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Prenatal dexamethasone treatment in the context of at risk CAH pregnancies: Long-term behavioral and cognitive outcome

Leif Karlsson[a], Anna Nordenström[a], Tatja Hirvikoski[b,c], Svetlana Lajic[a,*]

[a] Department of Women's and Children's Health, Karolinska Institutet, Pediatric Endocrinology Unit (Q2:08), Karolinska University Hospital, SE-171 76 Stockholm, Sweden

[b] Department of Women's and Children's Health, Pediatric Neuropsychiatry Unit, Center for Neurodevelopmental Disorders at Karolinska Institutet (KIND), Karolinska Institutet, SE-113 30 Stockholm, Sweden

[c] Habilitation and Health, Stockholm County Council, Sweden

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ABSTRACT

Dexamethasone (DEX) is used to prevent prenatal virilization in female fetuses with congenital adrenal hyperplasia (CAH). Since treatment has to be started before the genotype of the fetus is known, 7 out of 8 fetuses will be exposed to DEX without benefit. Previously, we have observed negative effects on cognition and behavior in DEX treated children. Here we evaluated neuropsychological functions, psychopathology and autistic traits in non-CAH DEX-treated adults exposed during the first trimester of fetal life (duration 6.2 ± 2.2 weeks). Cognitive functions, psychopathology and autistic traits were compared between DEX-treated subjects (n = 23) and non-exposed controls (n = 58). Cognitive outcome was also evaluated longitudinally for DEX-treated participants. We used neuropsychological tests (Wechsler Scales and the Stroop Interference Test) and questionnaires assessing executive functions (the Barkley Deficit in Executive Functioning Scale), psychopathology (the Montgomery Åsberg Depression Ratings Scale, the Hospital Anxiety and Depression Scale, the Liebowitz Social Anxiety Scale) and autistic traits (Autism Quota).

We did not observe any significant differences in cognition, psychopathology or autistic traits between DEX-treated individuals and population controls. A significant improvement in verbal working memory (p = 0.038) and in impulse inhibition (p = 0.011) was seen when subjects were evaluated longitudinally.

In summary, first-trimester DEX-exposed adult individuals do not show any significant neuropsychological deficits nor an increase in anxiety, depression or autistic traits, compared with a control group from the general population. The results also suggest that the observed deficits in executive functioning during childhood may improve with time.

1. Introduction

In the context of reducing the virilization of girls with congenital adrenal hyperplasia (CAH), prenatal dexamethasone (DEX) therapy has been administered during many decades world-wide. The treatment is effective in reducing virilization of the external genetalia, but the short- and long-term benefits in relation to the potential risks have only been studied in a minority of treated cases and have shown conflicting results (Forest et al., 1989; Hirvikoski et al., 2007; Hirvikoski et al., 2012; Lajic et al., 1998; Meyer-Bahlburg et al., 2012; New, 2001; Wallensteen et al., 2016). This is unsatisfactory considering the ethical dilemma associated with prenatal treatment of CAH, i.e., the fact that only 1 out of 8 fetuses benefit from the treatment and 7 out of 8 treated cases are exposed unnecessarily to glucocorticoids during the first trimester of fetal life. Therefore, long-term follow-up and evaluation of the risks and benefits of prenatal DEX therapy are necessary (Hirvikoski et al., 2012).

We have previously reported on the childhood outcome of the Swedish DEX-treated cohort. The cohort was generally well-adjusted; however, DEX-treated children were scored by their parents as being more sociable and by themselves as having more social anxiety, compared to untreated population controls (Hirvikoski et al., 2008; Hirvikoski et al., 2007). In addition, first-trimester DEX treatment in healthy children had long-lasting effects on verbal working memory capacity, measured between 7 and 17 years of age (Hirvikoski et al.,

Abbreviations: CAH, congenital adrenal hyperplasia; DEX, dexamethasone; WAIS, Wechsler Adult Intelligence Scale; WISC, Wechsler Intelligence Scales for Children; WMS, Wechsler Memory Scale; B-DEFS-SF, Barkley Deficit in Executive Functioning Scale – Short Form; MADRS, Montgomery Åsberg Depression Ratings Scale; LSAS-SR, Liebowitz Social Anxiety Scale-subclinical social anxiety; AQ10, Autism Quota

* Corresponding author.
E-mail address: Svetlana.Lajic@ki.se (S. Lajic).

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2007). These effects seem to be sex-dimorphic, since exposed girls were more affected (Wallensteen et al., 2016). In addition to the negative impact on executive functions, the girls exhibited broader effects on cognition, as reflected by lower scores on tests assessing verbal and nonverbal intelligence (Wallensteen et al., 2016).

Our previous findings that prenatal DEX exposure may have negative effects in short-term treated healthy individuals are supported by evidence from a Polish study showing that the treatment may have negative effects in girls without CAH but positive effects in girls with CAH treated until term (Maryniak et al., 2014). The negative effects in short-term treated cases without CAH were not replicated in an American study investigating long-term cognitive outcome; instead, in these studies, prenatally treated girls with CAH showed slower cognitive processing, compared to girls with CAH not treated with DEX (Meyer-Bahlburg et al., 2012).

Accumulating evidence, points toward the fact that early-life glucocorticoid exposure, either via treatment or via stress, strongly affects multiple physiological systems. Neurons within the amygdala, hippocampus, and the prefrontal cortex co-express both MR and GR at high levels (Colciago et al., 2015; de Kloet et al., 2005; Matsusue et al., 2014). These areas, important for executive functioning, emotional regulation, and memory are vulnerable to high doses of GCs (Funahashi, 2001; LeDoux, 2000; Opitz, 2014).

A recent study on children subjected to prenatal maternal stress during a natural disaster suggests that exposure *in utero* to either high levels of maternal subjective distress (endogenous cortisol exposure) or maternal illness during the first trimester of pregnancy is associated with behavioral changes in infants (Laplante et al., 2016). Furthermore, at 5½ years of age, children exposed *in utero* to high levels of maternal stress had lower Full-Scale IQs, Verbal IQs, and language abilities than children exposed to lower levels of prenatal maternal stress (Laplante et al., 2008). Prenatal synthetic GC administration (mostly DEX in 1 or 2 doses) during the third trimester has also been associated with adverse teacher-reported mental health in childhood and adolescence detected as general psychiatric disturbance and inattention at 8 years of age (Khalife et al., 2013). A study from the Netherlands showed that postnatal DEX treatment (0.5 mg/kg/day tapering off to 0.1 mg/kg/day) to have negative effects, especially in girls, when comparing untreated, hydrocortisone-treated, and DEX-treated preterm children. Thus, neonatal DEX treatment, but not hydrocortisone treatment, resulted in more problem behavior, assessed by the Child Behavior Check List (CBCL), and the scores were similar to those observed in untreated children born preterm (Ter Wolbeek et al., 2015).

In Sweden, prenatal DEX therapy is not currently offered in CAH risk pregnancies while awaiting additional follow-up data (Hirvikoski et al., 2012). In the present study, we focus on the long-term cognitive and behavioral outcome up to two decades post exposure. The study is based solely on short-term treated, healthy (i.e., not having CAH) adolescents and adults treated with DEX during the first trimester of fetal life. In addition, we evaluate the cognitive profile over time.

2. Material and methods

2.1. Subjects

This study is part of a large longitudinal project evaluating prenatal treatment with DEX in the context of CAH including subjects at risk of CAH treated prenatally with dexamethasone and healthy untreated controls from the Swedish general population (Karlsson et al., 2017; Wallensteen et al., 2016). Here, we focus on the long-term outcome in short-term, first trimester treated subjects without CAH (treatment duration, 6.2 ± 2.2 weeks). All subjects were initially contacted via an invitational letter. The control group was freshly recruited for this study (test naïve) and was identified via the Swedish Civil Registration System and randomly selected from the population of Stockholm County and matched for age and sex prior to the invitation to take part in the study.

In total, 23 DEX-treated subjects (DEX), 12 females and 11 males, and 58 population controls (C), 31 females and 27 males, were assessed. The positive response rate for the DEX-treated individuals was 85.7% and, for the population controls, 26.3%. The reasons for refusal are not known, but the complexity of the entire study protocol could be a factor of importance.

The majority of the DEX-treated subjects (n = 17) were also evaluated during childhood and were therefore assessed both between 7 and 17 years of age and as adults (Fig. 1) (Wallensteen et al., 2016).

The recruitment process and the demographic data for the study groups are summarized in Fig. 1 and Table 1. Age, the subjects' education and parental education did not differ between the groups (all $p > 0.1$, Table 1). Participants received 50 Euros for participation in the neuropsychological assessment plus reimbursement for travel expenses. Written informed consent was obtained from all participants and the study was approved by the Regional Ethics Committee of Stockholm.

2.2. Outcome measures of cognitive functions

In this report, we focus on behavioral outcomes assessed with self-rating questionnaires (measuring psychopathology, autistic traits and self-perceived executive dysfunctions) and neuropsychological tests (measuring general intellectual capacity, executive functions, and learning and memory functions). All subjects were assessed by trained psychologists following a strict study protocol and using standardized neuropsychological tests with good psychometric properties. The total time for the neuropsychological assessment was approximately one hour.

2.2.1. General intellectual ability (psychometric intelligence)

Psychometric intelligence was assessed using two subtests from the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (Wechsler, 2008a): "Matrices" for estimating fluid intelligence/nonverbal logical reasoning were used and "Vocabulary" for estimating verbal intelligence.

2.2.2. Executive functions

Executive functions were assessed using the Wechsler Adult Intelligence Scales-IV (WAIS-IV) subtests, "Digit-span" (verbal working memory) and "Coding" (processing speed). Visual-spatial working memory was assessed using the "Span Board" Test from the Wechsler Memory Scales-III (WMS-III) (Wechsler, 2008b) and the Stroop color-word test was used to measure the ability to inhibit an overlearned response (Golden and Freshwater, 1998). Finally, all subjects completed the Barkley Deficit in Executive Functioning Scale − Short Form (B-DEFS-SF) (Barkley, 2011).

2.2.3. Learning and long-term memory

The List learning subtest from WMS-III (Wechsler, 2008b) was used to measure learning and long-term memory.

2.2.4. Neuropsychological tests from follow-up during childhood

In order to investigate whether the cognitive abilities change with time in DEX-treated individuals, we compared the cognitive outcome data assessed during childhood with cognitive data assessed at adult age in 17 of 23 DEX-treated subjects. The scores from the Wechsler Intelligence Scales (Donders, 1997), subscales "Matrices", "Vocabulary", "Digit span", and " Coding" from the child (WISC) and adult (WAIS) versions, as well as the scores from the Stroop test, were used for this comparison.

The performance and the demographic data of the entire child cohort is presented elsewhere (Wallensteen et al., 2016). Here we compare the performance during childhood for the DEX-treated subjects, that were assessed during both childhood and adulthood, with the performance for the untreated children (healthy controls from the