Repeat Antenatal Steroid Exposure and Later Blood Pressure, Arterial Stiffness, and Metabolic Profile

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Objective To determine the relationship between repeat courses of antenatal corticosteroids (ACS) and risk factors for cardiovascular disease in adolescents and young adults.

Study design We assessed body mass index, blood pressure, arterial stiffness, blood lipids, and insulin resistance (IR) in a Swedish population-based cohort (n = 100) at a median age of 18 (range 14-26) years. Fifty-eight subjects (36 males) had been exposed to 2-9 weekly courses of antenatal betamethasone and 42 (23 males) were unexposed subjects matched for age, sex, and gestational age (GA).

Results There were no significant differences between the groups regarding body mass index, systolic or diastolic blood pressures, arterial stiffness measured by augmentation index, blood lipids, IR, or morning cortisol levels either in simple regression or in multivariable models. However, more subjects with elevated augmentation index had been exposed to repeat courses of ACS (n = 7) compared with unexposed subjects (n =1, $P = .06$), and glucose, insulin, and IR correlated inversely to GA at start of ACS ($P < .01$).

Conclusions Repeat courses of ACS did not correlate to adverse cardiovascular risk profile in adolescence and young adulthood, but long-standing effects on the arterial tree and glucose metabolism, the latter dependent on GA at ACS exposure, cannot be excluded. These observations have clinical implications for the ongoing discussion on short-term benefits and long-term safety of repeat ACS treatment. *(J Pediatr 2013;163:711-6)*.

Preterm delivery affects 6%-12% of all pregnant women each year.[1] Antenatal and neonatal care have steadily improved and infant survival after preterm birth can today be almost universal.[2] Although this development is welcomed, survivors after preterm birth face a worrisome increase in hypertension and diabetes, and even death from cardiovascular and metabolic causes in young adult life.[3-5] The mechanisms behind this increased long-term morbidity and mortality of prematurity are not known.

Antenatal corticosteroid (ACS) treatment has contributed to improve outcome after preterm birth.[6] It is administered to women at risk for preterm delivery to reduce the risk for respiratory distress syndrome and death of her preterm infant. The protective effect of ACS declines after 7-10 days.[7] Considering that up to 50% of women remain undelivered after 7-10 days,[8] and in view of the neonatal benefits, repeat courses of ACS could be considered in women at continued risk for preterm delivery.[9] However, unresolved concerns about safety still make such treatment regime controversial.[10]

Excess glucocorticoid exposure in fetal life has been suggested to be a major mechanism for adverse early programming.[11] Previous studies in animals have shown that both single and repeat courses of ACS can have lasting and negative side-effects on hypothalamic-pituitary-adrenal function,[12] nephron development, renin-angiotensin-aldosterone system, baroreceptor function,[11,13] elastin synthesis,[14] vascular function,[15] and glucose homeostasis.[16] These findings have raised concerns about metabolic and cardiovascular side-effects from ACS in humans as well. In support of a short-term somatic effect, we and others have found a dose-dependent decline in fetal size in response to ACS.[17,18] Long-term follow-up data are, however, scarce. Reassuringly, fetal exposure to excess glucocorticoids at moderately low gestational age (GA) was not associated with any changes in body size, blood lipids, blood pressure (BP), prevalence of diabetes, or history of cardiovascular disease in 30-year-old adults whose mothers had been randomized to a single course of ACS or placebo.[19] In contrast, a recent observational study reported increased aortic stiffness and altered glucose metabolism in young adults exposed to ACS.[20] So far, there are no data on whether repeat courses contribute to an adverse cardiovascular risk profile in adult life.

ACS	Antenatal corticosteroid	GA	Gestational age
AI	Augmentation index	HDL	High-density lipoprotein
Apo A1	Apolipoprotein A1	HOMA	Homeostatic model assessment
Apo B	Apolipoprotein B	IR	Insulin resistance
BMI	Body mass index	LDL	Low-density lipoprotein
BP	Blood pressure	SBP	Systolic BP
DBP	Diastolic BP		

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Methods

All participants in this cohort study were born at Danderyd Hospital, Stockholm, Sweden, between the years 1983-1996. The standard ACS treatment at the time and at this hospital consisted of an initial course of betamethasone 24 mg intramuscularly (8 mg q 8 h), followed by weekly courses of 12 mg betamethasone 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 subjects who had been exposed to repeat courses of ACS. Information on maternal age, parity, multiple pregnancy, smoking habits, infant sex, and anthropometry were retrieved from the Swedish Medical Birth Registry. All data were validated by scrutinizing maternal and infant hospital records. GA (recorded in completed weeks and based on last menstrual period in the first 5 years of the study period and from 1988 on ultrasonographic dating), details on ACS dose and exposure dates, as well as neonatal morbidity were retrieved from these patient records. Predefined exclusion criteria were maternal steroid use for other medical conditions, major fetal malformations, congenital viral infections, and chromosomal aberrations. The cohort has been described in more detail in a previous publication.[17]

The final sample of each group and how it was determined is shown in the **Figure**. Among the individuals exposed to multiple courses of ACS, 19 had received 2 courses, 14 received 3 courses, and 25 received 4 or more weekly courses.

Characteristics of the mothers, pregnancies, and participants are presented in **Table I**. Subjects exposed to multiple courses of ACS were more often twins/triplets compared with unexposed subjects. There were no other statistically significant differences between subjects exposed to multiple courses of ACS and unexposed controls. Mean GA at first ACS exposure was 28.7 weeks (range 22.9-32.1 weeks).

Participation among exposure groups differed significantly ($P = .01$); 64% of those exposed to 2 or more courses and 41% of the unexposed participated. Participation in the study was unrelated to maternal, pregnancy, or infant characteristics, apart from nonparticipants being slightly smaller as measured by birth weight SDS.

We measured waist circumference as well as height and weight and calculated body mass index (BMI = weight in kg/[height in m]^2). Elevated waist circumference was defined as >88 cm for females and >102 cm for males. For subjects aged ≥18 years, overweight was defined as BMI >25 and obesity as BMI >30 kg/m^2. For subjects below 18 years of age, we used pediatric standard reference for overweight and obesity.[21]

After at least 5 minutes of sitting rest, systolic BP (SBP) and diastolic BP (DBP) were measured in the left arm using a validated automated oscillometric device (Omron HEM 907 IntelliSense; Omron Healthcare, Kyoto, Japan) with an appropriately sized arm cuff. Three consecutive measures were performed at 2-minute intervals, and mean SBP and DBP values were calculated. For subjects below 18 years of age, an elevated SBP or DBP were defined as a pressure exceeding the 95th percentile for sex, age, and height in a reference population.[22] In subjects ≥18 years, elevated SBP and DBP were defined as >140/90 mm Hg.

A pulse wave analysis system (SCOR-Px; AtCor Medical, West Ryde, Australia) was used together with applanation tonometry (Millar transducer SPT-301; Millar Instruments, Houston, Texas) to noninvasively acquire the radial artery pressure waveforms. These waveforms were calibrated to conventionally measure brachial BP. Central aortic waveforms were derived from those obtained from the radial artery using a validated data transfer algorithm.[23,24] From the aortic waveforms, central aortic SBP and DBP were determined.

Identification of early and late systolic peaks in the aortic pressure curve allows quantification of an augmentation index (AI, %), presented at a standardized heart rate of 75 beats per minute. The AI is related to the speed of the central and peripheral pressure wave reflections and an increasing AI reflects increasing arterial stiffness. The mean value of 3 recordings, each comprising 10 consecutive pressure waves, was taken as the individual's reading. The coefficient of variation for AI measurements has previously been found to be 10% in our laboratory.[25] Elevated AI was defined as AI above 10% and 17% for men and women, respectively.[26] All measures were performed by the same trained research nurse, who was blinded to antenatal exposures.

From each participant, 5 mL blood was sampled to analyze glucose, insulin, triglycerides, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), apolipoprotein A1 (Apo A1) and apolipoprotein B (Apo B), lipoprotein(a), and cortisol concentrations in plasma or serum. All blood samples were morning fasting samples and were analyzed in an accredited (International Organization for Standardization 1518 [Geneva, Switzerland]; CAP, WADA, EFI, NMDP, GLP, JACIE) clinical chemistry laboratory at Karolinska University Hospital. From these analyses, we calculated HDL/LDL-ratio and Apo B/Apo A1-ratio. Cut-offs for deviating laboratory values were defined as cholesterol >4.89/5.88 mmol/L (men/women, respectively), triglycerides >2.07/2.35 mmol/L, HDL <0.6/0.74 mmol/L, LDL >3.02/3.62 mmol/L, Apo A1 <0.85/0.96 g/L, and Apo B >1.02/1.17 g/L.[27] Homeostatic model assessment (HOMA) is a method for assessing insulin resistance (IR) from basal fasting glucose and insulin.[28] HOMA-IR was calculated using a HOMA calculator (http://www.dtu.ox.ac.uk/homacalculator/index.php).

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

Data are presented as numbers, proportions (%), or mean and SD values. We aimed at recruiting a sample size of at least