Circulating Adrenocorticotropic Hormone (ACTH) and Cortisol Concentrations in Normal, Appropriate-for-Gestational-Age Newborns Versus Those With Sepsis and Respiratory Distress: Cortisol Response to Low-Dose and Standard-Dose ACTH Tests

Ashraf T. Soliman, Khaled H. Taman, Mohamed M. Rizk, Ibrahim S. Nasr, Hala AlRimawy, and Mohamed S.M. Hamido

In this crossover study, we compared the peak responses of cortisol to low-dose (1 μg/1.73 m^2) and standard-dose (250 μg/1.73 m^2) adrenocorticotropic hormone (ACTH) stimulation tests in 90 full-term newborns (37 to 42 weeks gestational age, birthweight > 2,500 g, aged 4 to 7 days): 30 with sepsis syndrome, 30 with respiratory distress (RD) and 30 normal infants. Basal cortisol and ACTH were measured in a fasting venous sample. Serum cortisol concentrations were measured 30 minutes after low-dose ACTH and 60 minutes after standard-dose ACTH by radioimmunoassay (RIA). The mean basal circulating cortisol concentration and peak cortisol responses to low-dose and standard-dose ACTH tests were higher in stressed infants with sepsis and RD compared to normal. Basal but not ACTH-stimulated cortisol concentrations were significantly higher in newborns with sepsis versus those with RD. Circulating cortisol concentrations after the low-dose ACTH test were correlated significantly with those obtained after the standard-dose ACTH test ($r = 0.814$, $P < .001$). Clinical subgrouping of septic newborns showed that those with leukopenia (5/10 died) and with meningitis (6/12 died) had significantly lower basal and peak cortisol responses to the low-dose ACTH test (but not the standard-dose ACTH test) versus those with leukocytosis (3/20 died) and without meningitis (2/18 died), respectively. In addition, septic newborns who died had significantly lower circulating cortisol concentrations and lower cortisol responses to the low-dose ACTH test (but not the standard-dose test) versus those who survived the stress. On an individual basis, only 2 septic newborns (both died) had low basal cortisol levels (<5 μg/dL) and cortisol responses less than 15 μg/dL after the low-dose ACTH test. Four more septic newborns had basal cortisol above 5 μg/dl but cortisol responses below 20 μg/dL after the low-dose ACTH test. These 4 newborns (4/30) with inadequate adrenocortical response to low-dose ACTH during sepsis had high mortality (3/4 died) and represented a subgroup of septic newborns that should be diagnosed, using a low-dose ACTH test, and treated early. These data suggest that the low-dose ACTH test may be more disciminatory than the standard-dose test among babies under stress. Increasing the cut-point level of basal cortisol in stressed infants to the lowest level of cortisol response to low-dose ACTH in normal newborns, followed by the use of a low-dose ACTH test, appears to select some newborns who need and may improve on corticosteroid therapy. Further studies are required to investigate whether supplementation with stress doses of hydrocortisone may improve the outcome in these patients.

SOME NEONATES admitted to the neonatal intensive care unit show circulatory and respiratory problems that improve after administration of corticosteroids. It is unclear whether these symptoms could be caused or affected by adrenal insufficiency.[1-5] Infants with signs of adrenal insufficiency have been reported to have cortisol levels, measured in random blood samples, that are inappropriately low for their severity of illness.[1-5] When treated with stress doses of hydrocortisone, their signs of cortisol deficiency resolved within 2 days of beginning treatment. Watterberg and Scott have found a correlation between a blunted response to adrenocorticotropic hormone (ACTH) stimulation in some very-low-birthweight infants and their subsequent development of bronchopulmonary dysplasia, a well-known sequela of very premature birth.[5]

Data on cortisol secretion by newborns during different types of stress, eg, sepsis and respiratory distress (RD), are still insufficient and their cortisol responses to different doses of ACTH are not standardized.[6-9] Recently, it was suggested that using a supraphysiological dose of exogenous ACTH (250 μg) may cause false-positive responses due to maximal stimulation of the adrenal cortex, and the test should be done by using lower doses of ACTH. The low-dose ACTH test could possibly diagnose early/mild cases of adrenal suppression in both infants and adults.[10-19] Three important questions should be answered in the newborns under stressful illness: (1) Is there corticotroph cell hypofunction in some stressed newborns? (2) Is there any difference in cortisol response to different stressful conditions, eg, RD versus sepsis and sepsis without versus with menengitis? (3) Can the low-dose ACTH test diagnose early/mild cases of adrenal insufficiency that can not be detected with the high-dose (unphysiologic) ACTH test in newborns? In this study, our aim was to find the answers to these questions. We performed a prospective comparative study assessing morning serum cortisol and ACTH and measured the serum cortisol responses to the 1-μg and 250-μg ACTH tests within the fourth to seventh days of life in full-term infants with and without stress.

MATERIALS AND METHODS

This study included 90 full-term newborn infants (gestational age 36 to 42 weeks, birthweight > 2,500 g) between the fourth and seventh day after birth, randomly selected from newborns born in Alexandria

From the Department of Pediatrics, University of Alexandria, Alexandria, Egypt; and the Institute of Postgraduate Childhood Studies, Ain Shams University, Cairo, Egypt.

Submitted May 8, 2002; accepted September 10, 2003.

Address reprint requests to Ashraf T. Soliman, MD, PhD, FRCP, Professor of Pediatrics and Endocrinology, University of Alexandria Children's Hospital, Abdel Sattar Mansour Street, Loran, Alexandria, Egypt.

0026-0495/04/5302-0008$30.00/0
doi:10.1016/j.metabol.2003.09.005

Table 1. ACTH and Cortisol Secretion in Newborns With and Without Stress

	ACTH (ng/mL)	Basal Cortisol (μg/dL)	Cortisol After LD ACTH (μg/dL)	Cortisol After SD ACTH (μg/dL)
Normal (n = 30)	50.2 ± 6.9	14.8 ± 1.9	38.1 ± 5	84 ± 6.9
Sepsis (n = 30)	30.8 ± 4.4*	44.8 ± 12.2*†	86.3 ± 13.3*	142.8 ± 17.7*
RD (n = 30)	51.4 ± 8.5	35 ± 7.1*	78.6 ± 9.8*	130.6 ± 18.4*

Abbreviations: LD, low-dose; SD, standard-dose.

*$P < .05$, sepsis and RD groups v normal.

†$P < .05$, RD v sepsis.

University Maternity Hospital, El Chatby, Alexandria, Egypt. These newborns were divided into 3 groups.

Group I consisted of 30 infants with sepsis syndrome according to the septic risk score system.[20] They were admitted to the neonatal special care unit (with all facilities of intensive care short of mechanical ventillation), Alexandria University Children's Hospital. Eighteen had a history of chorioamnionitis. All infants underwent sepsis screening and were started on broad-spectrum antibiotics. Cultures from blood and/or urine and/or cerebrospinal fluid were positive. Twelve of 30 had meningitis. Blood cultures were positive in 70% (21/30), with *Klebsiella* (14/21), *Escherichia coli* (4/21), and *Haemophilus influenza* (3/21) isolated. All had increased serial C-reactive protein concentrations (normal < 12.0 mg/L). Exclusion criteria included maternal diabetes, small for gestational age, and prepartum or intrapartum corticosteroid therapy in mothers. Their weights ranged from 2,550 to 4,100 g. Gestational age ranged between 36 and 41 weeks. All septic newborns who required intubation and mechanical ventillation were excluded because we decided to study the effect of sepsis and eliminate the potentially confounding other factors that might affect cortisol secretion.

Group II included 30 newborn infants with RD secondary to a pulmonary disease, according to the retraction scoring of Silverman.[21] They had the diagnoses of meconium aspiration (18/30), transient tachypnea of the newborn (TTN) (7/30), and neonatal pneumonia (5/30). Infants with RD due to nonpulmonary causes were excluded from the study. None of the infants had received postnatal glucocorticoid treatment, or treated with dexamethasone antenatally. Their weights ranged from 2,750 to 3,900 g and gestational age was between 37 and 42 weeks. All newborns with RD that required intubation and/or mechanical ventillation were excluded because we wanted to eliminate other factors that might affect cortisol secretion.

Group III consisted of 30 normal healthy infants, born to healthy nonstressed mothers by spontaneous vaginal delivery. They were studied during routine investigations for physiologic jaundice (unconjugated hyperbilirubinemia). Their weights ranged from 2,850 to 3,750 g, and gestational age ranged between 38 and 41 weeks. Their indirect bilirubin ranged between 7.5 and 14.8 mg/dL. None required exchange transfusion.

Infants were studied at 4 to 7 days of age to allow placental and maternal hormones to be metabolized. Venous blood samples were collected between 7 and 9 AM to standardize the environmental stimuli of the infants. A fasting venous sample was withdrawn for determination of circulating cortisol and ACTH. In the low-dose ACTH test, the subjects were given 1 μg/1.73 m^2 synthetic ACTH (Synacthen; Ciba-Geigy, Stein, Switzerland) as an intravenous bolus. On the next day (after 24 hours to allow adequate time for serum cortisol to return back to basal after the first stimulation and to fit with the routine blood collection time in the nursery), a standard-dose ACTH test (250 μg/1.73 m^2) was performed. Blood was collected 30 minutes after the low-dose ACTH test and 60 minutes after the high-dose ACTH test, because peak cortisol response to provocation occurs 30 minutes after a low-dose ACTH test and 60 minutes after a standard dose test.[22] Serum cortisol concentrations were measured by radioimmunoassay (RIA). ACTH dose preparations were performed using serial dilutions of ACTH in 0.9% NaCl.

Ethical Approval

The study was approved by the Research Ethics Committee of the University of Ain Shams, Cairo, Egypt. Informed parental consent was obtained for each newborn before commencement of the test.

Statistical Analysis

The descriptive statistics for the demographic data were expressed as the mean and SD. Kruskal-Wallis analysis of variance (ANOVA) was performed for multiple comparison. This test was followed by the Mann-Whitney *U* test to compare the 2 groups. The data are expressed as mean ± SD. *P* values less than .05 were considered statistically significant. Wilcoxon's rank sum test and Fisher's exact test were used for comparison of continuous variables and proportions where appropriate. Correlations were determined by linear regression analysis.

ACTH and Cortisol Assays

The plasma ACTH concentration was measured by double-antibody RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA), and serum cortisol was determined by solid-phase RIA (Diagnostic Products Corp, Los Angeles, CA). The interassay coefficients of variation of the ACTH assay were 4.4% and 3.7% at 10.1 and 79.3 pmol/L, respectively; those of the cortisol assay were 8.1%, 4.4%, and 4.0% at 159, 461, and 1,260 nmol/L, respectively. Plasma ACTH concentration in picomoles per liter can be converted to picograms per milliliter by multiplying by a factor of 4.5; likewise, the conversion of serum cortisol concentration from nanomoles per liter to micrograms per deciliter can be achieved by dividing by 27.6.

RESULTS

Mean baseline ACTH levels were significantly lower in infants with sepsis (mean [SD]) (30.8 [4.4] pg/mL) versus normal newborns (50.24 [6.9] pg/mL) and those with RD (51.4 [8.5] pg/mL). The mean basal circulating cortisol concentration was significantly increased in stressed infants with sepsis (44.77 [12.2] μg/dL) and RD (35 [7.1] μg/dL) versus normal infants (14.84 [1.87] μg/dL). This denoted adequate basal cortisol secretion in stressed newborns (Table 1 and Fig 1). None of the newborns had blood glucose ≤ 45 mg/dL in the collected samples.

Peak cortisol responses to low-dose and standard-dose ACTH tests were higher in stressed infants with sepsis (86.3 [13.3] μg/dL and 142.8 [17.75] μg/dL, respectively) and RD (78.6 [9.8] μg/dL and 130.6 [18.4] μg/dL, respectively) compared to normal infants (38.1 [5] μg/dL and 84 [6.9] μg/dL, respectively) (Table 1 and Fig 1). The percentage increments of

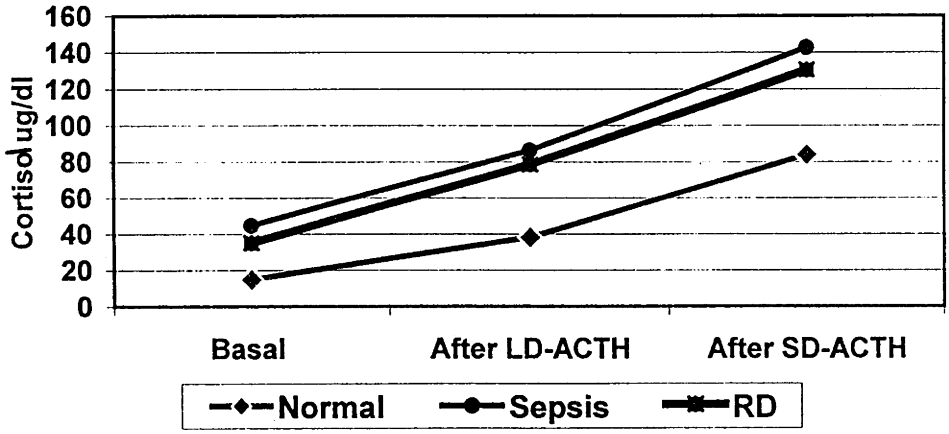

Fig 1. Mean values of basal and stimulated cortisol responses to low-dose (LD) and standard-dose (SD) ACTH tests.

serum cortisol, above baseline values, in response to the standard-dose ACTH test were significantly lower in infants with sepsis (319%) and those with RD (373%) versus normal infants (633%). The percentage of difference between peak values after low-dose and high-dose ACTH was significantly lower in infants with sepsis (126%) and RD (149%) versus those for normal infants (377%) (Fig 2). Mean peak cortisol levels attained on the 1-μg tests were significantly lower than those attained on 250-μg tests ($P < .001$).

Two of the normal newborns had subnormal basal cortisol level (<5 μg/dL) and one (3.3%) had subnormal cortisol response (<20 μg/dL) to the low-dose ACTH test. Two newborns with sepsis had low basal cortisol levels (<5 μg/dL) and low cortisol responses to the low-dose ACTH test (<15 μg/dL). All newborns with RD had basal cortisol levels greater than 5 μg/dL.

A basal cortisol level above 5 μg/dL and below 15 μg/dL was found in 11 of 30 septic newborns. Four of them also had low responses to low-dose ACTH (<20 μg/dL). Twelve of 30 of newborns with RD had basal cortisol levels greater than 5 μg and less than 15 μg. All of them had cortisol responses greater than 20 μg/dL to the low-dose ACTH test. All newborns with sepsis and RD with basal cortisol greater than 5 and less than 15 μg/dL had peak cortisol levels above 20 μg/dL after the high-dose ACTH test.

Septic newborns with leukocytosis (total leukocyte count > 5,000) had higher basal and stimulated cortisol levels compared to those with leukopenia. Those with meningitis had significantly lower basal and stimulated cortisol concentrations versus those without meningitis. Septic newborns who died had significantly lower stimulated cortisol levels versus those who survived (Table 2).

A highly significant correlation was found between peak serum cortisol levels after low- and standard-dose ACTH tests ($r = 0.812$, $P < .0001$, N = 90) and between these peaks on the one hand and basal cortisol levels on the other hand ($r = 0.854$ and $r = 0.62$, $P < .001$, respectively). Basal circulating ACTH concentrations were correlated significantly with basal cortisol levels ($r = -0.387$, $P < .001$).

DISCUSSION

Basal circulating cortisol concentrations increased significantly in our stressed newborns with sepsis (3-fold rise) and RD (2.3-fold rise) compared to normal newborns. However, any form of adrenal insufficiency, even if relatively mild,

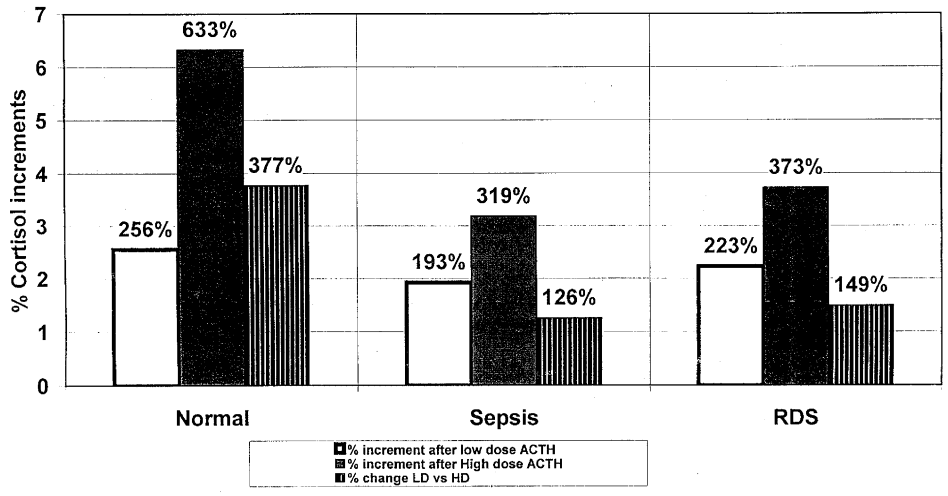

Fig 2. Percent increments of cortisol concentrations after low-dose (LD) and standard-dose (SD) ACTH tests and percent difference of responses between LD and SD ACTH in normal newborns and those with sepsis and RD.

Table 2. Prognosis and Cortisol Secretion in Subgroups of Septic Newborns

	Mortality	Basal Cortisol	Cortisol After LD ACTH	Cortisol After SD ACTH
TLC > 5,000 (n = 20)	25.00	49.8 ± 14.2	94.4 ± 16.5	145.9 ± 19.5
TLC < 5,000 (n = 10)	50.00	38.2 ± 9.5*	72.4 ± 11.4*	141.7 ± 16.3
Without menengitis (n = 18)	11.11	51.7 ± 12.2	99.9 ± 15.7	141.5 ± 15.4
With menengitis (n = 12)	50.00	37.3 ± 11.9*	76.5 ± 12.2*	145.2 ± 18.7
Survived (n = 22)		46.3 ± 13.2	98.5 ± 13.5	147.8 ± 21.2
Died (n = 8)		42.8 ± 11.4	56.3 ± 10.2*	139.5 ± 15.7

Abbreviations: LD, low-dose; SD, standard-dose; TLC, total leukocyte count.
*$P < .01$.

would certainly render the hypoxic and/or septic neonate susceptible to significant morbidity and mortality.[23-33]

Is There Corticotroph Cell Hypofunction in Some Stressed Newborns?

Although the criteria for the adequacy of cortisol levels in systemic inflammatory states is still hard to define in a rational fashion, especially in newborns, this appears to be true. Our data based on clinical subgrouping of septic newborns showed that septic newborns with leukopenia (5/10 died) and those with meningitis (6/12 died) had significantly lower basal and peak cortisol responses to low-dose ACTH tests versus those with leukocytosis (3/20 died) and without meningitis (2/18 died), respectively. On an individual basis, 4 septic newborns (3 of them died) with basal cortisol > 5 μg/dL and below 15 μg/dL had low responses to the low-dose ACTH test (<20 μg/dL). These 4 newbornsn (4/30) with inadequate adrenocortical response to the stress of sepsis and high mortality (3/4 died) represented a subgroup of septic newborns with inadequate cortisol that should be diagnosed and treated early.

Is There any Difference in Cortisol Response to Different Stressful Conditions?

Cortisol secretion differs significantly in subgroups of stressed newborns who differ in some clinical parameters (menengitis and leukopenia) and those who had poor prognosis. In addition, septic newborns who died had significantly lower circulating cortisol concentrations and lower cortisol responses to ACTH versus those who survived the stress (Table 2). Similarly, Melby and Spink demonstrated that accelerated adrenal secretory activity existed in adult patients with severe infections who survived sepsis.[34] Moreover, basal cortisol concentrations were significantly higher in newborns with sepsis versus those with hypoxic stress. Increasing the cut-point level of basal cortisol to greater than 5 μg/dL (eg, to 15 μg/dL) appears to increase the sensitivity of this test to detect mild forms of inadequate adrenocotical function during stress and those with higher morbidity and mortality.[6,35,36]

Can the Low-Dose ACTH Test Diagnose Mild/Early Cases of Adrenal Impairment During Stressful Conditions?

Although peak cortisol responses to both the low-dose and standard-dose ACTH tests were highly correlated ($r = 0.814$, $P < .001$), the standard-dose ACTH test appeared to be less discriminative versus the low-dose test in testing adrenal function in those newborns. In this study the following evidences supported this. (1) The cortisol response to the standard-dose ACTH test was greater than 20 μg/dL in all newborns with sepsis and RD, including those with basal cortisol levels less than 5 μg/dL as well as those with basal cortisol levels greater than 5 μg/dL. In contrast, 4 septic newborns, with basal cortisol greater than 5 and less than 15 μg/dL, had low responses to the low-dose ACTH test less than 20 μg/dL. Three of them died, and the fourth responded well to antibiotic therapy (14 days) and stress-dose of hydrocrtisone (7 days). These 4 septic newborns had an improper adrenocortical response to stress that was masked by the high pharmacological dose of ACTH in the standard test. Early selection of these newborns and initiating adequate replacement with stress-doses of corticosteroid might be beneficial in the course of treatment. (2) In addition, cortisol response to low-dose ACTH, but not to the standard-dose ACTH test, was significantly lower in those septic newborns with leukopenia and/or menengitis and those with fatal outcome versus those without leukopenia, meningitis, or those who survived the stress of sepsis. (3) In this study, a basal cortisol concentration less than 5 μg/dL was found in 2 septic newborns with fatal outcome (both had low cortisol response after < 15 μg/mL) after a low-dose ACTH test, but normal cortisol response (>20 μg/mL) after a standard-dose test.

All of these data suggested that the low-dose test might be more discriminatory than the standard-dose test among babies under stress. In agreement with our findings, some investigators suggested that defective adrenals may still respond to a pharmacological dose of 250 μg and suggested that using a supraphysiological dose of exogenous ACTH (250 μg) may cause false-positive responses due to maximal stimulation of the adrenal cortex, and the test of choice should be low-dose ACTH.[10-19,37]

In this study stimulated cortisol levels did not differ in newborns with sepsis versus those with RD. Their basal cortisol levels were comparable to stimulated levels (after the low-dose ACTH test) for normal newborns. These findings imply that a fair comparison between normal and stressed infants should be performed between basal circulating levels of cortisol in stressed infants (stimulated by the ongoing stress) versus cortisol levels after low-dose ACTH stimulation for the normal (nonstressed) newborns, ie, comparing stimulated cortisol levels (the disease stress in the former group and the low-dose ACTH in the normal newborn group). Comparing basal levels for stressed newborns with stimulated levels in normal newborns (all had cortisol responses > 15 μg/dL) revealed that 11 of 30 patients with sepsis had basal cortisol levels greater than

5 and less than 15 μg/dL (4 of the 11 newborns had low responses to low-dose ACTH) and 3 of them died. In addition, the finding of significantly lower basal and peak cortisol responses to the low-dose ACTH test in septic newborns with leukopenia and/or meningitis versus those with leukocytosis and those without meningitis suggested that the former groups are at high risk for impaired cortisol secretion. The presence of significantly lower circulating cortisol concentrations and lower cortisol responses to ACTH in those with fatal outcome versus those who survived the stress (Table 2) suggested that the low-dose ACTH test might be more sensitive in predicting mortality in these high-risk newborns.

Collectively, increasing the cut-point level for normal basal cortisol in stressed infants, to ≥ 15 μg/dL (the lowest level of cortisol response to low-dose ACTH in normal newborns), significantly increased the number of newborns who needed further testing using the low-dose ACTH test. Those septic newborns with impaired response to low-dose ACTH (<20 μg/dL) had significantly higher morbidity and mortality rates. Addition of corticosteroid therapy (stress-dose) may prove useful in these septic infants and may improve outcome.[6] However, this concept should be investigated carefully in a prospective double-blind study.

We found no significant increase in basal ACTH between normal newborns and those with sepsis or RD despite their increased cortisol levels in response to exogenous ACTH. It was previously suggested that infants with the systemic inflammation that accompanies the respiratory distress syndrome (RDS) may be unable to concurrently increase the activity of their hypothalamic-pituitary-adrenal axis to levels that are appropriate for the degree of their inflammation.[5,38-40] This nonelevated basal ACTH level in our newborns under stress could be explained in part by the extra-pituitary regulation of adrenocortical function that comes into major play in some forms of stress.[41-43] However, the lower ACTH level in our septic newborns compared to normal newborns and those with RD might suggest a suppressing effect of sepsis and/or some of its metabolites on the hypothalamic-pituitary axis. They also suggest that extra-pituitary mechanisms may assist in the maintenance of high cortisol levels in prolonged forms of neonatal stress.

In summary, the majority of sick full-term newborns with RD and sepsis have adequate adrenal cortical function in response to stress and do not appear to require corticosteroid supplementation (stress-doses of corticosteroids) in routine practice. The use in acutely ill newborn of a basal plasma cortisol level of less than 15 μg/dL as indicative of adrenal insufficiency appears to increase the number of newborns who have higher morbidity and who require further testing of adrenal function. Testing the response to low-dose ACTH appears to be useful as an additional measure of adrenal functional status in those septic infants with basal cortisol levels greater than 5 and less than 15 μg/dL and it might lead to more diagnoses of newborns who need treatment with corticosteroids.

REFERENCES

1. Arnold JD, Bonacruz G, Leslie GI, et al: Effect of clinical state and clinical interventions on characteristics of plasma cortisol secretion in neonates using deconvolution analysis. Pediatr Res 39:193A, 1996 (abstr)

2. Colasurdo MA, Hanna CE, Gilhooly JT, et al: Hydrocortisone replacement in extremely premature infants with cortisol insufficiency. Clin Res 37:180A, 1989 (abstr)

3. Ward RM, Kimura RE, Rich-Denson C: Addisonian crisis in extremely premature neonates. Clin Res 39:11A, 1991 (abstr)

4. Helbock HJ, Insoft RM, Conte FA: Glucocorticoid-responsive hypotension in extremely low birth weight newborns. Pediatrics 92: 715-717, 1993

5. Watterberg KL, Scott SM: Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. Pediatrics 95:120-125, 1995

6. Korte C, Styne D, Merritt TA, et al: Adrenocortical function in the very low birth weight infant: Improved testing sensitivity and association with neonatal outcome. J Pediatr 128:257-263, 1996

7. Metzger DL, Wright NM, Veldhuis JD, et al: Characterization of pulsatile secretion and clearance of plasma cortisol in premature and term neonates using deconvolution analysis. J Clin Endocrinol Metab 77:458-463, 1993

8. Ng PC: The fetal and neonatal hypothalamic-pituitary-adrenal axis. Arch Dis Child 82:250F-254, 2000 (suppl)

9. Sperling MA: Newborn adaptation: Adrenocortical hormones and ACTH, in Tulchinsky D, Ryan KJ (eds): Maternal-Fetal Endocrinology. Philadelphia, PA, Saunders, 1980, pp 387-408

10. Tordjman K, Jaffe A, Grazas N, et al: The role of the low dose (1 μg) adrenocorticotropin test in the evaluation of patients with pituitary diseases. J Clin Endocrinol Metab 80:1301-1305, 1995

11. Rasmuson S, Olsson T, Hagg E: A low-dose ACTH test to assess the function of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol 44:151-156, 1996

12. Dickstein G, Shechner C, Nicholson WE, et al: Adrenocorticotropin stimulation test: Effects of basal cortisol level, time of day, and suggested new sensitive low dose test. J Clin Endocrinol Metab 72: 773-778, 1991

13. Crowley S, Hindmarsh PC, Holownia P, et al: The use of low doses of ACTH in the investigation of adrenal function in man. J Endocrinol 130:475-479, 1991

14. Daidoh H, Morita H, Mune T, et al: Responses of plasma adrenocortical steroids to low dose ACTH in normal subjects. Clin Endocrinol 43:311-315, 1995

15. Dickstein G: Low-dose ACTH test—A word of caution: When and how to use it. J Clin Endocrinol Metab 82:322, 1997 (letter)

16. Broide J, Soferman R, Kivity S, et al: Low-dose adrenocorticotropin test reveals impaired adrenal function in patients taking inhaled corticosteroids. J Clin Endocrinol Metab 80:1243-1246, 1995

17. Weintrob N, Sprecher E, Josefsberg Z, et al: Standard and low-dose short adrenocorticotropin test compared with insulin-induced hypoglycemia for assessment of the hypothalamic-pituitary-adrenal axis in children with idiopathic multiple pituitary hormone deficiencies. J Clin Endocrinol Metab 83:88-92, 1998

18. Ammari F, Issa E, Millward E, et al: A comparison between short ACTH and insulin stress tests for hypothalamo-pituitary-adrenal function. Clin Endocrinol 44:473-476, 1996

19. Abdu TA, Elhadd TA, Neary R, et al: Comparison of the low-dose short synacten test (1 μg), the conventional dose short synacten test (250 μg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 84:838-843, 1999

20. Cunningham MD, Appendix J: Septic risk scoring tables. in

Gomella TL, (ed): Neonatology Basic Management. London, UK, Prentice-Hall International, 1989, pp 422-423

21. Silverman F: Fetus and neonatal infant, in Nelson W (ed): Nelson Textbook of Pediatrics (ed 12). Philadelphia, PA, Saunders, 1983, pp 334-348

22. Karlsson R, Kallio J, Toppari J, et al: Timing of peak serum cortisol values in preterm infants in low-dose and the standard ACTH tests. Pediat Res 45:367-369, 1999

23. Chrousos GP: Stressors, stress, and neuroendocrine integration of the adaptive response. The 1997 Hans Selye Memorial Lecture. Ann NY Acad Sci 851:311-335, 1998

24. Chrousos GP, Gold PW: A healthy body in a healthy mind—And vice versa. The damaging power of "uncontrollable" stress. J Clin Endocrinol Metab 83:1842-1845, 1998

25. Weismann DN, Herrig JE, McWeeny OJ, et al: Renal and adrenal responses to hypoxemia during angiotensin-converting enzyme inhibition in lambs. Circ Res 52:179-187, 1983

26. Tyler H, Ramsey H: Altered concentrations of aldosterone in neonatal calves during chronic hypoxia and subsequent recovery period. Adv Exp Med Biol 317:521-524, 1992

27. Raff H, Jankowski BM, Goodfriend TL, et al: The effect of exposure to hypoxia from birth on aldosterone in rabbits: Role of unesterified fatty acids. Am J Physiol 272:R1084-R1087, 1997

28. Pereira DN, Procianoy RS: Transient elevation of aldosterone levels in perinatal asphyxia. Acta Paediatr 86:851-853, 1997

29. Harlin CA, Tucker JM, Winkler CL, et al: Altered adrenal steroid production in term infants having respiratory acidosis. Acta Endocrinol (Copenh) 128:136-139, 1993

30. Hanukoglu A, Fried D, Nakash I, et al: Selective increases in adrenal steroidogenic capacity during acute respiratory disease in infants. Eur J Endocrinol 133:552-556, 1995

31. Yuan S-Z, Runold M, Lagercrantz H: Adrenalectomy reduces the ability of newborn rats to gasp and survive anoxia. Acta Physiol Scand 159:285-292, 1997

32. Tuor UI, Simone CS, Arellano R, et al: Glucocorticoid prevention of neonatal hypoxic-ischemic damage: Role of hyperglycemia and antioxidant enzymes. Brain Res 604:165-172, 1993

33. Tuor UI, Del Bigio MR: Protection against hypoxic-ischemic damage with corticosterone and dexamethasone: Inhibition of effect by a glucocorticoid antagonist, RU38486. Brain Res 743:258-262, 1996

34. Melby JC, Spink WW: Comparative studies on adrenal cortical function and cortisol metabolism in healthy adults and in patients with shock due to infection. J Clin Invest 37:1791-1797, 1985

35. Alkalay A, Klein A, Nagel R, et al: Evaluation of hypothalamic-pituitary-adrenal axis in premature infants treated with dexamethasone. Pediatr Res 27:193A, 1995 (abstr)

36. Grinspoon SK, Biller BMK: Laboratory assessment of adrenal insufficiency. J Clin Endocrinol Metab 79:923-931, 1994

37. Bangar V, Clayton RN: How reliable is the short synacthen test for the investigation of the hypothalamic-pituitary-adrenal axis? Eur J Endocrinol 139:580-583, 1998

38. Meduri GV, Chrousos GP: Duration of glucocorticoid treatment and outcome in sepsis: Is the right drug used the wrong way? Chest 114:355-360, 1998

39. Meduri GU, Headley S, Carson S, et al: Prolonged methylprednisolone treatment improves lung function and outcome of unresolving ARDS. A randomized, double-blind, placebo-controlled trial. JAMA 280:159-165, 1998

40. Chrousos GP: The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: Neuroendocrine and target tissue-related causes. Int J Obesity 24:S50-S55, 2000 (suppl)

41. Vermes I, Beishuizen A, Hampsink RM, et al: Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: Possible role of endothelin and atrial natriuretic hormone. J Clin Endocrinol Metab 80:1238-1242, 1995

42. Siegel LM, Grinspoon SK, Garvey GJ, et al: Sepsis and adrenal function. Trends Endocrinol Metab 5:324-332, 1994

43. Mastorakos G, Chrousos GP, Weber JS: Recombinant interleukin-6 activates the hypothalamic-pituitary-adrenal axis in humans. J Clin Endocrinol Metab 77:1690-1694, 1993