual orientation, sex-specific cognitive functioning and psychoneuroticism [31].

Improvements in neonatal care during the 1980s resulted in increased survival of very low birth weight infants, with increased susceptibility for development of cerebral lesions. At that stage, when the antenatal steroid beneficial effect was widely acknowledged, randomized studies, which allocated controls to non-treatment, were usually considered unethical. Thus, Doyle et al. [32] evaluated the developmental outcome at 5 years of age of 83 surviving children delivered between 1977 and 1982 with birth weight less than 1,000 g, 43 of whom were non-randomly exposed to antenatal betamethasone. Following adjustment for perinatal variables, no significant differences regarding growth, health and development were found between the exposed and the control children. The same authors conducted, at 14 years of age, a developmental evaluation of 130 VLBW children born during the early 1980s [33]. In this study, children who were non-randomly exposed to antenatal betamethasone were taller and had higher cognitive scores than controls. Premature infants born during and following the late 1980s were already the recipients of surfactant and were usually subjected to cranial ultrasound screening.

Salokorpi et al. [5] evaluated 82 infants at 2 years of age (mean birth weight 1,291 g, mean gestational age 30 weeks), whose mothers were enrolled in a randomized study conducted during 1989–1991 on the effect of antenatal dexamethasone. The incidence of cerebral palsy was 10% in the dexamethasone group and 22% in the placebo group. The improved outcome was attributed to the lower incidence of cerebral complications (intraventricular hemorrhage and periventricular leukomalacia) that was demonstrated among exposed infants during the neonatal period. A recent evaluation of 251 VLBW school-aged children [34] has demonstrated a beneficial effect of a single course of antenatal steroids on cognition in 91 children with neonatal cerebral lesions, but no effect among those with normal cerebral ultrasound.

Long-term studies following multiple courses of antenatal steroids

We discovered only three reports relating to long-term outcome following exposure to multiple courses of antenatal corticosteroids. French and co-workers [21] followed singleton infants born at <33 weeks gestation until 3 years of age. Ninety-nine of the assessed children were exposed to a single course of steroids, 35 of them to two or more courses and 193 had no antenatal exposure. At age 3 years, growth and severe disability outcomes did not appear to be related to increasing number of corticosteroids courses, despite the reduction of both birth weight and head circumference at birth with increasing number of courses. It has been acknowledged, however, that the low prevalence of disability and the relatively small number of patients treated with repeated courses gave the study a low power to detect such changes.

Esplin et al. [35] reported on the mental and psychomotor development of VLBW weight infants at 21 months of age, following antenatal exposure to none (n=157), single (n=201) or multiple (n=71) courses of steroids. Mental development was similar across the groups. However, controlling for various perinatal variables, exposure to multiple courses of steroids was independently associated with psychomotor delay.

In a small cohort study conducted in Germany [36], 28 infants who were delivered at a median gestational age of 35 weeks and exposed to more than five courses of antenatal betamethasone were matched by gender and gestational age with concurrent controls who were exposed to none or a single course. There was no significant difference between groups in head circumference, length and weight at birth, and at 4 years of age, or in the use of glasses or hearing aids. The ability to sit and to walk without assistance and to use two-word phrases was attained at similar ages.

Conclusion

There is strong evidence that exposure to a single course of antenatal steroids has no appreciable adverse effect on long-term outcome of infants delivered after 30 weeks of gestation, and may have a beneficial neuromotor and cognitive effect among the more premature survivors evaluated in recent studies.

The data available on long-term outcome following repeated courses of antenatal steroids are scarce and inconsistent. The evaluations were performed at infancy or at preschool age and the discrepancies in outcome might have originated from the different gestational ages at delivery, differences in dosages and timing of steroid administration, and from the inconsistent assessment methodology.

It was recently recommended [37] that because of insufficient scientific data from randomized clinical trials regarding efficacy and safety, repeat courses of antenatal corticosteroids not be used routinely but should be reserved for patients enrolled in randomized controlled trials. Since adverse neurologic outcome has been documented following postnatal administration of steroids, future studies should account for such an occurrence as well [38,39]. In addition to the assessment of the effect on neonatal morbidities, future recommendations should be supported by growth and neuropsychologic outcome data, thoroughly evaluated up to at least school-age.

VLBW = very low birth weight

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The idealist walks on tiptoe, the materialist on his heels

Malcolm de Chazal (1902-83), French writer