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Adrenocortical Steroids in Small-for-Gestational-Age Term Infants during the Early Neonatal Period[1,2]

HELMUTH G. DOERR, HANS T. VERSMOLD, FRANK BIDLINGMAIER, AND WOLFGANG G. SIPPELL

Department of Pediatrics, Division of Endocrinology [H.G.D.], and Department of Obstetrics and Gynecology, Division of Neonatology [H.T.V.], University of Munich, D-8000 Munich 2; the Department of Pediatrics [W.G.S.], University of Kiel, Kiel; and the Department of Clinical Biochemistry [F.B.], University of Bonn, Bonn, Federal Republic of Germany

ABSTRACT. We evaluated adrenocortical steroid concentrations at birth and during postnatal adaptation (2 h until 7 days) in 10 vaginally delivered term small-for-gestational-age (SGA) infants and 12 term appropriate-for-gestational age infants. Plasma aldosterone, 11-deoxycorticosterone, corticosterone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, cortisol, and cortisone were longitudinally measured by specific RIA after Sephadex LH-20 chromatography. Mean aldosterone was significantly higher in SGA than in appropriate-for-gestational-age infants (2 h to 7 days; $p < 0.001$). In SGA infants, cortisone and cortisol levels were significantly lower in umbilical artery ($p < 0.05$), and all glucocorticoid levels were significantly lower 12 h after birth ($p < 0.05$). Thereafter (24 h to 7 days), only 11-deoxycortisol levels remained significantly lower in SGA; corticosterone and cortisol levels were even higher ($p < 0.05$) in SGA 24 h after birth. The data suggest that SGA infants maintain high aldosterone levels throughout the 1st wk of life. Low cortisol and cortisone levels in umbilical artery as well as low glucocorticoid levels at 2 h and/or 12 h compared to term appropriate-for-gestational-age infants may reflect either a less stressful postnatal adaptation or, more likely, a reduced adrenocortical synthesis in term SGA infants. (*Pediatr Res* 25:115–118, 1989)

Abbreviations

SGA, small for gestational age
UA, umbilical artery
AGA, appropriate for gestational age

Perinatal problems in neonates with severe intrauterine growth retardation are frequent. They include asphyxia, a high neonatal mortality, electrolyte imbalance, hypoglycemia, cardiorespiratory problems, and neurologic abnormalities (1). Organ weights are significantly reduced (2); in particular, the adrenal cortex is small with respect to size and cell number (3).

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Reprint requests Helmuth G. Doerr, M.D., Division of Endocrinology, Department of Pediatrics, University of Munich, Lindwurmstr. 4, D-8000 Munich 2, Federal Republic of Germany.
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[2]Dedicated to Prof. Dieter Knorr on the occasion of his 65th birthday.

By contrast, the stressful nature of being an SGA infant should be reflected in an increased adrenal steroid response. Only few and contradictory results on corticosteroid levels in SGA infants have been reported (4–6), partly combining data from infants born by various modes of delivery, or infants at various postnatal and gestational ages. Because of the amount of blood necessary for the determination of corticosteroids, these studies were limited to single steroids such as cortisol (5) or aldosterone (7, 8). For the same reason, longitudinal studies throughout the early neonatal period are not available. However, with our micromethod of multisteroid analysis (9, 10) we were able to approach this question.

To assess adrenocortical function in term infants with severe intrauterine growth retardation, we therefore measured all physiologically important mineralocorticoids, glucocorticoids, and progestins at birth and longitudinally during the first hours and days of life. By selecting only severely growth-retarded infants (<3rd percentile), delivered vaginally at term and with normal Apgar scores, we tried to eliminate most of the confounding factors.

MATERIALS AND METHODS

We studied 10 SGA infants (five males, five females) of 38–41 wk gestation with a mean birth wt of 2360 g (range 2000–2680 g). Gestational age was defined by the menstrual history and confirmed by ultrasound in the 1st trimester. In all newborn infants, the Dubowitz score was assessed, which agreed within 1 wk with the gestational age by dates. All weights were less than the 3rd percentile (11), and more than −2 SD less than the mean (12) for gestational age. Infants with otherwise abnormal physical findings, congenital infection, or chromosomal anomalies were excluded. The infants were delivered spontaneously by the vaginal route. Apgar scores were 8–10 at 1 min and 9–10 at 5 min. According to our routine care of SGA infants less than the 3rd percentile, the infants received during the first day of life intravenous glucose (5 mg/kg·min) to maintain normoglycemia, followed by oral glucose and breast feeding. The postnatal course was uncomplicated, in particular no electrolyte disturbances were observed.

The mothers (age 25–36 y) were healthy, in normal nutritional state, received no drugs, and had no signs of infection. Infants of mothers with preeclampsia were excluded. A small placenta was present in seven of the 10 cases. For ethical reasons, a simultaneous control group could not be studied. Therefore, the data were compared to 12 term AGA infants of 39–41 wk gestation and birth wt of 2900–4000 g (between 10th and 90th percentile). Their data have been reported previously (13, 14).

Plasma samples of 100–250 μl were obtained from the UA at the time of birth and during routine blood sampling from a peripheral vein or by heel prick at the age of 2, 12, and 24 h, and 4 and 7 days. Blood samples were collected into EDTA-tubes and centrifuged immediately. The plasma was stored at −20°C until assayed. Levels of unconjugated aldosterone, corticosterone, 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, cortisol, and cortisone were measured from the same small plasma sample. The micromethod of multisteroid analysis has been previously described and evaluated (9, 10). In brief, it included the addition of tracer amounts of each of the eight steroids to a 250-μl plasma sample, extraction with methylene chloride, and a mechanized Sephadex LH-20 chromatography for the simultaneous separation of the steroids. Each isolated steroid fraction was quantitated by RIA after a small aliquot was branched off for internal standard recovery counting. Coefficients of variation of the complete assay (including extraction, chromatography, and RIA were between 6.9 and 14.5% within assays and between 11.9 and 16.3% between assays, for all eight steroids.

For statistical comparisons (two-tailed) between the means of two samples either parametric (Student's *t* test) or nonparametric tests of significance (Mann-Whitney's U-test) were used. Statistical comparisons of more than two means of paired samples, *i.e.* analyzing the postnatal course of the mean plasma levels of a given steroid, were made using the ranked ANOVA according to Friedman in combination with Wilcoxon and Wilcox's multiple comparison of paired samples. Informed consent was obtained from all mothers, and the study was approved by the local ethics committee.

RESULTS

Mineralocorticoids. Mean aldosterone levels (Fig. 1) were significantly higher in term SGA infants than in AGA infants from age 2 h until 7 days. In SGA infants, the aldosterone levels increased slightly after birth (2 h) and remained unchanged thereafter.

Concentrations of 11-deoxycorticosterone (Fig. 2) in term SGA and AGA infants decreased in parallel from UA to day 7. In SGA infants, the decrease in 11-deoxycorticosterone levels with age was significant between UA and 2 h ($p < 0.05$), 2 h and 24 h. ($p < 0.05$), 24 h and 4 days ($p < 0.05$). The level at day 7 was only about 3% of the UA level ($p < 0.001$). Mean values in SGA infants were significantly lower than in AGA infants only at 2 h.

Glucocorticoids. Levels of 11-deoxycortisol (Fig. 3) in SGA infants were significantly lower than in AGA infants from 2 h until 7 days after birth. In SGA infants, they declined initially, from 2 to 12 h ($p < 0.05$), and showed only little variation thereafter.

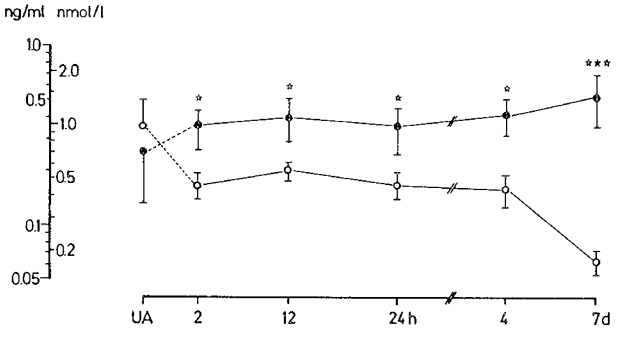

Fig. 1. Plasma aldosterone concentrations (mean ± SEM, logarithmic scale) in UA and from 2 h to 7 days of age in term SGA infants (●) and term AGA infants (○). Significant differences, SGA *versus* AGA: ★, $p < 0.05$; ★★★, $p < 0.001$.

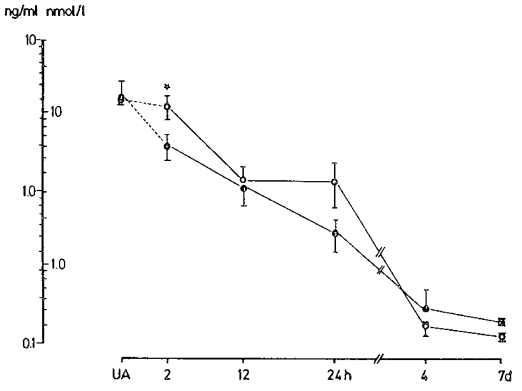

Fig. 2. Plasma 11-deoxycorticosterone concentrations (mean ± SEM). (●) term SGA infants; (○) term AGA infants. Significant differences, SGA *versus* AGA: ★, $p < 0.05$.

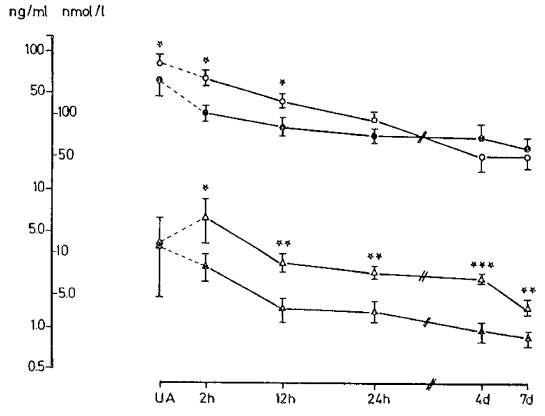

Fig. 3. Plasma cortisone (○) and 11-deoxycortisol (△) concentrations (mean ± SEM). *Closed symbols:* term SGA infants; *open symbols:* term AGA infants. Significant differences, SGA *versus* AGA: ★, $p < 0.05$; ★★, $p < 0.02$; ★★★, $p < 0.001$.

Mean cortisone levels (Fig. 3) in SGA infants initially declined to about half the UA level at 2 h ($p < 0.05$) and remained unchanged thereafter. In SGA infants, cortisone levels were significantly lower than in AGA infants in UA, at 2 h and at 12 h after birth.

Mean corticosterone levels (Fig. 4) initially declined in SGA infants (UA to 12 h: $p < 0.01$) and increased thereafter. The lowest level, at 12 h, was significantly lower than in AGA infants at 12 h. At 24 h after birth, corticosterone levels were significantly higher in SGA than in AGA infants; AGA infants had their lowest level at this time.

Mean cortisol levels in SGA infants (Fig. 4) showed variations similar to those of corticosterone throughout the study period. In SGA, the levels at birth (UA) and at 12 h were significantly lower than in AGA infants, whereas the level at 24 h was significantly higher than in AGA. Thereafter, no significant differences were observed between the two groups.

Progestins. Mean progesterone levels (Fig. 5) in SGA infants declined rapidly by almost three orders of magnitude from UA until day 7 ($p < 0.001$). There were no differences between SGA and AGA infants.

After birth, the levels of 17-hydroxyprogesterone in SGA infants decreased until 24 h ($p < 0.01$) and did not vary significantly thereafter. Mean 17-hydroxyprogesterone levels were significantly higher in SGA infants than in AGA infants at 12 h and 24 h after birth.

No differences between female and male infants were observed for any steroid.

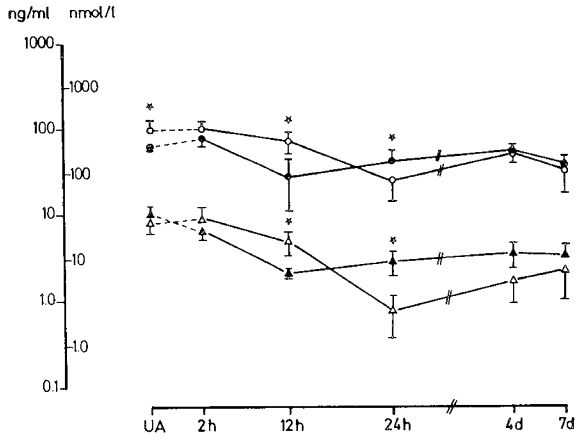

Fig. 4. Plasma cortisol (O) and corticosterone (Δ) concentrations (mean ± SEM). *Closed symbols:* term SGA infants; *open symbol:* term AGA infants. Significant differences, SGA *versus* AGA: ★, $p < 0.05$.

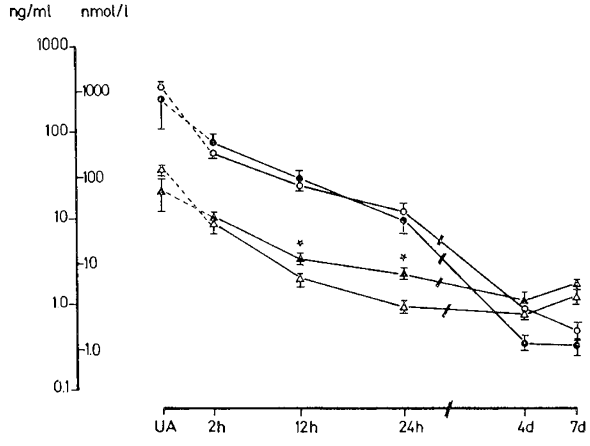

Fig. 5. Plasma progesterone (O) and 17-hydroxyprogesterone (Δ) concentrations (mean ± SEM). *Closed symbols:* term SGA infants; *open symbols:* term AGA infants. Significant differences, SGA *versus* AGA: ★, $p < 0.05$.

DISCUSSION

The adrenal cortex plays an important role during postnatal adaptation of the newborn (15). Infants with severe intrauterine growth retardation have frequent perinatal problems (1). Naeye (16) reported that the fetal zone of the adrenal cortex is even more reduced than the permanent zone. Dehydroepiandrosterone-sulfate, which is secreted mainly by the fetal zone, was found to be lower in umbilical cord (17) and on the 1st day of life (18) in newborns with intrauterine growth retardation. The question is whether the biologically active Δ4-corticosteroids of the permanent zone of the adrenal cortex, necessary for the period of adaptation to extrauterine life, are also reduced.

There are no longitudinal studies on plasma aldosterone and 11-deoxycorticosterone levels in term SGA infants during the first hours and days of life. In our study, both mineralocorticoids showed a different pattern. Whereas aldosterone levels were consistently higher in SGA infants than in AGA infants, 11-deoxycorticosterone levels were not different from those of AGA infants. It has been shown that the renin-angiotensin-aldosterone system is highly active during the neonatal period, particularly in premature infants (19, 20). Our data on high aldosterone levels in SGA infants also suggest an activation of this system, whereas in two other studies (7, 8), limited to the 2nd day, and to the 7th day of life, respectively, no difference was found between SGA and AGA infants. Sulyok *et al.* (8), however, described a tendency to higher plasma renin activity and urinary aldosterone excretion in intrauterine growth-retarded neonates. Polycythemia with high blood viscosity is a common problem in SGA infants (21). In the present study, mean hematocrit was 62% on the 1st day of life. Thus, hyperaldosteronism could contribute to improving blood viscosity by reducing sodium and water excretion.

At birth, elevated fetal (UA) cortisol concentrations have been related to the stress of delivery (22). Thus, our results of lower fetal cortisol levels in SGA infants suggest either a less stressful delivery or an inappropriate response to the stress of birth. Postnatally, both active glucocorticoids—cortisol and corticosterone—show a similar course in SGA infants and in AGA infants, with the only difference that the lowest values in SGA infants were reached early at 12 h after birth, whereas in AGA infants the lowest values were found at 24 h after birth. The reason is unclear. Again it can be speculated that postnatal adaptation in the first 12 h of life is less stressful in SGA infants or that the adrenal cortex is not able to react adequately to stress. Two earlier studies (23, 24) of adrenal function in intrauterine growth-retarded infants have shown abnormal cortisol secretion rates and a decreased steroid response to stress, whereas Reynolds *et al.* (25) reported a normal cortisol response to ACTH stimulation in intrauterine growth-retarded infants. Hypoglycemia, a frequent condition in SGA infants, can be excluded as a possible factor influencing adrenal steroid response, because normoglycemia was maintained in all infants by initial intravenous glucose followed by early oral glucose supply.

Regarding the levels of the inactive glucocorticoids, cortisone and 11-deoxycortisol, cortisone levels were lower in SGA infants from birth up to 12 h of age, and 11-deoxycortisol levels were lower from 2 h until day 7 of age. This is the first report of these steroids in SGA infants during the early neonatal period. It has been demonstrated that cortisone is a major blood corticosteroid in term AGA infants and that it decreases after birth (26). This should also apply to SGA infants. However, it remains unclear why the synthesis of cortisone (and of 11-deoxycortisol) is reduced in the SGA group. One could speculate that altered enzymatic activities of the adrenal cortex of term SGA infants may affect glucocoticoid production immediately after birth.

Our study shows the first results on longitudinal plasma levels of progesterone and 17-hydroxyprogesterone in SGA infants during the early neonatal period. UA levels of both progestins were not different between SGA and AGA infants, suggesting that fetal progestin levels are not correlated with fetal weight (27). The rapid postnatal decline of progesterone in term SGA infants, which is nearly parallel to that in AGA infants (13), reflects the predominant placental origin of this steroid. Levels of 17-OH-progesterone in SGA infants also decline postnatally but not to the same extent as in AGA infants, so that the levels at 12 h and 24 h after birth were significantly higher. The reason is unclear. However, a decreased rate of metabolism due to altered enzymatic activities might play a role, as suggested also for premature infants (20, 28, 29).

The approach to the study of adrenocortical function in the early neonatal period requires the assessment of individual steroids. Our present data provide evidence that adrenocortical function in the early neonatal period of severely growth-retarded term infants is different from that of term AGA infants. We can only speculate that elevated aldosterone levels suggest an activation of the renin-angiotensin-aldosterone system, whereas lower glucocorticoid levels point to either a less stressful postnatal adaptation or, more likely, to a reduced adrenocortical synthesis in SGA infants. Considering that delivery and early neonatal life is a period of rapid adaptation to various stresses, the pathophysiologic meaning of such data remains to be further evaluated.

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Erratum

An error was made in printing the article Regional Brain Glucose Utilization in Adenylosuccinase-Deficient Patients Measured by Positron Emission Tomography (Pediatr Res 24:238-242, 1988).

Please note that the legend of Figure 2, p 240 should read **Fig. 2. Images of regional glucose utilization at the level of the basal ganglia (*upper panels*) and at the level of the cerebellum (*lower panels*), in patient B with adenylosuccinase deficiency (*A*), in a normal study (*B*) and in a case of phenylketonuria (*C*). Glucose metabolic rates (μmol/100 g·min) are proportional to the color scale. In order to improve the quality of the images, a different scale is used for each subject, as indicated.**