Cognitive Outcome in Adolescents and Young Adults after Repeat Courses of Antenatal Corticosteroids

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Objective To investigate whether repeat courses of antenatal corticosteroids have long-term effects on cognitive and psychological functioning.

Study design In a prospective cohort study, 58 adolescents and young adults (36 males) who had been exposed to 2-9 weekly courses of betamethasone in utero were assessed with neuropsychological tests and behavior self-reports. Unexposed subjects (n = 44, 25 males) matched for age, sex, and gestational age at birth served as a comparison group. In addition, individuals exposed in utero to a single course (n = 25, 14 males) were included for dose-response analysis. Group differences were investigated using multilevel linear modeling.

Results Mean scores obtained in 2 measures of attention and speed were significantly lower in subjects exposed to 2 or more antenatal corticosteroids courses (Symbol Search, $P = .009$; Digit Span Forward, $P = .02$), but these were not dose-dependent. Exposure to repeat courses of antenatal corticosteroids was not associated with general deficits in higher cognitive functions, self-reported attention, adaptability, or overall psychological function.

Conclusions Although this study indicates that repeat exposure to antenatal corticosteroids may have an impact on aspects of executive functioning, it does not provide support for the prevailing concern that such fetal exposure will have a major adverse impact on cognitive functions and psychological health later in life. *(J Pediatr 2013;163:441-6)*.

Administration of antenatal corticosteroids to women at risk of premature delivery is common and has proven benefits for preterm infants.[1,2] There is compelling evidence that a single course of antenatal corticosteroids significantly reduces neonatal mortality and severe neonatal morbidity (such as respiratory distress and intraventricular hemorrhage) without adverse long-term effects.[3-5] In contrast, controversy exists as to whether the practice of repeating corticosteroids every 7-14 days for women who remain undelivered is beneficial or not. Large randomized controlled trials have reported conflicting results. The Australasian Collaborative Trial of Repeat Doses of Steroids Study Group found that repeat courses reduced neonatal morbidity,[6] and the Multiple Courses of Antenatal Corticosteroids for Preterm Birth Collaboration Group and National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network could not confirm improved preterm birth outcomes after repeat corticosteroid courses.[7,8] However, repeat treatments were associated with decreased weight,[6-8] length,[7] and head circumference at birth.[6,7] The latest Cochrane review concluded that repeat courses of corticosteroids were associated with a reduction in the incidence and severity of neonatal lung disease and a small reduction in size at birth.[9]

Glucocorticoid receptors are expressed in the human fetal brain and, therefore, high doses of synthetic glucocorticoids (eg, dexamethasone and betamethasone) could adversely affect the developing brain.[10] Studies from nonhuman primate models indicate that fetal glucocorticoid overexposure can cause abnormal development of motor, affective, and cognitive behaviors.[11]

Previous studies have followed exposed children up to 6 years of age and found that children exposed to repeat courses of antenatal corticosteroids were not different in general cognitive abilities compared with those in placebo control groups.[12-15] However, the Australasian Collaborative Trial of Repeat Doses of Steroids Study Group found that a higher proportion of children in the repeat exposure group had attention scores within the clinical range.[12] Because clinical symptoms of inattention often are associated with deficits in executive functions (ie, the purposeful and future-oriented control of thoughts, behavior, and emotions), these findings raise concern that repeat exposure to antenatal corticosteroids may affect the development of executive functions. Consistent with this notion is an earlier report of increases in distractibility and aggressive behavior after exposure to 3 or more corticosteroid courses.[13]

On this basis, we hypothesized that exposure to multiple courses of antenatal corticosteroids will be associated with poorer executive functions later in life. To

WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children

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test this hypothesis, a prospectively identified Swedish perinatal cohort of adolescents and young adults who had been exposed to at least 2 and up to 9 courses of antenatal corticosteroids, was thoroughly assessed and compared with an unexposed reference group. An additional group who had been exposed to a single course of antenatal corticosteroids was also included to assess potential dose-response effects.

Methods

All participants in this study were born at Danderyd Hospital, Stockholm, Sweden, between the years 1983-1996. The cohort has been described in a previous study, focusing on the effect of antenatal corticosteroids on size at birth.[16] The standard antenatal corticosteroid treatment consisted of an initial course of betamethasone 24 mg intramuscularly (8 mg q 8 h), followed by weekly courses of 12 mg betamethasone continued until delivery or until pregnancy reached 34 gestational weeks. From a prospectively collected hospital registry including all mothers undergoing antenatal care and all infants admitted for neonatal care, we identified 94 infants exposed to repeat courses of antenatal corticosteroids. During the entire study period, there were standard protocols for serial ophthalmologic screening of all infants born before 32 weeks of gestation. Serial cranial ultrasound was introduced a few years into the study period. Predefined exclusion criteria included maternal steroid use for other medical conditions and fetal anomalies, congenital viral infections, and chromosomal aberrations. In the cohort, the majority were born moderately preterm or at term, and there were no subjects who suffered from significant intraventricular hemorrhage or who developed periventricular leukomalacia. One subject suffered from retinopathy of prematurity.[16]

Four of the 94 subjects exposed to repeat corticosteroid courses could not be found or had moved from Sweden by the time of follow-up. The remaining 90 were invited to participate. To get an age- and sex-matched reference group of unexposed subjects, we identified 103 subjects born at the same gestational age as the study group from the hospital's birth registry. For dose-response analyses, we also included a group of subjects exposed to a single course of antenatal corticosteroids (n = 48) by using the same criteria as for the reference group. Subjects in the single-course group were born prior to the administration of the second course, and, as a result, the group was slightly more preterm than the other groups. In total, 241 participants were invited to the follow-up. Of these 127 accepted and were assessed according to the protocol. Characteristics of the mothers, pregnancies, and participants (neonatal and at follow-up) are presented in **Table I**. Participation among exposure groups differed significantly ($\chi^2_2 = 9.10$, $P = .01$); 64.4% of those exposed to 2 or more courses, 42.7% of the unexposed, and 52.0% exposed to a single course participated. Those who declined to participate in the study (n = 114) did not differ from participants with regards to maternal, pregnancy, or infant characteristics apart from nonparticipants being slightly smaller as indicated by birth weight SDS ($M_{part} = -0.4$ vs $M_{non\text{-}part} = -0.8$; $P = .03$; **Table II** available at www.jpeds.com)

The neuropsychological test battery included tests from Wechsler scales (Wechsler Intelligence Scale for Children [WISC]-III and Wechsler Adult Intelligence Scale [WAIS]-III, Swedish versions),[17,18] from Delis-Kaplan Executive Function System,[19] and the Cambridge Neuropsychological Test Assessment Battery.[20] The tests, grouped into 5 broadly defined domains, included the following: (1) general cognitive ability; (2) memory and learning; (3) working memory; (4) attention and speed; and (5) cognitive flexibility and inhibition. The last 3 domains reflect executive functions.

All tests were administered and scored in accordance with manual instructions. All participants were assessed between October 2008-April 2010 by the same psychologist (J.S.) who was blinded to exposure group and gestational age at birth. The assessments were performed in the same room and at approximately same time of the day. Measures on psychological health were obtained from the following self-report forms: the Achenbach Adult or Youth Self-reports[21,22]; the World Health Organization's screen for attention deficit hyperactivity disorder[23]; and a quality of life inventory.[24] All participants signed informed consent forms. Participants under the age of 15 were required to have their legal guardian's signature. The study was approved by the regional Ethical Review Board in Stockholm, Sweden.

Statistical Analyses

Raw scores were generally used in the analyses because the tests used do not have norms for the entire age range of the participants (14-26 years). An exception was the vocabulary test. The raw scores for the WISC and WAIS versions of Vocabulary are not comparable. Scores on the same scale was achieved by a z-transformation using the means and SDs from the Swedish norms for WISC and WAIS, respectively. Comparisons concerning group characteristics (**Table I**) were made using Fisher exact test or ANOVA. Differences in outcome variables were initially tested by comparing the unexposed and those exposed to 2 or more courses (Student t test). Outcomes that differed significantly ($P < .05$) in the univariate tests were included in a mixed regression model. This mixed regression model corrects for age-at-testing, which compensated for the age component in the raw test scores. Parents' education, a strong indicator of socioeconomic status that impacts test score outcome was also included in the model. To not over specify the model and given the size of the cohort (n = 102), no further covariates were included. The lack of independence in multiple gestations was adjusted for as a random effect in the model. Binary outcome variables were analyzed using logistic regression. No corrections for multiple analyses were made. A P value of <.05 (2-sided) was considered to indicate statistical significance. With our given sample, we had a power of 0.8 to detect a group difference of 0.56 or more (ie, medium effect size). The