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Evaluation of behavioral problems after prenatal dexamethasone treatment in Swedish adolescents at risk of CAH

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ABSTRACT

Prenatal dexamethasone (DEX) treatment in congenital adrenal hyperplasia (CAH) is effective in reducing virilization in affected girls, but other lasting effects are largely unknown. Here, we explore potential side effects of the treatment that will eventually help to make risk benefit analyses of the treatment. Therefore, we investigated the long-term effects of such prenatal DEX treatment on behavioral problems and temperament in children aged 7–17 years. Standardized parent-completed questionnaires were used to evaluate adaptive functioning, behavioral and emotional problems (using CBCL), social anxiety (SPAI-C-P), and temperament (EAS). Self-reports were used to assess the children's own perception of social anxiety (SASC-R). The study compared 34 DEX-treated children and adolescents who were treated during the first trimester of fetal life and do not have CAH with 66 untreated controls from the Swedish population. No statistically significant differences were found between groups, suggesting that healthy children who were treated with DEX during early fetal life seem to be well adjusted without major behavioral or emotional problems as assessed by their parents. Moreover, self-reported social anxiety was not increased in DEX-exposed children and adolescents. In fact, the control group scored higher on items assessing anxiety in new, social situations. Nevertheless, for some of these comparisons, non-significant moderate to large effect sizes were observed, implying that the null findings should be interpreted with caution and require studies on larger, internationally combined cohorts.

1. Introduction

Fetal endocrine therapy for the prevention of prenatal virilization of genitalia in girls affected with classic congenital adrenal hyperplasia (CAH) has been used in many medical centers around the world since the mid-80s (David and Forest, 1984; Forest et al., 1989; Lajic et al., 1998; New, 1990). The treatment is effective in reducing virilization but the short- and long-term risk versus benefit has not been sufficiently investigated.

The dilemma connected with the prenatal treatment of CAH is that, due to the recessive mode of inheritance it is necessary to initiate the therapy early in gestation (before gestational week (GW) 7) in order for it to be optimally effective. In most centers, a prenatal diagnosis cannot be made until the end of the first trimester and 7 out of 8 fetuses will thus be subjected to high doses of glucocorticoids (GCs) during embryogenesis without benefit. Girls with CAH are treated during the entire gestational period, but, nevertheless, also in these cases, where the child benefits from the treatment, a risk benefit assessment must be considered. The dose of DEX that is given to the pregnant woman is 20 μ/kg body weight (normally 1.5 mg/day) and corresponds to at least three times a normal hormone replacement dose. The fetus thus receives about 30–60 times its usual, physiologic glucocorticoid exposure during mid-gestation (Miller, 2015).

To date, in the context of CAH, only a few studies have investigated long-term effects of prenatal DEX treatment on human behavior. Moreover, these studies report mixed effects and do not allow strong inferences about harms related to the treatment (for a review, see (Lajic et al., 2008, 2011; Miller, 2015). Furthermore, some studies do not distinguish between DEX-treated children with and without CAH, which can have additional or modulating effects on outcome measurements. In our previous reports on the Swedish DEX-treated cohort we investigated 26 treated cases (with and without CAH) at age 7–17 years and found no differences on parent-reported behavioral/emotional problems compared to the untreated population controls. However, DEX-treated children were scored by their parents as sociable and by themselves to have more social anxiety (Hirvikoski et al., 2008; Hirvikoski et al., 2007). In addition, DEX exhibited long-lasting effects on cognitive abilities in healthy children treated during the first trimester of pregnancy, observed as a lower verbal working memory capacity with a large effect size (Cohen's $d = 0.80$) (Hirvikoski et al., 2007).

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Merging evidence from both animal and human studies, on antenatal glucocorticoid exposure, points toward a strong effect on several physiological systems. Most studies are designed to mimic therapy during late gestation in fetuses at risk of being born preterm. Animal research in rodents and non-human primates provides a magnitude of plausible mechanisms indicating how prenatal events can program the fetus for later adversity during adolescence and adult life (Harris and Seckl, 2011). Specifically, prenatal events can have functional and structural effects on the brain resulting in altered behaviors as well as metabolic changes and hypertension, hyperlipidemia and hyperglycemia in rats (Drake et al., 2010; Nyirenda et al., 2006). Altered responses to stress and even transgenerational whole genome methylation changes have been reported in off-spring to guinea pigs treated during the end of pregnancy (Crudo et al., 2012; Iqbal et al., 2012).

Long-term programming effects of fetal exposure to glucocorticoids whether trans-placental from exogenous administration to the mother as in pregnancies at risk of preterm birth, or due to endogenously elevated levels due to maternal stress, have been shown to affect the hypothalamic-pituitary-adrenal (HPA) axis and behavior in the offspring. In a follow-up of 209 children exposed to synthetic GCs in late pregnancy (due to a risk of preterm birth) and born at term there was an increase in cortisol responses to psychosocial stress, with greater effects seen in girls (Alexander et al., 2012; Khalife et al., 2013). In a Finnish prospective study, prenatal GC administration (late pregnancy) was found to be associated with adverse mental health in childhood and adolescence detected as general psychiatric disturbance and inattention at 8 years of age, as assessed by their teachers (Rutter B2 scale) (Khalife et al., 2013). Prenatal maternal stress and elevated maternal cortisol levels in late gestation are associated with a fearful temperament of the infant at 2 months of age and persists into adolescence, measured as increased fear/anxiety with the Child Behavior Checklist (CBCL). The effects are observed in girls but not in boys, indicating that the female fetus is more susceptible than the male fetus to the consequences of exposure to maternal cortisol with respect to fear and anxiety (Sandman et al., 2013). Moreover, there is an association between fetal exposure to high levels of maternal cortisol early in gestation and subsequent affective problems in children mediated by an enlarged amygdala (Buss et al., 2012).

Based on our previous findings, no prenatal DEX treatment has been initiated in Sweden since 2010, awaiting further results confirmatory or contradicting. Following up on our previous studies we now report on an extended study including nearly *all* DEX-treated cases in Sweden, investigating the long-term behavioral consequences of prenatal DEX treatment. In contrast to our previous publications, this study reports solely on *healthy* (i.e. without CAH) children and adolescents (aged 7–17 y) at risk of classic CAH and treated in fetal life. Therefore, our results cannot be affected by additional or modulating effects of CAH, long-term exposure to prenatal DEX, or postnatal glucocorticoid treatment.

2. Methods

2.1. Subjects

Since 1984, prenatal DEX therapy was used in 77 pregnancies in Sweden to avoid virilization in female fetuses with CAH. Four mothers were treated twice and four of the pregnancies resulted in miscarriages or termination. A total of 73 children and adults in Sweden today have received prenatal DEX treatment. We report the behavioral outcome of all children aged 7–17 years at risk of, but without CAH, who were treated with DEX during the first trimester of fetal life during the period of 1984–2010 (i.e., healthy, short-term DEX). In the first 40 pregnancies the women were treated before 1997 and 26 of their children were included in our first reports on neurocognitive outcomes (Hirvikoski et al., 2011; Hirvikoski et al., 2008; Hirvikoski et al., 2007), while the rest of the cases in the current extended study were treated after 1997 (n = 33, 30 of which did not have CAH). We were not able to reach 6 DEX-treated mothers (7 treated pregnancies) in this extended study. In addition, one family declined participation and one child had died in an accident before 7 years of age. The participation rate was 65% among the DEX-treated healthy subjects and 55% for healthy controls. The reason for refusal among controls is not known, but the length of the total neuropsychological assessment (2 h) and the fact that the evaluation also included other analyses, such as blood sampling, could be factors of importance. For a detailed description of the study group in our first evaluation of the DEX cohort, see Hirvikoski et al., 2007 (Hirvikoski et al., 2007).

In total, 100 subjects (34 DEX-treated subjects (DEX), 16 females and 18 males; 66 population controls (C), 36 females and 30 males) were evaluated (average test age: 10.5 y, SD: 2.6 y). The groups did not differ statistically in terms of age, birth weight and length, gestational age, or parental education (Table 1).

2.2. Procedures

All families were initially contacted via an invitational letter. The participants received 50 Euro for participating in the assessment plus reimbursement of travel expenses. The present assessment procedures were part of a larger test battery that was administered at the same time-point. The healthy controls were identified via the Swedish Population Registry of the Stockholm population and were matched for sex and age. The presence of a clinical psychologist during the assessment made it possible to ask for clarification of items, if necessary. The parents and children filled out the questionnaires independently of each other. All parents gave their written informed consent and the study was approved by the Regional Ethics Committee in Stockholm.

2.3. Outcome measures

2.3.1. Behavioral/emotional problems

Behavioral problems in children were assessed with two parental ratings (CBCL/4–18, Child Behavioral Checklist for ages 4–18; SPAI-C-P, the Social Phobia and Anxiety Inventory for Children – Parent Report), and one self-report scale for children (SASC-R, Social Anxiety Scale for Children - Revised). The CBCL for ages 4–18 (CBCL/4–18) is a parentally reported 113-item child psychiatric screening instrument that provides both broadband and narrowband scales. It was used to quantify internalizing and externalizing problems as well as other behavioral aspects, such as depressive, social, and attention problems and delinquent and aggressive behaviors (Achenbach, 1991). The SPAI-C-P is a 26-item parent-report measure covering cognitive, physiological and behavioral symptoms of social phobia according to DSM-IV (Beidel et al., 1995; Higa et al., 2006). SPAI-C-P includes subscales for 'Public Performance' (PP), 'Assertiveness/General Conversation' (AGC), and 'Traditional Social Encounters' (TSE). The self-report scale SASC-R (Social Anxiety Scale for Children – Revised) was used for assessments of children's self-perception of social anxiety and avoidance (La Greca et al., 1988; La Greca and Stone, 1993). It is divided into the subscales 'Fear of Negative Evaluation (FNE), and two subscales reflecting 'Social Avoidance and Distress' in new social situations or in general (SAD-New and SAD-General).

2.3.2. Competence profile/adaptive functioning

The CBCL total competence score, measuring adaptive functioning, is a sum of scores from three subscales (Activities scale, Social scale, School scale) (Achenbach, 1991).

Temperament was quantified using the Emotionality-Activity-Sociability-Shyness Temperament Survey for children (EAS) with the