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Antenatal Corticosteroids and the Renin-Angiotensin-Aldosterone System in Adolescents Born Preterm

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Abstract

Background—Antenatal corticosteroid (ANCS) treatment hastens fetal lung maturity and improves survival of premature infants, but the long-term effects of ANCS are not well-described. Animal models suggest ANCS increases the risk of cardiovascular disease through programmed changes in the renin-angiotensin (Ang)-aldosterone system (RAAS). We hypothesized that ANCS exposure alters the RAAS in adolescents born prematurely.

Methods—A cohort of 173 adolescents born prematurely was evaluated, of whom 92 were exposed to ANCS. We measured plasma and urine Ang II and Ang-(1–7) and calculated Ang II/Ang-(1–7) ratios. We used general linear regression models to estimate the difference in the RAAS between the ANCS-exposed and unexposed groups, adjusting for confounding variables.

Results—In unadjusted analyses, and after adjustment for sex, race, and maternal hypertension, ANCS exposure was associated with increased urinary Ang II/Ang-(1–7) [estimate 0.27 (95% CI

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0.03, 0.5), $p = 0.03$], increased plasma Ang-(1–7) [0.66 (0.26, 1.07), $p = 0.002$], and decreased plasma Ang II/Ang-(1–7) [−0.48 (−0.91, −0.06), $p = 0.03$].

Conclusions—These alterations indicate an imbalance in the urinary RAAS, promoting the actions of Ang II at the expense of Ang-(1–7), which over time may increase the risk of renal inflammation and fibrosis and ultimately hypertension and renal disease.

Introduction

Antenatal corticosteroids (ANCS), given to pregnant women expected to deliver prematurely to accelerate fetal lung maturity, increases survival and improves outcomes in the offspring, but the long-term effects of ANCS are not well-characterized (1–3). Data from preclinical models that simulate human exposure suggest that ANCS may increase the risk for hypertension (HTN) and cardiovascular disease (4, 5). The increased risk may be mediated in part by chronic dysregulation of the renin-angiotensin (Ang)-aldosterone system (RAAS), leading to increased renal and cardiovascular disease in adulthood (6, 7). Human studies offer conflicting conclusions regarding relationships between ANCS exposure and cardiovascular outcomes in adolescents and young adults and have not evaluated the effect of ANCS exposure on the RAAS (8–12).

The RAAS includes the Ang-converting enzyme (ACE)/Ang II pathway and the ACE2/Ang-(1–7) pathway, is important in renal and cardiovascular development, and is subject to developmental changes early in life (13, 14). Ang II is a vasoconstrictor, enhances sodium retention directly and through stimulation of aldosterone, and promotes inflammation and fibrosis, while Ang-(1–7) has variable effects on sodium transport and glomerular filtration and has anti-inflammatory and anti-fibrotic effects in numerous organ systems, including the kidney (6, 15–19). An altered RAAS is associated with adverse health outcomes, including HTN and chronic kidney disease (20). RAAS components measured in the urine are markers of the intrarenal RAAS (21–23). We measured RAAS components in adolescents born prematurely to evaluate the hypothesis that ANCS exposure is associated with long-term alteration of the balance between Ang II and Ang-(1–7) in plasma and urine.

Results

Study Population (Table 1)

Reflective of the larger ANCS study's design, approximately half the study sample was born to mothers who received ANCS (53%). The majority of subjects were female (55%), 43% were black, and 35% were overweight/obese at 14 years of age. Maternal HTN complicated 36% of pregnancies. Blacks were less likely to receive ANCS. The ANCS group had a higher rate of maternal HTN and was taller.

ANCS Exposure and Urinary RAAS

There were no differences in Ang II, Ang II/creatinine, Ang-(1–7), or Ang-(1–7)/creatinine (Table 1). Ang II/Ang-(1–7) was higher in the ANCS group and this difference persisted when adjusting for race, sex, and maternal HTN [estimate 0.27 (95% CI 0.03, 0.5), $p = 0.03$] (Table 2).

ANCS Exposure and Plasma RAAS

There were no differences in plasma renin activity (PRA), aldosterone, aldosterone-to-renin ratio (ARR), or Ang II (Table 1). The ANCS group had higher plasma Ang-(1–7) and lower Ang II/Ang-(1–7), and these differences persisted when adjusted for race, sex, and maternal HTN [Ang-(1–7): 0.66 (0.26, 1.07), $p = 0.002$; Ang II/Ang-(1–7): −0.48 (−0.91, −0.06), $p = 0.03$] (Table 2, Figure 1). The associations of ANCS with higher plasma Ang-(1–7) and lower Ang II/Ang-(1–7) were stronger among black study participants (Figure 2) [Ang-(1–7): 1.13 (0.61, 1.66), $p < 0.001$; Ang II/Ang-(1–7): −0.91 (−1.48, −0.33), $p = 0.003$].

Although log-transformed waist-to-height ratio was associated with both plasma Ang-(1–7) and Ang II/Ang-(1–7) [−1.44 (−2.65, −0.23), $p = 0.02$; 2.26 (1.04, 3.47), $p < 0.001$], adding waist-to-height ratio to the regression models did not substantially alter the association between ANCS and plasma RAAS.

Discussion

Among adolescents born prematurely, ANCS exposure was associated with increased urinary Ang II/Ang-(1–7), increased plasma Ang-(1–7), and decreased plasma Ang II/Ang-(1–7). The increased urinary Ang II/Ang-(1–7) among preterm adolescents exposed to ANCS may be due to a higher renal (urinary) Ang II. This shift in the kidney, towards Ang II and away from Ang-(1–7), is consistent with the finding that offspring of pregnant ewes exposed to clinically relevant doses of ANCS (betamethasone given at 0.6 gestation: the equivalent of about 24 weeks gestation in humans) develop alterations in the renal RAAS, decreased renal function, and elevated blood pressure as adults. RAAS alterations include attenuated responses to Ang-(1–7), enhanced responses to Ang II, increased expression of the Ang II type 1 receptor, increased serum ACE activity, decreased serum ACE2 activity, and decreased proximal tubular ACE2 activity and expression. Together these alterations indicate an imbalance in the RAAS which promotes the actions of Ang II at the expense of Ang-(1–7) (6, 7, 24, 25).

Over time, elevated renal Ang II levels could increase the risk for renal inflammation and fibrosis and may lead to HTN and renal disease (26). This mechanism could accentuate other perinatal renal insults such as ischemia and nephrotoxic exposure (21, 27). In contrast to RAAS alterations in urine, plasma levels of Ang-(1–7) were higher among ANCS-exposed adolescents, which might serve to attenuate the physiologic effects of an elevated Ang II to Ang-(1–7) ratio in the kidney. A potential explanation for this finding is that it may reflect a compensatory upregulation to counteract further inflammation and fibrosis by Ang II as ACE2 expression and elevated Ang-(1–7) levels are evident in several pathologic states (28, 29). ANCS exposure could also directly lead to increased systemic or vascular ACE2/Ang-(1–7) pathway activity.

Consistent with data showing obesity is associated with an upregulated ACE/Ang II pathway (30), we found that waist-to-height ratio, a measure of central adiposity, was associated with decreased plasma Ang-(1–7) and increased plasma Ang II/Ang-(1–7). Obesity-driven RAAS dysregulation is associated with inflammation, insulin resistance, and metabolic disease (31). Racial differences in PRA and aldosterone are well-documented. Our finding that associations between ANCS and the RAAS were stronger among black study participants suggests the possibility that long-term effects of ANCS might differ for blacks and non-blacks.

Our study is limited by the non-randomized allocation of the exposure (ANCS), leaving open the possibility of confounding due to factors we did not measure. We could not fully account for all the potential factors that influence the RAAS, such as genetic influences and dietary variability. Further, we lack measurements of RAAS enzymatic activity, specifically ACE and ACE2, which could better characterize the profiles of the ACE/Ang II and ACE2/Ang-(1–7) pathways in this cohort.

In conclusion, in a cohort of adolescents born prematurely, ANCS exposure was associated with alterations in the RAAS, specifically increased urinary Ang II/Ang-(1–7), increased plasma Ang-(1–7), and decreased plasma Ang II/Ang-(1–7). An altered systemic and intrarenal RAAS may modify an individual's cardiovascular risk profile and negatively impact kidney function later in life.

Methods

Study Participants

Study participants were recruited from among living members of a premature birth cohort of 193 patients born between January 1, 1992 and June 30, 1996 at a regional perinatal center (Forsyth Medical Center in Winston Salem, NC). This cohort included i) children with whom we had contact through at least one year of age, ii) were not wards of the state, and iii) were successfully contacted at 14 years of age. Sixty-two percent of those contacted were enrolled (n = 193). Of the 193 cohort subjects, seven were excluded from the analysis (two were twins, three had congenital anomalies, and two had maternal oral steroid use). The members of the cohort were evaluated at 14 years of age as part of a larger study of ANCS exposure and cardiovascular and metabolic outcomes among preterm adolescents (Figure 3). We report the measurements made at the third study visit, at which 173 subjects were evaluated (92 of 94 in the ANCS group, 81 of 92 in the unexposed group). All the subjects provided urine specimens and 120 provided blood specimens. More detailed information on materials and methods, including specific inclusion and exclusion criteria, have been published previously (32). The Wake Forest School of Medicine and Forsyth Medical Center Institutional Review Boards approved the study. We obtained informed consent from parents or legal guardians and assent from participants.

Data Collection

Perinatal characteristics were recorded from medical records and research databases. We recorded the presence of maternal hypertension during pregnancy (maternal HTN) and ANCS exposure, defined as maternal treatment with betamethasone and/or dexamethasone (one subject's mother received dexamethasone only and one subject's mother received both betamethasone and dexamethasone). Birth characteristics were noted, including i) sex, ii) GA, and iii) birth weight. Birth weight z score was determined (33). We categorized subjects as born SGA if their birth weight percentile was less than or equal to the 10% (34).

Demographic information was recorded at 14 years of age, including parental-reported race (black vs non-black), and height, weight, and waist circumference were measured. We calculated BMI (kg/m^2) and waist-to-height ratio, and defined overweight/obese as BMI ≥85% for age and sex (35). Sexual maturity was rated (1 to 5) using a self-reported questionnaire completed in private and was summarized as the average of both determinants of secondary sexual characteristics (external genitalia development and pubic hair in males; breast development and pubic hair in females) (36). Resting blood pressure was measured with a mercury manometer after the subject was seated quietly for at least five minutes, and the average of three measurements was recorded according to established guidelines (37). Blood pressure z scores were calculated (38).

Laboratory Measurements

Blood was collected from participants in the seated position to measure PRA, aldosterone, Ang-(1–7), and Ang II. A spot urine sample was provided to measure Ang-(1–7), Ang II, and creatinine. We calculated ARR, the Ang II/Ang-(1–7) ratio in the plasma and urine, and the urinary Ang-(1–7) and Ang II concentrations corrected for creatinine. Specific laboratory methods have been published previously (39).

Statistical Analyses

Distributions of continuous variables were described with the mean and *SD* or the median and IQR. We used natural logarithmic transformation to improve the distributional characteristics of the continuous variables when appropriate. Values below the minimum detectable thresholds were assigned one-half those threshold values (39). For between-group comparisons of continuous variables, we used the t-test and Wilcoxon Rank-Sum test; for comparisons of categorical variables we used the Chi-square and Fisher's Exact tests. Correlations were assessed with Pearson or Spearman correlation coefficients.

We used general linear regression models to evaluate the relationship of ANCS exposure and RAAS outcomes. We evaluated effect modification using product terms (ANCS × modifier). To identify variables that might confound the ANCS – RAAS relationships we evaluated bivariate relationships between each potential confounder and ANCS and each potential confounder and RAAS outcome. Potential confounders were included in the multivariate models if either of the following were found: i) an association with both the RAAS measure and ANCS at $p < 0.2$, or ii) a >10% change in the regression coefficient for ANCS estimated with general linear models. In addition, sex, race, and maternal HTN were identified a priori as potential confounders and effect modifiers, based on the results of previous studies (39, 40). The criterion for inclusion in the final multivariate model was $p < 0.05$. For comparisons of the ANCS-exposed and unexposed groups, a two-sided alpha of 0.05 was considered statistically significant. We used Enterprise Guide software, Version 7.11 of the SAS System for Windows (SAS Institute Inc., Cary, NC) for all analyses.

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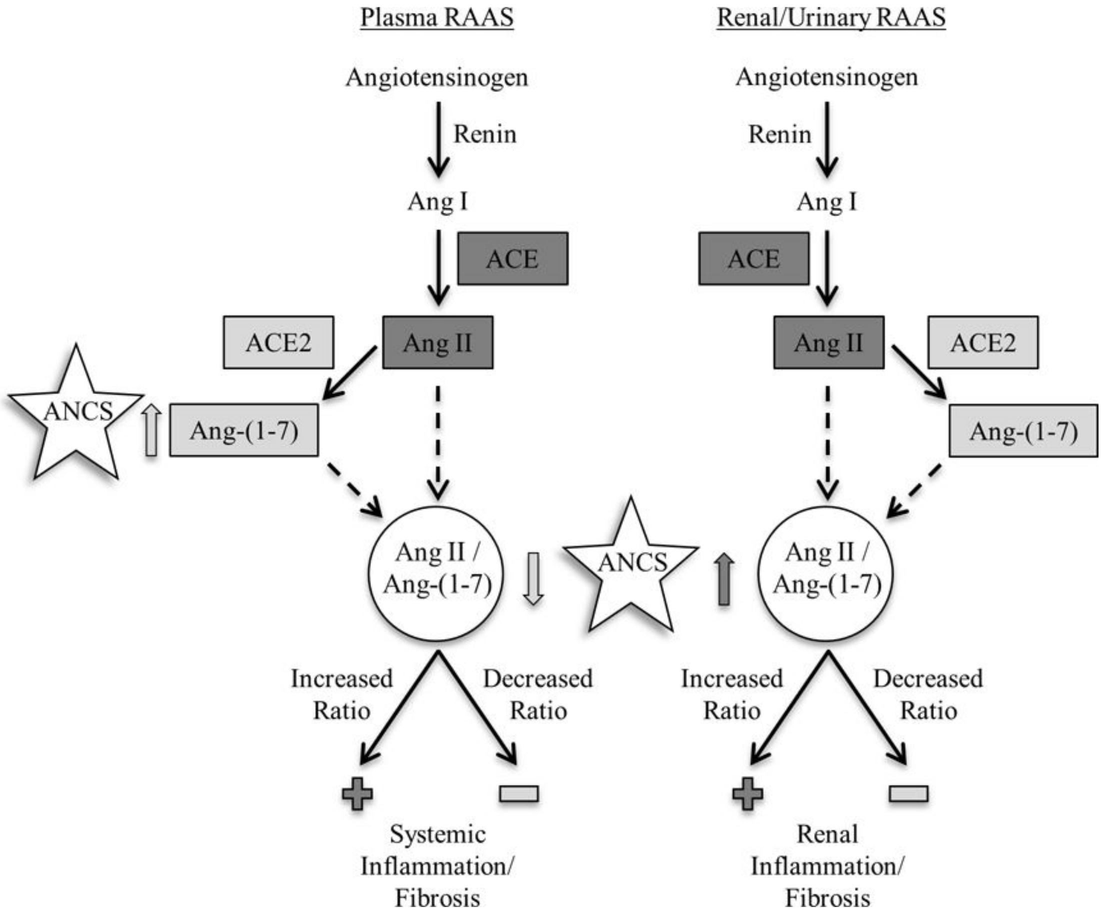

Figure 1.

Relationship between ANCS and RAAS

Gray arrows indicate direction of association with the RAAS: dark gray indicates upregulation of Ang II and light gray indicates upregulation of Ang-(1–7).

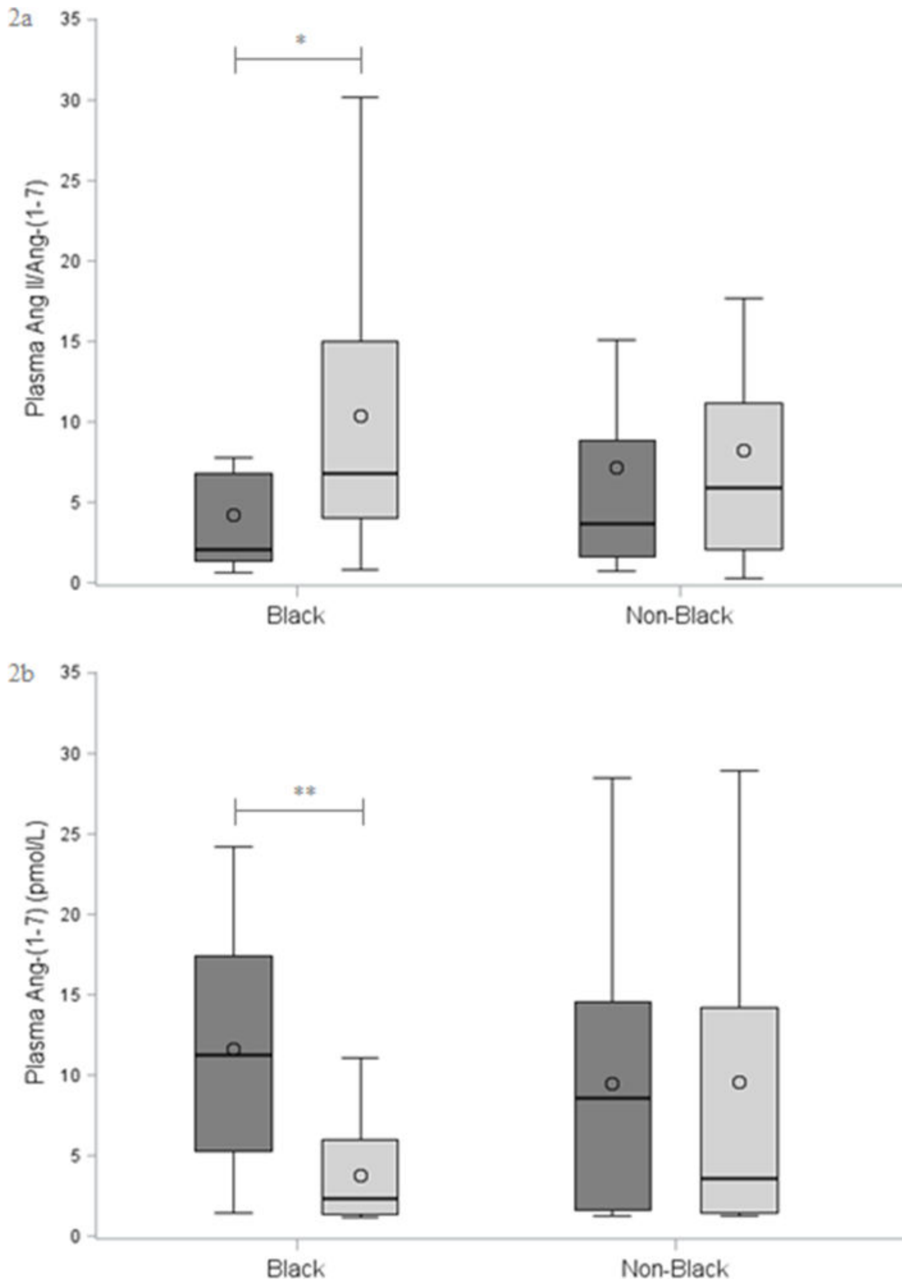

Figure 2.

ANCS and RAAS Stratified by Race

2a: Plasma Ang II/Ang-(1–7)

2b: Plasma Ang-(1–7)

*$p = 0.002$, **$p < 0.001$. ANCS = dark gray; No ANCS = light gray. Bar denotes median, circle denotes mean, box indicates IQR, and whiskers include ≤1.5x IQR. Between-group comparisons by Wilcoxon Rank-Sum test.

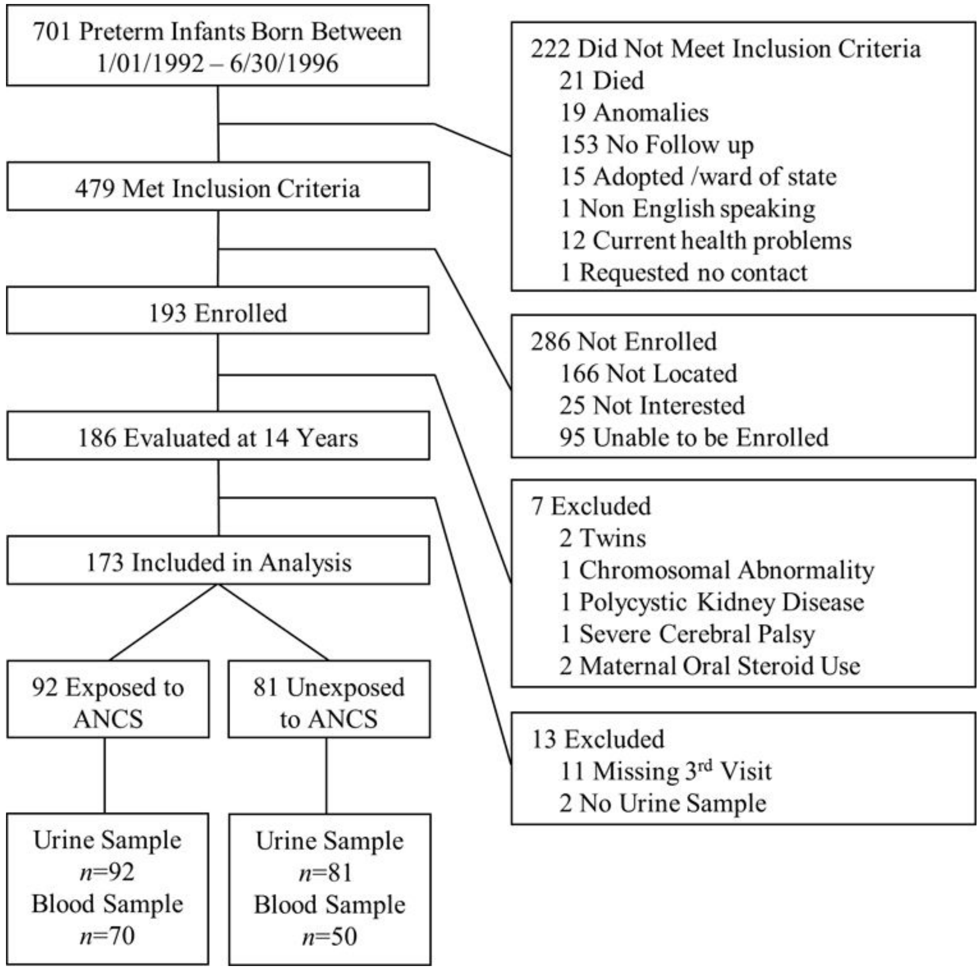

Figure 3.
Study Participant Flow Diagram

Table 1

Clinical Characteristics and the Renin-Angiotensin-Aldosterone System Profile at 14 Years

Clinical Characteristics	All Subjects $N = 173$	ANCS 92 (53%)	No ANCS 81 (47%)
Male	78 (45%)	44 (48%)	34 (42%)
Black	74 (43%)	27 (29%) *	47 (58%)
Maternal Hypertension	63 (36%)	40 (43%) *	23 (28%)
GA (weeks)	27.8 (2.6)	27.7 (2.4)	27.9 (2.9)
Birth Weight (g)	1053 (265)	1033 (269)	1075 (261)
Birth Weight z Score	−0.29 (0.84)	−0.35 (0.74)	−0.22 (0.93)
SGA	21 (12%)	9 (10%)	12 (15%)
Height (cm)	161.6 (9.3)	163.2 (8.9) *	159.8 (9.5)
Weight (kg)	56.0 [47.5, 69.5]	56.6 [48.7, 68.6]	56.0 [46.3, 71.8]
BMI (kg/m^2)	21.1 [18.6, 26.5]	20.5 [18.4, 26.0]	22.5 [19.0, 26.6]
Overweight/Obese	60 (35%)	28 (30%)	32 (40%)
Waist-to-Height Ratio	0.46 [0.42, 0.53]	0.45 [0.42, 0.51]	0.48 [0.43, 0.54]
Sexual Maturity Rating[a]	4.5 [4.0, 5.0]	4.5 [4.0, 5.0]	4.5 [4.0, 5.0]
Systolic Blood Pressure	106.3 (9.9)	107.2 (10.4)	105.2 (9.2)
Systolic Blood Pressure z Score	−0.40 (0.89)	−0.36 (0.98)	−0.45 (0.79)
Diastolic Blood Pressure	61.3 (8.9)	61.6 (8.9)	60.9 (8.9)
Diastolic Blood Pressure z Score	−0.28 (0.78)	−0.26 (0.79)	−0.29 (0.77)
Urinary RAAS Profile	$N = 173$	$n = 92$	$n = 81$
Ang-(1–7) (pmol/L)	70.1 [48.6, 94.8]	70.9 [44.6, 94.4]	68.7 [49.0, 98.4]
Ang-(1–7)/Creatinine (pmol/g)	0.41 [0.31, 0.59]	0.39 [0.29, 0.61]	0.43 [0.33, 0.57]
Ang II (pmol/L)	9.3 [6.3, 15.3]	10.5 [6.5, 16.6]	8.7 [5.9, 13.8]
Ang II/Creatinine (pmol/g)	0.05 [0.04, 0.1]	0.06 [0.04, 0.11]	0.05 [0.03, 0.1]
Ang II/Ang-(1–7)	0.15 [0.1, 0.23]	0.17 [0.1, 0.27] *	0.14 [0.1, 0.19]
Plasma RAAS Profile	$N = 120$	$n = 70$	$n = 50$
PRA (pmol Ang I/L/h)	2.4 [1.2, 3.2]	2.5 [1.4, 3.2]	1.9 [1.0, 3.0]
Aldosterone (pmol/L)	9.9 [5.3, 14.1]	9.9 [6.2, 13.3]	9.9 [4.3, 17.8]
ARR (pmol/L per pmol Ang I/L/h)	4.2 [3.0, 6.6]	4.1 [3.1, 6.2]	4.6 [2.5, 8.7]
Ang-(1–7) (pmol/L)	5.6 [2.9, 13.5]	9.0 [2.6, 14.7] *	2.7 [1.4, 7.0]
Ang II (pmol/L)	21.5 [16.7, 32.1]	22.3 [17.1, 33.3]	21.0 [15.6, 29.1]
Ang II/Ang-(1–7)	3.7 [1.9, 6.8]	3.0 [1.6, 7.8] *	6.3 [3.5, 13.3]

N (%), mean (*SD*), median [IQR].

[a] $n = 154$.

* Denotes significant difference between groups with $p < 0.05$ by chi-square test, t-test, or Wilcoxon Rank-Sum test.

Table 2

Relationship Between Antenatal Corticosteroid Exposure and the Renin-Angiotensin-Aldosterone System

	Unadjusted		Adjusted[a]		Stratified[a]		
	Estimate (95% CI)	*p* Value	Estimate (95% CI)	*p* Value		Estimate (95% CI)	*p* Value
Urine Ang II/Ang-(1–7)	0.26 (0.04, 0.48)	0.02	0.27 (0.03, 0.5)	0.03	–	–	–
Plasma Ang II/Ang-(1–7)	−0.49 (−0.88, −0.11)	0.01	−0.48 (−0.91, −0.06)	0.03	Black[b]	−0.91 (−1.48, −0.33)	0.003
					Non-Black[c]	−0.21 (−0.78, 0.36)	0.46
Plasma Ang-(1–7)	0.65 (0.28, 1.02)	<0.001	0.66 (0.26, 1.07)	0.002	Black[b]	1.13 (0.61, 1.66)	<0.001
					Non-Black[d]	0.37 (−0.18, 0.92)	0.19

General linear regression models.

[a]Adjusted for sex, race, and maternal HTN;

[b]$n = 15$;

[c]$n = 54$;

[d]$n = 55$.