Metabolic and cognitive effects after early prenatal dexamethasone treatment

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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By

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ABSTRACT

Congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency (21OHD), is a disease with an inborn error of the adrenal steroid synthesis. This enzyme deficiency leads to cortisol shortage and androgen excess. If left untreated, CAH is potentially life-threatening especially in the neonatal period, but girls are also affected in the prenatal period with virilization caused by the surplus of adrenal androgen. Prenatal dexamethasone (DEX) treatment will minimize the androgen levels and reduce virilization. However, because the development of genitalia occurs in early gestation, the treatment must start in gestational week (GW) 6-8 to be efficient. Because of the recessive mode of inheritance and because genotyping of the fetus is not possible until GW 12, statistically, 7 of 8 fetuses will be treated unnecessarily during the first trimester of fetal life. This quandary emphasizes the importance of investigating the potential risks of DEX treatment. Glucocorticoid (GC) exposure during fetal development is known to negatively affect the child (e.g. cognition, behavior and metabolism and altered brain morphology).

This thesis is part of a long-term study of children without CAH who were prenatally treated with DEX because of the potential risk of having CAH. Specifically, the thesis investigates the effects of DEX treatment on cognition (study I), behavior (study II), metabolism (study III) and blood pressure (study IV). Forty-two DEX-treated children and young adults without CAH (age range, 4-26 years) and 75 controls from the general population matched for age and sex were included in the studies. We identified a negative effect on cognition in DEX-treated girls but not in boys. Girls did worse on test assessing verbal IQ, non-verbal IQ and verbal working memory. There were no differences in behavioral problems, evaluated by parents and self-rated questionnaires in treated versus non-treated children. We found a lower HOMA-β in girls, but not in boys (another sex-dimorphic effect), suggesting a lower beta-cell function due to prenatal DEX exposure. In the younger age group (<16 years), fasting glucose levels were higher in the treated group in both sexes. In the older age group (≥16 years), total cholesterol and LDL cholesterol levels were higher in the exposed group in both sexes. When we assessed 24-hour ambulatory blood pressure, the only significant finding was higher pulse pressure in the younger age group during nighttime measurements.

In conclusion, early prenatal DEX treatment seems to have a sex-dimorphic effect on cognition and glucose metabolism. It also affects blood lipids in both sexes. Owing to these findings, and other negative findings previously shown in this cohort, the safety of prenatal DEX treatment is questionable. New, and an earlier prenatal diagnosis is needed to avoid treating healthy fetuses and males with CAH.

LIST OF SCIENTIFIC PAPERS

I. **Lena Wallensteen ,** Marius Zimmermann, Malin Thomsen Sandberg , Anton Gezelius, Anna Nordenstrom, Tatja Hirvikoski, Svetlana Lajic
Sex-dimorphic effects of prenatal treatment with dexamethasone.
Journal of Clinical Endocrinology and Metabolism, 101(10): 3838-3846, 2016

II. **Lena Wallensteen**, Leif Karlsson, Valeria Messina, Anton Gezelius, Malin Thomsen Sandberg, Anna Nordenström, Tatja Hirvikoski, Svetlana Lajic
Evaluation of behavioral problems after prenatal dexamethasone treatment in Swedish children and adolescents at risk of congenital adrenal Hyperplasia
Hormones and Behavior, 98: 219–224, 2018

III. **Lena Wallensteen**, Leif Karlsson, Valeria Messina, Anna Nordenström, Svetlana Lajic
Perturbed beta-cell function and lipid profile after early prenatal dexamethasone exposure in individuals without CAH
Journal of Clinical Endocrinology and Metabolism, 105(7): e2439–e2448, 2020

IV. Leif Karlsson**, Lena Wallensteen**, Anna Nordenström, Rafael Krmar, Svetlana Lajic
Effects on blood pressure after early prenatal dexamethasone exposure in individuals without CAH
Manuscript

Related publications not included in the thesis:

Valeria Messina, Tatja Hirvikoski, Leif Karlsson, Sophia Vissani, **Lena Wallensteen,** Rita Ortolano, Antonio Balsamo, Anna Nordenström, Svetlana Lajic
Good overall behavioural adjustment in children and adolescents with classic congenital adrenal hyperplasia
Endocrine, 68(2):427-437, 2020