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Evaluation of behavioral problems after prenatal dexamethasone treatment in Swedish children and adolescents at risk of congenital adrenal hyperplasia

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ABSTRACT

Prenatal dexamethasone (DEX) treatment in congenital adrenal hyperplasia (CAH) is effective in reducing virilization in affected girls, but potential long-term adverse effects are largely unknown. In this report we intended to explore potential side effects of DEX therapy to enhance the adequacy of future risk benefit analyses of DEX treatment. We investigated the long-term effects of first trimester prenatal DEX treatment on behavioral problems and temperament in children and adolescents aged 7–17 years. The study included 34 children and adolescents, without CAH, who had been exposed to DEX during the first trimester and 67 untreated controls. Standardized parent-completed questionnaires were used to evaluate adaptive functioning and behavioral/emotional problems (CBCL), social anxiety (SPAI-C-P), and temperament (EAS) in the child. Self-reports were used to assess the children's perception of social anxiety (SASC-R). No statistically significant differences were found between DEX-treated and control children and adolescents, suggesting that, in general, healthy children treated with DEX during early fetal life are well adjusted.

1. Introduction

Fetal endocrine therapy for the prevention of prenatal virilization of genitalia in girls affected by classic congenital adrenal hyperplasia (CAH) has been used in many medical centers worldwide since the mid-1980s (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 only been investigated in a minority of treated cases.

The dilemma associated with prenatal dexamethasone (DEX) treatment of CAH is due to the recessive mode of inheritance of the disorder and the necessity to initiate the therapy early on in gestation, i.e., before gestational week (GW) 7 in order to achieve the full efficacy of the treatment. In most centers a prenatal diagnosis cannot be made until the end of the first trimester and thus 7 out of 8 fetuses will be subjected to high doses of glucocorticoids (GCs) during embryogenesis without benefit. Girls with CAH are treated during the entire gestational period, but even in these cases in which the child benefits from the treatment, a risk benefit assessment must be performed.

To date, only a few studies have investigated the long-term effects of prenatal DEX-treatment on human behavior. Moreover, these studies report contradictory effects and do not allow strong conclusions about the possible 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) in the age range of 7–17 years and found no differences in parent-reported behavioral problems (using the Child Behavior Checklist, CBCL), compared with untreated population controls. However, DEX-treated children were scored by their parents to be more sociable and they scored themselves as having more social anxiety (Hirvikoski et al., 2007, 2009). In addition, DEX exhibited long-lasting effects on cognitive abilities in healthy children treated during the first trimester of pregnancy, in the form of a lower verbal working memory capacity (Hirvikoski et al., 2007).

Evidence from both animal and human research on antenatal GC

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exposure indicates a strong effect on several physiological systems. Most of the animal and human studies are designed to mimic late gestation GC treatment aimed at augmenting lung maturation and reducing the risk of stroke and cerebral hemorrhage when there is a risk of preterm birth. Other studies have focused on the effects of early prenatal GC exposure, both DEX treatment in the context of CAH and studies on maternal stress. In addition, when discussing outcome, it is important to consider possible differences related to dosing. Prenatal treatment, as used in pregnancies at risk of pre-term delivery use dexamethasone or betamethasone at a dose of 24 mg, divided into 2–4 doses per day. Treatment is given to the woman at risk during GW 24 to 34 and can be repeated once (Roberts and Dalziel, 2006). For the prevention of genital virilization in girls with CAH, the pregnant woman is given dexamethasone at a dose of 20 μg/kg body weight per day (maximum 1.5 mg per day) divided into 3 doses (Forest et al., 1989). The treatment starts around GW 6 and continues until the results of the chorionic villous sampling have been obtained, usually in GW 12 to 14, or until term. The dose of dexamethasone used corresponds to at least three times the normal hormone replacement dose in adults and thus the fetus is exposed to about 30–60 times the usual, physiologic glucocorticoid levels during mid-gestation (Miller, 2015).

Animal research in rodents and non-human primates provides a number of plausible mechanisms for how prenatal events can program the fetus for later adversity in adolescence and adult life. Specifically, prenatal events can have functional and structural effects on the brain, resulting in altered behaviors and responses to stress in addition to metabolic changes and even effects on whole genome methylation (Crudo et al., 2012; Drake et al., 2010; Drake and Walker, 2004; Harris and Seckl, 2011; Iqbal et al., 2012; Nyirenda et al., 2006; Seckl, 2004).

Long-term programming effects of fetal exposure to GCs, whether from exogenous administration to the mother as in pregnancies at risk of preterm birth or because of endogenously elevated levels in maternal prenatal stress, have been shown to affect the HPA axis and behavior in the offspring. In a follow-up of 209 children exposed to synthetic GCs in late pregnancy and born at term, there was an increase in the cortisol response to psychosocial stress, with greater effects seen in girls (Alexander et al., 2012; Khalife et al., 2013). In a Finnish prospective study late prenatal GC administration was 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 were associated with fearful temperament (measured as increased fear/anxiety using the CBCL) of the infant at 2 months of age and persisted into adolescence. The effects were observed in girls, but not in boys, indicating that the female fetus is more susceptible to the consequences of exposure to maternal cortisol (Sandman et al., 2013). Moreover, there is a probable association between fetal exposure to high levels of maternal cortisol early on in gestation and subsequent affective problems in children mediated by an enlarged amygdala (Buss et al., 2012).

Based on our previous findings, prenatal DEX treatment has not been initiated in Sweden since 2010, awaiting further long-term studies. In this follow-up study we report on nearly ***all*** DEX-treated cases in Sweden, again investigating the long-term behavioral consequences of prenatal DEX therapy. In contrast to our previous reports this study was based solely on ***healthy*** (i.e., not CAH-affected) children and adolescents (aged 7–17 years) at risk of classic CAH and treated during early fetal life. Because the children did not have CAH, the treatment was stopped after the first trimester. Therefore, our results are not affected by the additional or modulating influence of CAH, full-term exposure to prenatal DEX, or postnatal GC treatment.

2. Methods

During 1984–2010, DEX-treatment in Sweden was initiated in 77 pregnancies to avoid virilization in female fetuses with CAH. Four of the women were treated twice and four pregnancies resulted in miscarriages or termination, resulting in 73 DEX-exposed individuals available for follow-up. Since 1999, DEX-treatment has only been offered as part of a clinical study – the PREDEX study. The purpose of the study is to evaluate the efficacy of the treatment in addition to short- and long-term safety for mothers and children. The children have been followed repeatedly with behavioral, cognitive and physiological testing. In this report we present the behavioral outcome of an extended cohort consisting of all children aged 7–17 years at risk of, but not having CAH and who were treated with DEX during the first trimester of fetal life in 1984–2010 (i.e. healthy, short-term DEX).

2.1. Subjects

All families were initially contacted via an invitational letter. The participants received 50 Euro for their participation in the neuropsychological assessment and reimbursement of travel expenses. The healthy controls were identified via the Swedish Population Registry. The controls were randomly selected among individuals of the same age and gender. For practical reasons, all controls were selected from the Stockholm area. The DEX-treated cases were recruited nationwide. All children and parents answered the questionnaires as part of a larger psychological follow-up, completing the questionnaires independently of one another. All parents gave their written informed consent and the study was approved by the Regional Ethics Committee in Stockholm.

27 out of the first 40 treated pregnancies (1984–1997) resulted in children not affected by CAH. Of these, 10 declined participation while 17 children were included in our first reports on neurocognitive and behavioral outcome (Hirvikoski et al., 2007, 2008, 2011). The rest of the mothers were treated after 1997 and included in the clinical study PREDEX from start. From 33 pregnancies, 30 children not affected by CAH were born and of those, 17 participated in the extended follow-up presented here. We were not able to reach 6 DEX-treated mothers (7 treated pregnancies) in this extended study. In addition, one family declined participation (one child). One child had died in an accident before 7 years of age and 4 children had at the time point of recruitment not reached 7 years of age and were therefore not eligible for inclusion in the follow-up. In total, 34 DEX-treated children not affected by CAH were included in our final study cohort (Fig. 1).

The participation rate was 65% (34 of 52 subjects) for the DEX-treated healthy subjects and 55% (67 of 122 subjects) for the healthy controls. The reason for refusal among controls was not known, but the length of the neuropsychological assessment (2 h) and that the evaluation also included other analyses, such as blood sampling, could be a factor. For a detailed description of the study group in our first evaluation of the DEX cohort, see Hirvikoski et al. (2007).

In total, 101 subjects (34 DEX-treated subjects (DEX), 15 females and 19 males, and 67 population controls (C), 36 females and 31 males) were evaluated between the age of 7 and 17 years (average test age: 10.5 years, SD: 2.6 years). Groups did not differ in age, birth weight, birth length and gestational age (all $ps > 0.05$). Both groups were socio-economically well-adjusted with most parents employed.

There were a higher proportion of parents in the female control group (89.7%) with higher education (bachelor's degree or higher) compared with the parents of the female DEX-treated group (47.6%) ($\chi^2(1) = 10.68$, $p = 0.001$). This pattern was similar, though not significant, for the male control group (67.9%) versus the male DEX-treated group (57.1%) ($\chi^2(1) = 0.593$, $p = 0.441$). The DEX-treated cases and their families lived throughout Sweden (59% lived in less urban areas) while the controls were recruited from the Stockholm area.

2.2. Outcome measures

2.2.1. Behavioral problems

Behavioral problems in children were assessed with two parental