Aldosterone-Signaling Defect Exacerbates Sodium Wasting in Very Preterm Neonates: The Premaldo Study

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Context: The neonatal period, notably in preterm infants, is characterized by high sodium wasting, implying that aldosterone, the main hormone regulating sodium reabsorption, is unable to maintain sodium homeostasis.

Objective: This study sought to assess aldosterone secretion and action in neonates according to gestational age (GA).

Design and Setting: This was a multicenter prospective study (NCT01176162) conducted between 2011 and 2014 at five neonatology departments in France. Infants were followed during their first 3 months.

Participants: The 155 newborns included were classified into three groups: Group 1 (n = 46 patients), <33 gestational weeks (GW); Group 2 (n = 67 patients), 33–36 GW; and Group 3 (n = 42 patients), ≥37 GW.

Main Outcome Measures: Plasma aldosterone was measured in umbilical cord blood. Urinary aldosterone (UAldo) was assessed at day 0, day 3, month 1, and month 3 postnatal. The correlation between UAldo and the urinary Na/K ratio was determined as an index of renal aldosterone sensitivity.

Results: UAldo significantly increased with GA: from 8.8 ± 7.5 μg/mmol of creatinine (Group 1) to 21.1 ± 21.0 (Group 3) in correlation with plasma aldosterone levels in all groups ($P < .001$), demonstrating its reliability. The aldosterone/renin ratio significantly increased with GA, suggesting an aldosterone secretion defect in preterm infants. UAldo and urinary Na/K were correlated in very preterm but not in term neonates, consistent with very preterm neonates being renal-aldosterone sensitive and term neonates being aldosterone resistant.

Conclusions: Very preterm infants have a previously unrecognized defective aldosterone secretion but conserved renal aldosterone sensitivity in the neonatal period, which modifies the current view of sodium balance in these infants and suggests alternative management approaches. **(*J Clin Endocrinol Metab* 100: 4074–4081, 2015)**

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Abbreviations: CI, confidence interval; D0, day 0; D3, day 3; GA, gestational age; GW gestational weeks; M1, month 1; M3, month 3; MR, mineralocorticoid receptor; ROC, receiver-operating characteristic; UAldo, urinary aldosterone.

At birth, the human kidney displays tubular immaturity, associating sodium wasting and an impaired ability to reabsorb water (1). These characteristics are exacerbated in premature infants (2). The inability to maintain homeostatic functions is a major problem for the 10% of neonates born preterm (3). Neonatologists have to find a balance between the life-threatening risk of dehydration and the morbidity associated with excessive sodium and water supplementation, such as bronchopulmonary dysplasia (4), patent ductus arteriosus, and necrotizing enterocolitis (5), which are the most common causes of morbidity and mortality in the most immature preterm children (6, 7). A better understanding of water and sodium regulation during the neonatal period is required for developing new therapeutic strategies for the management of very preterm infants.

Sodium homeostasis in humans is mainly controlled by the renin-angiotensin-aldosterone system. Aldosterone, a steroid hormone, is synthesized in the zona glomerulosa of the adrenal cortex. It regulates sodium reabsorption by activating the mineralocorticoid receptor (MR), a transcription factor (8). In the distal nephron, most MR-target genes are involved in sodium reabsorption and potassium excretion, including, for example, the genes encoding the Na-K-ATPase pump, or the alpha subunit of the epithelial sodium channel (8).

Preterm infants display both renal tubular immaturity and sodium wasting (1), and this suggests that the renin-angiotensin-aldosterone-MR pathway may not be fully functional. We previously demonstrated physiological and transient renal aldosterone resistance in term neonates (9): plasma aldosterone and renin concentrations in umbilical cord blood are high for term births, contrasting with functional signs of hypoaldosteronism (high serum potassium concentration, urinary sodium loss, and an urinary Na/K ratio >1). This aldosterone resistance or pseudohypoaldosteronism is associated with a weak or undetectable renal MR expression at birth (10).

However, it is not known whether this aldosterone-signaling defect is also present in preterm neonates and to what extent it contributes to the sodium wasting observed. To address this issue, we conducted a multicenter observational study involving preterm and term newborn infants with followup for their first 3 months of life. Our aims were, first, to assay aldosterone in the preterm and term infants and, second, to determine the progress of renal aldosterone resistance during the postnatal period, by correlating urinary aldosterone (UAldo) concentration as a noninvasive index of aldosterone levels, and markers of renal mineralocorticoid signaling.

Patients and Methods

Patients

We enrolled 155 neonates in five neonatology departments in France (Clamart, Poissy, Kremlin-Bicêtre, Poitiers, and Lille) into this multicenter observational study. Inclusion criteria were mothers age 18–45 years old, no diabetes mellitus type 1 or 2 prior to pregnancy, and none of the following maternal treatments prior to pregnancy: systemic or inhaled glucocorticoid therapy, hormonal treatment for adrenal or pituitary insufficiency, or antihypertensive drugs. Gestational age (GA) was determined by a first-trimester ultrasound scan. No infant had a congenital malformation at birth. Deliveries were either vaginal or by cesarean section. Prematurity was mainly spontaneous and it was either due to preterm labor or preterm premature rupture of membranes. Infants with a birth weight less than the 10th percentile for GA (11) were excluded. Corticosteroid therapy prior to birth or during hospitalization and major neonatal complications were recorded during followup.

Role of the funding source

Our study was funded by a grant from the French Ministry of Health and from Assistance Publique, Hôpitaux de Paris (Premaldo PHRC 2009 AOM 09175), Inserm and Université Paris-Sud and has been registered on ClinicalTrials.gov (NCT01176162). The funding source had no role in study design, collection, analysis, interpretation of data, nor in the writing of the report, or in the decision to submit the paper for publication. Only the authors had access to the study data and were responsible for publication decisions.

Blood and urinary samples

Venous blood samples were collected from umbilical cords into EDTA and heparinized tubes and immediately transferred to the laboratory for centrifugation. Supernatants were stored at −20°C. Single-spot urinary samples were collected onto a gauze compress settled in the diaper during the first 24 hours of life (D0), on day 3 (D3), and after 1 month (M1 ± 3 d) and 3 months (M3 ± 1 wk). Compresses not contaminated by meconium or feces were stored at −20°C before subsequent processing. Ethical considerations prevented 24-hour urinary collection.

Hormonal and biochemical analyses

Plasma aldosterone and renin concentrations as well as electrolytes, proteins, and creatinine levels were measured in umbilical cord blood. Hemolyzed samples were excluded from the analysis. Aldosterone, electrolyte, and creatinine concentrations were determined in urine samples extracted from compresses. All measurements were made centrally in the Kremlin-Bicêtre department of hormonology and biochemistry and processed in the same parallel experiment, as previously described (9). Briefly, active renin and aldosterone plasma concentrations were assessed using the Renin III generation RIA kit and the Aldo-RIA CT kit, respectively (CIS-Bio International). UAldo was assayed after acid hydrolysis of aldosterone 18-glucuronide during for 18 hours at 30°C. For measurements on random urine samples, values of UAldo output were corrected for creatinine excretion. Electrolytes, Blood Urea Nitrogen (BUN), total proteins, and creatinine were measured with the automat Modular P (Roche). Sodium waste was determined as the fractional excretion of sodium

(FeNa) calculated with the following equation: (plasma creatinine × urinary sodium)/(plasma sodium × urinary creatinine) % at D0 and as the urinary Na/creat and Na/K ratios at all postnatal stages.

Statistics

Clinical and biological characteristics at birth, urinary electrolyte concentrations, and aldosterone excretion values are expressed as means ± SD with the range as well as median and interquartiles. Analyses of variance were performed to compare the mean urinary electrolyte or aldosterone excretion values between the three groups. Nonparametric methods were used: Kruskal-Wallis tests for global comparison between the three groups followed by a Mann-Whitney *U* test with a Bonferroni's correction for pairwise comparisons. Correlations between two parameters or comparisons between values of the same parameter at two different times were studied by calculating Spearman correlation coefficients and using Wilcoxon signed-ranks test, respectively. A two-sided $P < .05$ was considered to indicate statistical significance. We computed a receiver-operating characteristic (ROC) curve using DeLong's method. Regression estimates from this model defined a diagnostic signature, and the area under the curve, sensitivity, and specificity were used to evaluate this signature.

All statistical analyses were performed using SAS software version 9.3 (SAS Institute) for correlations, and the GraphPad Prism software version 6 (GraphPad software, Inc.) for ROC curves.

Study approval

Informed and written consent was obtained from both parents prior to inclusion in the study. The study was approved by the National Data Protection Authority and was conducted in accordance with the Declaration of Helsinki and after approval of the relevant ethical committee (CPP, Comité de Protection des Personnes, Ile de France).

Results

Clinical and biological characteristics of the newborn infants

The 155 newborn infants included were classified into three groups according to their GA at birth: Group 1 (very preterm), less than 33 GW; Group 2 (moderate to late preterm), 33–36 GW; and Group 3 (term), at least 37 GW. Selected clinical, biochemical, and hormonal characteristics of the patients are shown in Table 1.

Table 1. Clinical, Biochemical, and Hormonal Characteristics of the Patients at Birth (D0)

	Group 1 (<33 GW)			Group 2 (33–36 GW)			Group 3 (≥37 GW)		
Characteristic	**Mean ± SD**	**Range**	**Median (IQR)**	**Mean ± SD**	**Range**	**Median (IQR)**	**Mean ± SD**	**Range**	**Median (IQR)**
Clinical data									
Subjects, n	46			67			42		
Sex ratio, M/F	24/22			32/35			25/17		
Mean GA, wk	30.4 ± 1.5[a,b]	26–32		34.0 ± 1.0[e]	33–36		39.3 ± 1.3	37–41	
BW at birth, g	1546 ± 325[a,b]	895–2240		2120 ± 357[e]	1360–3150		3309 ± 402	2550–4030	
Cord blood plasma									
Na, mmol/L	137 ± 3.3	129–145	137 (135–139)	138 ± 4.2	118–146	138 (136–140)	139 ± 2.3	132–143	139 (137–140)
K, mmol/L	6.6 ± 2.4[c]	3.6–13.6	5.8 (4.7–8.2)	5.9 ± 1.6	3.8–12.5	5.6 (4.6–6.7)	6.2 ± 2.3	4.2–12.1	5.0 (4.6–7.3)
Protein, g/L	44 ± 5[a]	33–57	45 (40–48)	48 ± 4[f]	35–62	47 (44–51)	59 ± 6	47–74	58 (56–62)
Creatinine, μmol/L	39.9 ± 19.7[c,d]	18–107	37 (30–43)	53.5 ± 18.3	18–95	52 (42–61)	51.8 ± 15.4	18–100	51 (42–59)
Aldosterone, ng/dL	36.8 ± 35.0[a,b]	3.0–136.6	23.5 (14.6–48.4)	58.5 ± 39.4[e]	3.7–187.2	51.9 (32.1–80.3)	103.8 ± 65.4	15.7–272.2	91.1 (48.6–143.7)
Renin, ng/dL	13.2 ± 14.2	0.8–68.3	8.0 (4.4–15.8)	8.9 ± 8.7	0.3–44.7	6.7 (2.7–10.1)	8.3 ± 6.7	1.2–36.6	5.9 (4.2–10.1)
Aldosterone/renin ratio	5.0 ± 5.9[a,b]	0.4–33.1	2.9 (1.4–6.8)	18.7 ± 40.6	0.5–284.0	7.4 (3.6–17.7)	22.9 ± 34.1	1.1–199.3	12.1 (7.0–28.8)
Urine at D0									
Na/creatinine, mmol/mmol	69.8 ± 45.9[a,d]	15.8–180.0	54.0 (34.1–107.4)	47.3 ± 50.9[e]	4.5–333.3	34.0 (18.7–56.2)	10.0 ± 8.4	0.8–33.1	7.2 (3.3–13.5)
K/creatinine, mmol/mmol	20.2 ± 8.5[a,d]	2.0–46.4	22.0 (14.8–25.1)	16.1 ± 7.1[e]	4.8–35.6	14.9 (9.3–22.2)	7.5 ± 3.8	1.9–19.3	7.4 (4.3–9.0)
Urinary Na/K	4.4 ± 4.3[a]	0.8–21.5	2.8 (1.8–6.1)	3.2 ± 3.1[e]	0.4–15.0	2.0 (1.2–3.6)	1.3 ± 0.9	0.3–4.4	1.1 (0.7–1.5)
FeNa, %	1.90 ± 1.51[a]	0.4–6.7	1.3 (0.8–2.6)	1.88 ± 1.78[e]	0.2–8.0	1.3 (0.7–2.5)	0.37 ± 0.35	0.0–1.4	0.3 (0.1–0.5)
Aldosterone/creatinine, μg/mmol	8.8 ± 7.4[a]	0.7–27.4	6.8 (2.8–11.8)	10.6 ± 9.2[e]	0.6–48.8	7.9 (5.6–12.9)	21.1 ± 21.0	2.2–100.0	17.21 (8.8–25.2)

Abbreviation: BW, birth weight.

Patients were classified into three groups according to GA at birth (groups 1, 2, and 3).

Kruskal-Wallis tests followed by Mann-Whitney *U* tests with Bonferroni's correction for pairwise comparisons were used for overall comparisons between the three groups. Statistical differences are expressed as follows:

[a] $P < .001$ between Group 1 and Group 3.

[b] $P < .001$ between Group 1 and Group 2.

[c] $P < .01$ between Group 1 and Group 3.

[d] $P < .01$ between Group 1 and Group 2.

[e] $P < .001$ between Group 2 and Group 3.

[f] $P < .01$ between Group 2 and Group 3.

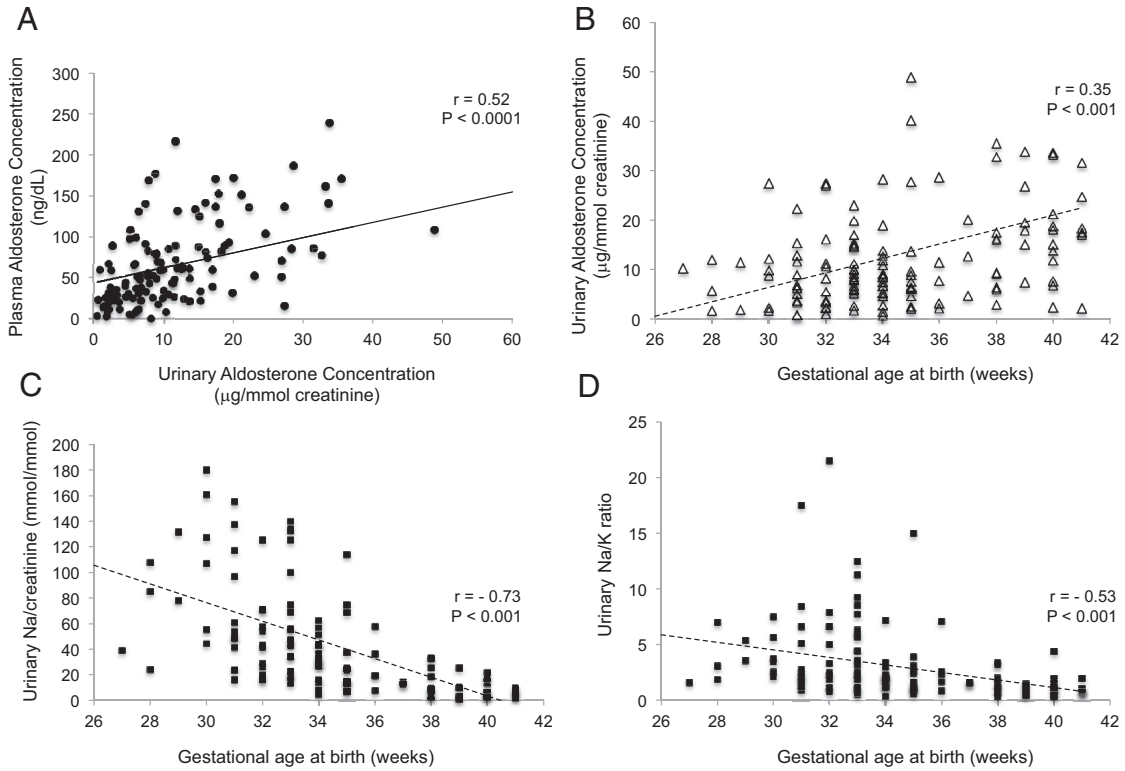

Figure 1. UAldo is a reliable index of aldosterone secretion in neonates and its correlation with gestational age is in the opposite direction of those of sodium-wasting and urinary Na/K ratio at birth. A, Plasma aldosterone concentration as a function of UAldo concentration. Each dot represents one patient. B, UAldo concentration (Δ) as a function of GA. Each Δ represents one patient. C, Urinary sodium excretion (urinary Na/creatinine) (■) as a function of GA. Each ■ represents one patient. D, Urinary Na/K ratio (■) as a function of GA. Each ■ represents one patient. For presentation purposes, the two highest values do not appear on the graphs. Linear regression lines are presented with Spearman's correlation coefficient (r) and its statistical significance (*P* values). Similar results were obtained when the two highest values in Group 3 (term neonates) were excluded from the analysis. The observed differences remained significant.

Mean serum potassium concentration (>5.5 mmol/L) at birth was high in all groups, whereas serum sodium concentration was within the normal range, consistent with biological signs of functional hypoaldosteronism (aldosterone insufficiency and/or resistance) at birth in all newborn infants.

Plasma aldosterone concentrations at birth (mean ± SD) increased significantly with GA (36.8 ± 35.0 ng/dL or 102.1 ± 97.0 pmol/L in Group 1; 58.5 ± 39.4 ng/dL or 162.3 ± 109.1 pmol/L in Group 2; and 103.8 ± 65.4 ng/dL or 287.9 ± 181.2 pmol/L in Group 3; see Table 1). Plasma aldosterone/renin ratio (mean ± SD) was significantly lower in Group 1 (5.0 ± 5.9) than in Group 2 (18.7 ± 4.1) and Group 3 (22.9 ± 34.1), highly suggestive of inappropriate aldosterone secretion at birth in very preterm infants.

Urinary electrolytes and aldosterone excretion

Our simple and noninvasive method of urine collection—a single urine sample obtained during the first hours of life—facilitated measurements of the excretion of both urinary electrolytes and aldosterone. UAldo concentrations (Table 1 and Supplemental Figure 1) were significantly lower in Group 1 than in Groups 2 and 3 (8.8 ± 7.5, 10.6 ± 9.2, and 21.1 ± 21.0 μg/mmol of creatinine, in Groups 1, 2, and 3, respectively; $P < .001$). UAldo was positively and significantly correlated with plasma aldosterone concentration at birth in the entire cohort (Figure 1A; $P < .001$), and was therefore a reliable index of aldosterone secretion by neonates. Sodium wasting was assessed as the urinary Na/creatinine ratio (69.8 ± 45.9, 47.3 ± 50.9, and 10.0 ± 8.4 mmol/mmol of creatinine, in Groups 1, 2, and 3, respectively; $P < .001$; Table 1); as expected, it was significantly higher in preterm than in term infants. Both UAldo concentrations (Figure 1B) and sodium wasting at birth correlated with GA but in opposite directions (Figure 1, C and D), suggesting an association between defective mineralocorticoid signaling and sodium wasting at birth in all newborn infants. Similarly, UAldo concentration correlated positively and FeNa negatively with GA ($P < .001$; Supplemental Figure 2), further supporting this possibility.

Evolution of UAldo concentrations over time

UAldo concentrations were studied over time in the three groups (Figure 2, Supplemental Table 1). UAldo con-

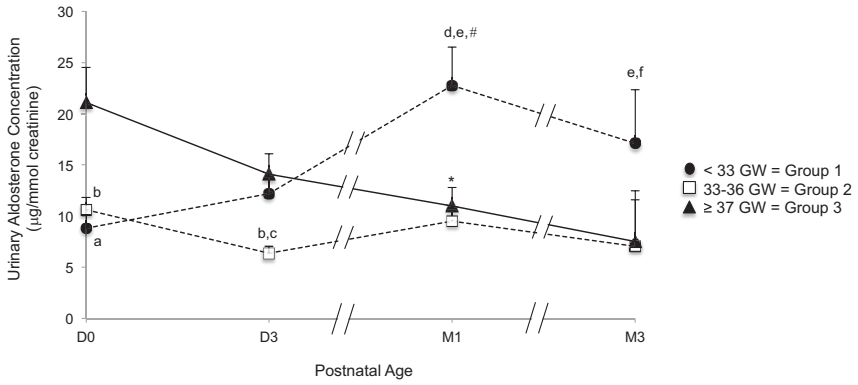

Figure 2. The changes in UAldo concentration during the first months of life depend on gestational age at birth. Each ●/□/▲ represents the mean ± SEM of UAldo (UAldo) concentrations for a gestational age group at a particular time point. Statistical differences are illustrated as follows: A, $P < .001$ between Group 1 and Group 3; B, $P < .001$ between Group 2 and Group 3; C, $P < .01$ between Group 1 and Group 2; D, $P < .001$ between Group 1 and Group 2; E, $P < .05$ between Group 1 and Group 3; F, $P < .05$ between Group 1 and Group 2. #, $P < .001$; and *, $P < .05$ between mean values at D0 and M1 within one group; Kruskal-Wallis tests followed by Mann-Whitney *U* tests with Bonferroni's correction for pairwise comparisons were used for overall comparisons between the three groups. Wilcoxon signed-rank test was used for comparisons between values of the same variable at two different time points.

centrations progressively declined from 21.1 ± 21.0 µg/mmol at D0 to 7.5 ± 5.0 µg/mmol at M3 in Group 3; in Group 2, UAldo concentrations remained stable until M1 (~10 µg/mmol), and thereafter decreased at the same rate as Group 3, and with superimposable values. In sharp contrast, UAldo concentrations in Group 1 increased during the first postnatal month, reaching a peak at M1 (22.8 ± 13.1 µg/mmol) significantly higher than the values for the other groups at the same time point ($P < .001$), yet similar to the UAldo concentration values for Group 3 at D0. Thereafter, UAldo concentrations declined, paralleling the decrease of UAldo concentrations for the other groups.

Evolution of aldosterone sensitivity

Renal aldosterone responsiveness was assessed in the three groups at birth (D0) and at M1 by measuring the correlation between UAldo concentrations and the urinary Na/K ratio, as the former directly regulates the latter (12) (Figure 3A).

At birth, there was no detectable correlation between UAldo concentrations and urinary Na/K ratio in term neonates (Group 3: r = −0.19; $P = .26$), indicating renal resistance to aldosterone action. Such renal aldosterone resistance was also observed in the moderate and late preterm neonates (Group 2: r = −0.20; $P = .13$). However, very preterm neonates (Group 1) were significantly sensitive to aldosterone (r = −0.57 for the relationship between UAldo and urinary Na/K; $P < .001$). Between D0 and M1, very preterm infants became resistant to aldo-

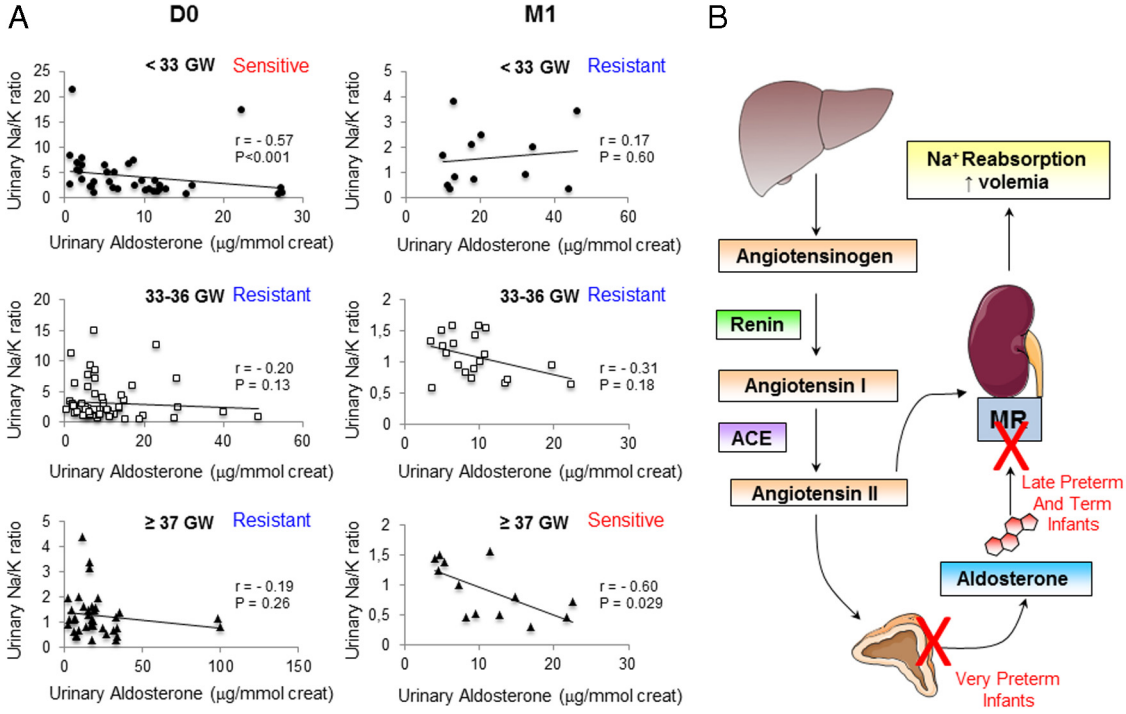

Figure 3. Variation in aldosterone sensitivity with GA and postnatal development. A, Correlation between UAldo concentration and the urinary Na/K ratio at D0 and at M1. Each ●/□/▲ represents one value. Linear regression lines are presented for the readability of the figure, accompanied by Spearman's correlation coefficient (r) and its statistical significance (*P* values). B, Scheme showing the two levels of mineralocorticoid signaling defects at birth in very preterm or in moderate preterm and term infants.

sterone (r = 0.17; P = .60), other preterm infants remained resistant to aldosterone (r = −0.31; P = .18), and term infants developed renal sensitivity to aldosterone (r = −0.60; P = .029).

Ratio between UAldo concentration and urinary Na excretion as a predictive marker to discriminate between aldosterone sensitivity and resistance

To assess its value as an index for predicting renal mineralocorticoid sensitivity, the UAldo concentration/urinary Na excretion ratio at birth was compared between the two most functionally divergent groups as described above, ie, Group 1 (sensitive to aldosterone action) and Group 3 (resistant to aldosterone action). The ROC curve obtained had an area under curve of 0.95 ± 0.02, 95% confidence interval (CI), 0.91–0.99; P < .0001 (Figure 4A). With the use of a cutoff value of 0.51 for the diagnostic signature, renal aldosterone sensitivity was predicted with a specificity of 86.8%; 95% CI, 74.6–97.0; and a sensitivity of 89.2%; 95% CI, 71.9–95.6 (Figure 4B). This index may therefore be a useful tool to distinguish between neonates sensitive to aldosterone action and those who are resistant. Hence, newborn infants with a UAldo concentration/urinary Na excretion ratio below 0.51 could be considered to be aldosterone sensitive, despite aldosterone secretion deficiency.

Discussion

This multicenter observational study of preterm and term infants has several major consequences. It demonstrates that UAldo concentrations measured from a single urinary spot can reliably evaluate aldosterone secretion in neonates. Indeed, UAldo concentrations correlated strongly with plasma aldosterone concentrations at birth. This method is noninvasive and reproducible, and could thus become a useful tool in preterm infants.

We measured aldosterone secretion at birth, and found that very preterm infants have a defective aldosterone biosynthesis or secretory pathway, which is not the case for term infants (Figure 3B). This aldosterone secretion deficiency may account for their high sodium wasting during the neonatal period and may reflect the immaturity of the adrenal cortex. During development, the fetal adrenal cortex is mainly composed of the fetal zone, which synthesizes and secretes androgens, most notably dehydroepiandrosterone sulfate (13). Plasma cortisol concentrations at birth are low in very preterm infants (14). After 30 GW, the fetal adrenal cortex resembles a rudimentary form of the adult adrenal cortex and becomes able to synthesize cortisol (15) and, our study suggests, aldosterone. In human and sheep, angiotensin II receptors are abundantly expressed in the zona glomerulosa of the fetal adrenal gland after 16 GW, such that it is unlikely to be involved in the aldosterone secretion defect observed (16, 17). It has been suggested that the fetal adrenal cortex contains an immature set of enzymes; in particular low 11β-hydroxylase activity (CYP11B1), responsible for elevated 17-hydroxyprogesterone levels (18) (leading in preterm infants to frequent false-positive screening results for congenital adrenal hyperplasia) (19) as well as, in a similar manner, conceivable low CYP11B2 activity, may be responsible for low aldosterone and cortisol biosynthesis in very preterm infants (14).

A major difference between the very preterm and term infants in our study, was antenatal corticosteroid admin-

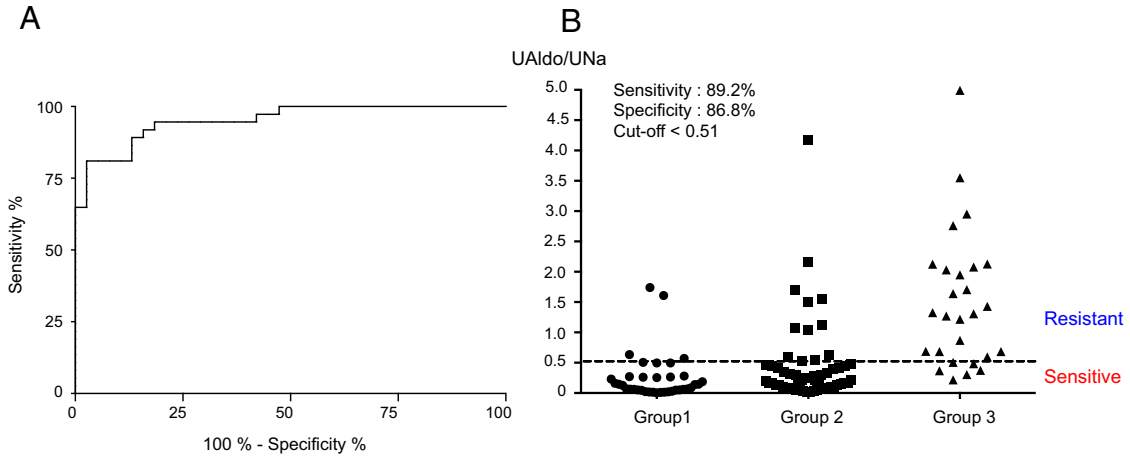

Figure 4. Index of aldosterone sensitivity. A, receiver operating characteristic curve comparing the UAldo concentration/urinary Na excretion ratio between aldosterone-sensitive (Group 1) and aldosterone-resistant (Group 3) infants at birth. Regression estimates from this model defined a diagnostic signature, and we used the under the curve, sensitivity, and specificity to evaluate the ability of this signature to discriminate between aldosterone sensitivity and resistance. B, Panel showing the cutoff value (dotted line) with the highest accuracy for all newborns (groups 1, 2, and 3).

istration (betamethasone) for prevention of neonatal respiratory distress syndrome (20). However, no difference in UAldo concentrations was observed between neonates from Group 2 who did (n = 49) and did not (n = 12; P = .36) receive antenatal betamethasone. Thus, it is highly unlikely that antenatal corticosteroid administration was responsible for the low aldosterone levels observed in preterm infants. This view is also supported by a previous and similar observation on aldosterone cord levels (21).

This work confirms our previous findings of a physiological partial aldosterone resistance in term neonates, with high levels of aldosterone and renin that contrast with functional signs of hypoaldosteronism (9). This hormonal unresponsiveness is linked to the weak expression of renal MRs at birth (10). We confirm this hormonal resistance at birth in term infants with high levels of aldosterone and unresponsive kidneys, as indicated by the lack of correlation between UAldo concentrations and the Na/K urinary ratio. On the contrary, despite low aldosterone levels, we found that very preterm infants were sensitive to aldosterone: UAldo concentrations correlated with the Na/K ratio at birth. This sensitivity was transient and very preterm infants became resistant to aldosterone during the first month of life. Most likely these observations are the result of the transient renal MR expression observed during fetal development (10). It is also likely that individual polymorphisms in genes of the mineralocorticoid signaling pathway might be involved in the biological variability observed in the results in each Group of neonates that will need to be further investigated.

One limitation of our study, particularly for changes in UAldo concentrations with age, is the number of data points and urinary samples missing from M1 and thereafter; this is a consequence of the transfer of many preterm infants from a Neonatal Intensive Care Unit to other pediatric centers within a few weeks of birth, and the difficulties of urine collection in an outpatient clinic setting. Despite this limitation, we were able to describe different evolutionary patterns of UAldo concentrations during the first months of life, depending on GA at birth. There was a postnatal surge in aldosterone secretion in very preterm infants, with UAldo concentrations at M1 reaching those of term infants at birth. This postnatal surge is probably due to both adrenal maturation and renal MR down regulation (10). Thereafter, UAldo concentrations decreased similarly to those of term infants, but with a noticeable delay. This abnormal progress of the UAldo concentration profile with age, most notably the low neonatal UAldo concentrations and the postnatal surge in very preterm infants, may play an important role in the pathogenesis of some of the adverse postnatal outcomes observed in this population. Primarily, it affects sodium reabsorption with high sodium loss in very preterm infants requiring sodium supplementation to maintain sodium and water homeostasis (22, 23) Secondarily, it may contribute to the pathogenesis of bronchopulmonary dysplasia (23, 24). However, further investigation is required to explore this issue.

Finally, we show that the UAldo concentration/Na excretion ratio is a potential predictive index of renal sensitivity to aldosterone action. This index could serve as a useful, sensitive, and selective measure to distinguish between aldosterone-sensitive and aldosterone-resistant preterm infants and identify those, particularly in the moderate preterm group (Figure 4B), who may benefit from aldosterone supplementation. This marker should be validated in further prospective studies.

In conclusion, our results demonstrate defective aldosterone secretion but conserved renal aldosterone sensitivity during the first days of life of very preterm infants. These findings mean that the current view of water and electrolyte balance in preterm neonates needs to be reevaluated, and suggest an alternative management approach for the very preterm infants.

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