0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(12):6380–6385

doi: 10.1210/jc.2005-0734

Effect of Dose on Response to Adrenocorticotropin in Extremely Low Birth Weight Infants

Kristi L. Watterberg, Michele L. Shaffer, Jeffery S. Garland, Elizabeth H. Thilo, Mark C. Mammel, Robert J. Couser, Susan W. Aucott, Corinne L. Leach, Cynthia H. Cole, Jeffrey S. Gerdes, Henry J. Rozycki, and Conra Backstrom

Division of Neonatology (K.L.W.) and General Clinical Research Center (C.B.), University of New Mexico School of Medicine, Albuquerque, New Mexico 87131; Health Evaluation Sciences (M.L.S.), The Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033; St. Joseph Regional Medical Center (J.S.G.), Milwaukee, Wisconsin 53210; Department of Pediatrics (E.H.T.), University of Colorado School of Medicine, Denver, Colorado 80262; Department of Pediatrics (M.C.M.), Children's Hospital of St. Paul, University of Minnesota School of Medicine, St. Paul, Minnesota 55101; Division of Neonatology (R.J.C.), Children's Hospital and Clinics of Minneapolis, Minneapolis, Minnesota 55102; Department of Pediatrics (S.W.A.), Johns Hopkins University School of Medicine, Baltimore, Maryland 21205; Department of Pediatrics (C.L.L.), State University of New York at Buffalo, Buffalo, New York 14260; Department of Pediatrics (C.H.C.), Tufts University School of Medicine, Boston, Massachusetts 02111; Newborn Pediatrics (J.S.G.), Pennsylvania Hospital, University of Pennsylvania, Philadelphia, Pennsylvania 19107; and Department of Pediatrics (H.J.R.), Virginia Commonwealth University, Richmond, Virginia 23284

Context: Various cosyntropin doses are used to test adrenal function in premature infants, without consensus on appropriate dose or adequate response.

Objective: The objective of this study was to test the cortisol response of extremely low birth weight infants to different cosyntropin doses and evaluate whether these doses differentiate between groups of infants with clinical conditions previously associated with differential response to cosyntropin.

Design: The design was a prospective, nested study conducted within a randomized clinical trial of low-dose hydrocortisone from November 1, 2001, to April 30, 2003.

Setting: The setting was nine newborn intensive care units.

Patients: The patients included infants with 500–999 g birth weight.

Intervention: The drug used was cosyntropin, at 1.0 or 0.1 μg/kg, given between 18 and 28 d of birth.

Main Outcome Measure: We measured the cortisol response to cosyntropin.

Results: Two hundred seventy-six infants were tested. Previous hydrocortisone treatment did not suppress basal or stimulated cortisol values. Cosyntropin, at 1.0 *vs.* 0.1 μg/kg, yielded higher cortisol values ($P < 0.001$) and fewer negative responses (2 *vs.* 21%). The higher dose, but not the lower dose, showed different responses for girls *vs.* boys ($P = 0.02$), infants receiving enteral nutrition *vs.* not ($P < 0.001$), infants exposed to chorioamnionitis *vs.* not ($P = 0.04$), and those receiving mechanical ventilation *vs.* not ($P = 0.02$), as well as a positive correlation with fetal growth ($P = 0.03$). A response curve for the 1.0-μg/kg dose for infants receiving enteral nutrition (proxy for clinically well infants) showed a 10th percentile of 16.96 μg/dl. Infants with responses less than the 10th percentile had more bronchopulmonary dysplasia and longer length of stay.

Conclusions: A cosyntropin dose of 0.1 μg/kg did not differentiate between groups of infants with clinical conditions that affect response. We recommend 1.0 μg/kg cosyntropin to test adrenal function in these infants. **(*J Clin Endocrinol Metab* 90: 6380–6385, 2005)**

THE APPROPRIATE DOSE of cosyntropin [ACTH-(1–24)] necessary to provide meaningful information about adrenal function is a highly debated issue in both children and adults (1–3). This is particularly true in premature infants, in which the normal response to ACTH stimulation has not been well defined (3–5). The standard cosyntropin dose of 250 μg for both adults and infants has been criticized by many as providing supraphysiological stimulation that may underestimate adrenal insufficiency (6). Lower doses, such as 1.0 μg/1.73 m^2 in adults and 0.1 μg/kg in infants, have been suggested to be more sensitive for revealing relative adrenal insufficiency, but the ability of such low doses to evaluate adrenal function in premature infants has been tested only in a small number of infants (3, 5, 7).

Several studies of premature infants have reported decreased adrenal response to stimulation in sicker infants, in those with restricted fetal growth, and in those who subsequently developed bronchopulmonary dysplasia (BPD) (4, 8–11). Conversely, infants exposed to intrauterine inflammation (chorioamnionitis) have higher responses to ACTH stimulation than those not exposed (12). As part of a randomized trial of low-dose hydrocortisone (HC) therapy to prevent BPD in extremely low birth weight (ELBW) infants (13), we tested the response of these infants to one of two different doses of cosyntropin, 0.1 or 1.0 μg/kg, to determine whether either dose would differentiate between groups of infants with clinical conditions such as those listed above.

First Published Online September 13, 2005

Abbreviations: BPD, Bronchopulmonary dysplasia; ELBW, extremely low birth weight; HC, hydrocortisone.

Based on this information, we then constructed a reference range for normal response to a specific dose of ACTH in this population.

Patients and Methods

Population

The study population included all infants enrolled in a multicenter randomized trial of early low-dose HC therapy in the first 2 wk of life to prevent BPD (13). Infants were eligible for that study between 12 and 48 h of life if they were 500–999 g birth weight and mechanically ventilated. Exclusions were major congenital anomaly, congenital sepsis, previous treatment with postnatal glucocorticoid other than HC, or at least triplet gestation. The study protocol was approved by institutional review boards at all participating institutions, and parental consent was obtained before enrollment. Sample size was planned to be 790 infants.

Design

Beginning at 12–48 h of life, infants received an equal volume of normal saline placebo or low-dose HC sodium succinate (Solu-Cortef Plain; Pharmacia & Upjohn, Kalamazoo, MI), 1 mg/kg·d (≈8–10 mg/m^2·d), divided twice a day for 12 d, followed by 0.5 mg/kg·d for 3 d. ACTH testing was performed more than 48 h after the last dose of study drug and before 28 d of life. Infants were not tested within 48 h of receiving open-label glucocorticoid.

We estimated that approximately 600 infants would survive to undergo ACTH testing. Because ongoing individual randomization would have unnecessarily increased the complexity of the clinical trial, the randomization was designed in sequence, as follows: the first 150 infants would be given 1.0 μg/kg cosyntropin (Cortrosyn; Amphastar Pharmaceuticals, Rancho Cucamonga, CA) iv or im, the second 250 infants would receive 0.1 μg/kg, and the remainder of the infants would be tested with 0.2 μg/kg. However, patient enrollment in the study was stopped due to an unexpected adverse event (increased spontaneous gastrointestinal perforation). Therefore, a 0.2-μg/kg dose could not be evaluated.

Standardized tables were used at all centers for serial dilutions of cosyntropin, and all volumes were more than or equal to 0.1 ml. Blood was obtained for cortisol determination before and 30 min after administration of cosyntropin. Specimens were analyzed in duplicate by RIA (Diagnostic Products, Los Angeles, CA) at the Tufts–New England Medical Center General Clinical Research Center. Intraassay variation was 9.1%, and interassay variation was 10.2%. Cross-reactivity was 6.8% with 11-deoxycortisol, 3.9% with cortisone, and less than 1.0% with other naturally occurring steroids.

We chose 30 min after ACTH as the time point to evaluate the cortisol response to ACTH because previous investigators have reported that response to very low-dose ACTH begins to diminish after that time (6, 7). Although response to higher-dose ACTH may continue to rise from 30 to 60 min, the difference is not marked; thus, 30 min was selected as an appropriate time point for both doses (7). We chose the peak stimulated cortisol value as the most reliable measure of adrenal response (6). Cortisol values are presented as microgram per deciliter; to convert to nanomoles per liter, multiply by 27.6.

A lack of enteral intake on the day of the test was used as a marker of acute illness. BPD was defined as supplemental oxygen therapy at 36 weeks estimated postmenstrual age. All placental histology was reviewed by one of two central readers for evidence of chorioamnionitis, defined as inflammatory cells in the placental membranes (Nancy Joste and Marcia Wills, University of New Mexico, Albuquerque, NM).

Statistical analysis

All cortisol values were log transformed for analysis, and all analyses were adjusted for gestational age. Linear mixed-effects models were used to compare cortisol values (14). Generalized estimating equations with a logit link were used to compare the number of infants who showed no rise in cortisol after stimulation (15). These analyses are extensions of multiple linear regression and logistic regression, respectively, and allow for correlation within twin gestations. Kernel density estimation was used to generate a nonparametric estimate of the probability density for the stimulated cortisol responses based on the observed cortisol values (16). All statistical tests were conducted using a significance level of 0.05.

Results

Of the 360 infants enrolled, 324 survived to the ACTH testing window, and 276 were tested. Forty-eight infants were not tested due to systemic steroid exposure (n = 25), death during the testing window (8), withdrawal of parental consent (3), or unknown reason (12). Baseline characteristics were similar between infants tested with 1.0 μg/kg and those tested with 0.1 μg/kg cosyntropin (Table 1).

Comparison between routes of administration (iv *vs.* im) (Table 2) showed that infants receiving a cosyntropin dose of 0.1 μg/kg im had a significantly lower response than those receiving the medication iv ($P = 0.02$). Therefore, the infants who had received the lower dose im were removed from all subsequent analyses. There was no difference in response between the two routes of delivery for infants receiving 1.0 μg/kg, and all values from those infants were included.

Basal and stimulated cortisol values were then compared between HC-treated and placebo infants (Table 3). Comparisons between these groups were made for both the entire population tested and the subset who were tested 48–72 h after the last dose of study drug. No differences were apparent between groups at any point; therefore, all values were combined for subsequent analyses. Thirty-three infants were tested more than 48 h after receiving open-label dexamethasone. Dexamethasone-treated infants had slightly lower basal cortisol values (median, 9.7 *vs.* 11.9 μg/dl; 268 *vs.* 328 nmol/liter). After adjusting for gestational age and basal cortisol concentration, there was no significant difference between dexamethasone-exposed and unexposed infants in the stimulated values for either dose, and these values were included in the analyses.

Basal cortisol concentrations were similar for patients receiving either dose of cosyntropin; however, stimulated cortisol values in response to 1.0 μg/kg cosyntropin were significantly higher than for 0.1 μg/kg ($P < 0.001$) (Table 4). Twenty (21%) of the infants receiving 0.1 μg/kg cosyntropin showed a negative response (*i.e.* a decrease in cortisol concentration after stimulation) compared with three (2%) of those receiving 1.0 μg/kg ($P < 0.001$).

Table 5 displays the stimulated cortisol responses for spe-

TABLE 1. Study population characteristics

Characteristic	Total population (n = 276)	Dose 0.1 μg/kg (n = 129)	Dose 1.0 μg/kg (n = 147)
Birth weight (g) (mean ± SD)	743 ± 126	755 ± 117	732 ± 133
Gestational age at birth (wk)	25.5 ± 1.6	25.8 ± 1.7	25.2 ± 1.5
Postnatal age at study (d) [median (25–75%)]	20 (19–21)	20 (19–21)	20 (19–21)
Male/female	139/137	66/63	73/74

TABLE 2. Cortisol response to iv *vs.* im injection

Cosyntropin	0.1-μg/kg dose		1.0-μg/kg dose	
	iv (n = 100)	im (n = 29)	iv (n = 129)	im (n = 18)
Baseline [μg/dl (n)]	12.1 (99) (8.4–17.5)	8.6 (29) (6.7–13.4)	10.6 (128) (7.7–14.0)	13.2 (16) (9.4–17.5)
Poststimulation [μg/dl (n)]	17.4 (98) (12.0–23.0)	13.8 (29)[a] (9.7–16.9)	24.5 (128) (20.1–33.8)	27.6 (17) (22.9–35.3)
Negative responses	20 (21%)	7 (24%)	3 (2%)	0

Cortisol values are presented as median (25th to 75th percentile) for ease of reading; however, all cortisol values were log-transformed for analysis as described in *Patients and Methods.* To convert cortisol values to nanomoles/liter, multiply by 27.6.
[a] The im dose response significantly different from iv dose response, $P = 0.02$.

cific clinical conditions. Cortisol response to the 0.1-μg/kg dose of cosyntropin was not different between groups for any of these clinical conditions. Cortisol response to the 1.0-μg/kg dose of cosyntropin was higher in girls than in boys ($P = 0.02$) and higher in infants exposed to histological chorioamnionitis ($P = 0.04$). Response was lower in acutely ill infants ($P < 0.0001$) and in those infants receiving mechanical ventilation ($P = 0.02$). There was a trend toward lower values in infants who subsequently developed BPD ($P = 0.06$). No significant correlation was found between stimulated cortisol concentrations and gestational age. However, the 1.0-μg/kg dose of cosyntropin showed a significant positive correlation with increasing birth weight for gestation ($P = 0.03$). No such correlation was seen when infants were stimulated with 0.1 μg/kg ($P = 0.24$).

Because the 0.1-μg/kg dose did not discriminate between groups for any clinical factor evaluated, we used the data from infants tested with the 1.0-μg/kg dose to construct a reference range for response to ACTH. Values from infants who were not being enterally fed on the day of the test (a marker for acute illness) were excluded from the construction of the curve (Fig. 1). The 10th percentile of this response curve was 16.96 μg/dl (468 nmol/liter). Evaluating clinical outcomes of infants with stimulated values less than 17 μg/dl *vs.* those with values more than or equal to 17 μg/dl, we found that a response of less than 17 μg/dl to a dose of 1.0 μg/kg cosyntropin was associated with an increased incidence of BPD (84 *vs.* 55%; $P = 0.046$) and an increased length of stay (for all of these infants, median of 117 *vs.* 94 d, $P = 0.025$; for survivors only, 113 *vs.* 94, $P = 0.072$). Only three tested infants subsequently died; therefore, association with mortality could not be evaluated.

Because more than 10% of the infants tested with 0.1 μg/kg had a negative response to cosyntropin, we could not construct a response curve similar to that described above for the 1.0-μg/kg dose. Therefore, after removing values obtained from infants not enterally fed on the day of the test and from those who had received cosyntropin im, we compared outcomes between the 14 infants (19%) with a negative response to the 59 infants (81%) with a positive response. There was no difference between the two groups in either incidence of BPD (36% for infants with negative responses *vs.* 56% for the group with positive responses) or length of stay (median of 95 d for infants with negative responses *vs.* 96 d for the group with positive responses).

Discussion

Adrenal function testing in preterm infants has been complicated by a lack of agreement both about the appropriate dose of cosyntropin (ACTH) to use and the appropriate response for this population. In this study, we evaluated the functional utility of two commonly used doses of ACTH by testing their ability to distinguish between groups of infants with clinical conditions associated previously with different responses to ACTH (4, 8–12). We included a very low dose (0.1 μg/kg), similar to that recommended by many for testing in other populations (6), and a 10-fold higher dose, within the range used previously by investigators describing cor-

TABLE 3. Comparison of cortisol concentrations for HC-treated *vs.* placebo infants[a]

Cortisol (μg/dl)	HC-treated (n = 128)	Placebo (n = 119)
Basal concentration (range)	11.7 (8.2–15.7) (2–156)	11.2 (8.0–15.0) (2–47)
Poststimulation, 0.1 μg/kg ACTH (range)	17.3 (11.6–23.2) (4–94)	15.5 (11.8–18.7) (5–136)
Poststimulation, 1.0 μg/kg ACTH (range)	23.6 (20.1–34.1) (4–48)	25.6 (21.5–33.4) (14–50)
Negative responses	12 (9.7%)	11 (9.4%)
Infants tested 48–72 h after study	(n = 13)	(n = 13)
Poststimulation, 0.1 μg/kg ACTH	23.5 (7.6–28.6)	12.7 (12.3–14.1)
Poststimulation, 1.0 μg/kg ACTH	31.4 (25.5–34.4)	22.8 (18.5–27.3)
Negative responses	1 (8%)	3 (23%)

Values are presented as median (25–75%) in micrograms per deciliter. To convert cortisol values to nanomoles per liter, multiply by 27.6.
[a] Infants receiving low-dose cosyntropin im have been removed because these values were lower than the iv responses for the low-dose group only (for values, see Table 2).

TABLE 4. Basal cortisol and response to cosyntropin dose of 0.1 *vs.* 1.0 μg/kg[a]

Cortisol (μg/dl)	Total population	0.1 μg/kg dose	1.0 μg/kg dose
Basal (n)	11.4 (243)	12.1 (99)	11.1 (144)
	(8.1–15.6)	(8.4–17.5)	(7.9–14.5)
Poststimulation	22.2 (241)	17.4 (98)	24.6 (145)[b]
	(16.9–31.7)	(12.0–23.0)	(20.8–34.0)
Negative responses	23 (9.5%)	20 (21%)	3 (2%)[b]

Data are presented as median (25th to 75th percentile) for ease of reading; however, all cortisol values were log-transformed for analysis as described in *Patients and Methods.* To convert cortisol values to nanomoles per liter, multiply by 27.6.

[a] Infants receiving low-dose cosyntropin im have been removed because these values were lower than the iv responses for the low-dose group only (for values, see Table 2).

[b] Significantly different from 0.1-μg/kg dose, $P < 0.001$.

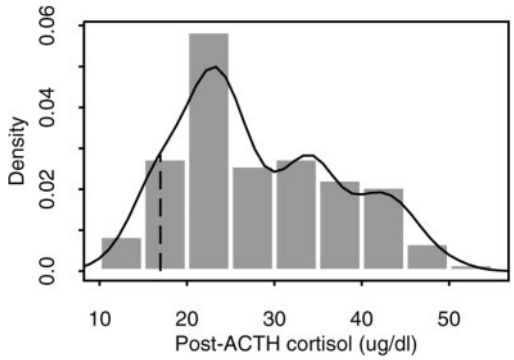

FIG. 1. Histogram of the stimulated cortisol values after a dose of 1.0 μg/kg cosyntropin, with a smoothed curve of the response superimposed. Only infants receiving enteral nutrition on the day of the stimulation test (n = 116) are included. The 10th percentile is noted by the *dotted line*, at 17 μg/dl (469 nmol/liter).

relations with clinical conditions (4, 8–12). Using these results, we then created a response curve for this population.

In this study, a cosyntropin dose of 0.1 μg/kg was not functionally useful; that is, the cortisol response to this dose was not different between groups for any of the clinical factors evaluated. Additionally, a negative response to this dose of cosyntropin did not correlate with the development of BPD or length of stay. However, the higher dose of 1.0 μg/kg did yield significantly different responses between groups in those clinical situations. Although the differences between the groups were not large, they were consistent and statistically significant, strengthening the evidence that this dose, but not the 0.1-μg/kg dose, is a useful tool to assess adrenal function in this population.

We also found a significantly higher response to that dose in girls than in boys, a finding that is consistent with the apparent increased maturity and better outcomes of premature girls compared with boys at equivalent gestational ages (17, 18). The higher dose of cosyntropin produced a more consistent response than did the lower dose. Only three patients (2%) had a negative response to the higher dose compared with a 21% negative response rate in infants who received 0.1 μg/kg. In addition, im injection of 0.1 μg/kg resulted in significantly lower responses than did iv injection, suggesting inadequate drug delivery at the lower dose, although it is possible that these patients would have shown a higher response after additional time.

Previously, Korte *et al.* (5) examined the response of very low birth weight infants to cosyntropin doses of 0.1 and 0.2 μg/kg. Those investigators defined a basal cortisol value of less than 5 μg/dl (138 nmol/liter) as diagnostic of adrenal insufficiency. When they then administered ACTH, they found that many more infants with basal values less than 5 μg/dl responded to a dose of 0.2 μg/kg than to 0.1 μg/kg. They concluded that the lower dose was more sensitive in revealing adrenocortical insufficiency; however, they did not detect any association between response to ACTH and clinical outcomes (5). In contrast, investigators using cosyntropin doses larger than 0.1 μg/kg have previously shown differences in cortisol response for factors such as acute illness (4), fetal growth (9), enteral nutrition (19), chorioamnionitis (12), and BPD (4, 10, 11). We were able to confirm these associations with an ACTH dose of 1.0 μg/kg but not 0.1 μg/kg.

Most previous studies describing a relationship of stimulated cortisol response to clinical illness in very preterm infants have been performed during the first week of life (4, 5, 9, 10, 12). In this study, we found that ELBW infants who

TABLE 5. Poststimulation cortisol values (μg/dl) separated by clinical characteristics

Clinical characteristic	Dose 0.1 μg/kg[a]		Dose 1.0 μg/kg	
	Present	Absent	Present	Absent
Female (n)	17.9 (43)	17.1 (55)	25.9 (74)	23.7 (71)[b]
	(11.8–22.8)	(11.7–20.8)	(21.9–35.6)	(18.8–31.7)
Chorioamnionitis (n)	17.3 (44)	18.0 (41)	26.6 (58)	23.6 (57)[b]
	(11.9–23.3)	(12.3–20.8)	(21.5–35.3)	(20.1–30.5)
Infant "npo" on day of test (n)	17.6 (23)	17.3 (74)	23.0 (26)	25.6 (116)[b]
	(13.1–20.8)	(12.0–23.5)	(18.4–25.0)	(21.3–35.2)
Infant ventilated on day of test (n)	17.2 (70)	18.3 (28)	23.7 (98)	26.7 (46)[b]
	(12.1–23.5)	(11.7–22.9)	(19.8–32.6)	(22.4–34.6)
BPD (n)	17.2 (54)	17.5 (41)	24.1 (84)	25.7 (58)[c]
	(11.8–21.9)	(12.7–23.0)	(19.1–33.2)	(22.0–34.4)

Data are presented as median (25th to 75th percentile) for ease of reading; however, all cortisol values were log transformed for analysis as described in *Patients and Methods.* To convert cortisol values to nanomoles per liter, multiply by 27.6. npo, No enteral nutrition.

[a] Infants receiving low-dose cosyntropin im have been removed because these values were lower than the iv responses for the low-dose group only (for values, see Table 2).

[b] Significantly different from "characteristic present," $P < 0.05$.

[c] $P = 0.06$.

continued to have significant clinical illness also continued to have a decreased response to adrenal stimulation through the first month of life. Previously, using human CRH to stimulate the adrenal axis, Ng *et al.* (20) reported that infants who were mechanically ventilated had lower stimulated cortisol values at 1 wk of life. By 2 wk of age, however, infants who continued to be mechanically ventilated had higher stimulated cortisol values than those who were not ventilated (20), suggesting that the hypothalamic-pituitary-adrenal axis rapidly adapted to extrauterine life. A difference in the maturity of the infants in the two study populations (28 *vs.* 25.5 wk) may explain why our results differ.

The large sample size of this study enabled us to construct an ACTH response curve for ELBW infants who are clinically doing well and to compare this with previous reports. It has been difficult to construct a normal response curve for ELBW infants, because so many of these infants have significant ongoing and/or intercurrent illnesses. We chose the designation "no enteral nutrition" on the day of the test as a marker of acute illness and found that those infants had a significantly lower response than infants receiving enteral nutrition. After excluding this group of infants, we found that the magnitude of the response to 1.0 μg/kg in the clinically well infants was similar to stimulated cortisol concentrations in other populations (Fig. 1), as well as similar to values seen in a previous, smaller study that separated clinically well from ill ELBW infants in the first week of life (4). Infants with responses below the 10th percentile of this curve (<17 μg/dl) had increased incidence of adverse outcomes (BPD and increased length of stay), suggesting that a lower response has physiological consequence. No such associations were seen with the lower dose of cosyntropin.

Determining an appropriate dose of and response to cosyntropin in this population is essential for evaluation of adrenal function. Relative adrenal insufficiency (insufficient adrenal reserve to respond appropriately to stress or critical illness) has been linked with cardiovascular instability and increased mortality in seriously ill adults and children (21–23). A recent multicenter trial showed that HC replacement therapy reduced mortality in adults with septic shock and relative adrenal insufficiency (24). Extremely premature infants may be at increased risk for relative adrenal insufficiency due to their developmental immaturity (25). The multicenter study in which these infants were enrolled showed reduced mortality and increased survival without BPD after low-dose HC therapy in infants exposed to chorioamnionitis (13). Conversely, infants with very high cortisol values were at higher risk for spontaneous gastrointestinal perforation (13). Whether administering an ACTH stimulation test before treating with HC would allow us to optimize the patient population treated remains to be discovered.

We conclude from this large, prospective study that a cosyntropin dose of 0.1 μg/kg, approximately equivalent to the very low-dose testing now used by many in adults (6), does not adequately assess adrenal function in ELBW infants. However, a dose of 1.0 μg/kg administered to infants who were not acutely ill on the day of testing produced a cortisol response similar to that seen in other populations. This dose also was able to distinguish between groups of infants with clinical conditions of interest in this patient population. We therefore recommend a cosyntropin dose of 1.0 μg/kg to evaluate adrenal reserve in this population.

Acknowledgments

Received April 6, 2005. Accepted September 6, 2005.

Address all correspondence and requests for reprints to: Kristi L. Watterberg, M.D., Department of Pediatrics/Neonatology, MSC10 5590, 1, University of New Mexico, Albuquerque, New Mexico 87131-0001. E-mail: kwatterberg@salud.unm.edu.

This work was supported by National Institute of Child Health and Human Development Grant R01-HD38540, General Clinical Research Centers Programs at the University of New Mexico Grant MO1 RROOO54, Tufts–New England Medical Center Grant 5MO1 RROO997, and University of Colorado Grant MO1-RROOO69.

References

1. **Chrousos GP** 2001 Clinical perspective: adrenal suppression versus clinical glucocorticoid deficiency in the premature infant: no simple answers. J Clin Endocrinol Metab 86:473–474
2. **Dickstein G** 2001 Hypothalamo-pituitary-adrenal axis testing: nothing is sacred and caution in interpretation is needed. Clin Endocrinol (Oxf) 54:15–16
3. **Karlsson R, Kallio J, Irjala K, Ekblad S, Toppari J, Kero P** 2000 Adrenocorticotropin and corticotropin-releasing hormone tests in preterm infants. J Clin Endocrinol Metab 85:4592–4595
4. **Huysman MWA, Hokken-Koelega ACS, DeRidder MAJ, Sauer PJJ** 2000 Adrenal function in sick very preterm infants. Pediatr Res 48:629–633
5. **Korte C, Styne D, Merritt TA, Mayes D, Wertz A, Helbock HJ** 1996 Adrenocortical function in the very low birth weight infant: Improved testing sensitivity and association with neonatal outcome. J Pediatr 128:257–263
6. **Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F, Lahav M** 1991 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
7. **Karlsson R, Kallio J, Toppari J, Kero P** 1999 Timing of peak serum cortisol values in preterm infants in low-dose and the standard ACTH tests. Pediatr Res 45:367–369
8. **Scott SM, Watterberg KL** 1995 Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. Pediatr Res 37:112–116
9. **Bolt RJ, van Weissenbruch MM, Popp-Snijders C, Sweep CGJ, Lafeber HN, Delemarre-van de Waal HA** 2002 Fetal growth and the function of the adrenal cortex in preterm infants. J Clin Endocrinol Metab 87:1194–1199
10. **Watterberg KL, Scott SM** 1995 Evidence of early adrenal insufficiency in babies who develop bronchopulmonary dysplasia. Pediatrics 85:120–125
11. **Watterberg KL, Gerdes JS, Cook KL** 2001 Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. Pediatr Res 50:190–195
12. **Watterberg KL, Scott SM, Naeye RL** 1997 Chorioamnionitis, cortisol and acute lung disease in very low birth weight infants. Pediatrics 99:E6
13. **Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC, Couser RJ, Garland JS, Rozycki HJ, Leach CL, Backstrom C, Shaffer ML** 2004 Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: multicenter trial. Pediatrics 114:1649–1657
14. **Laird NM, Ware JH** 1982 Random-effects models for longitudinal data. Biometrics 38:963–974
15. **Liang K-Y, Zeger SL** 1986 Longitudinal data analysis using generalized linear models. Biometrika 73:13–22
16. **Silverman BW** 1986 Density estimation for statistics and data analysis. London: Chapman and Hall
17. **Elsmen E, Hansen PI, Hellstrom-Westas L** 2004 Preterm male infants need more initial respiratory support and circulatory support than female infants. Acta Paediatr 93:529–533
18. **Hoekstra RE, Ferrara B, Couser RJ, Payne NR, Connett JE** 2004 Survival and long-term neurodevelopmental outcome of extremely premature infants born at 23–26 weeks' gestational age at a tertiary care center. Pediatrics 113:e1–e6
19. **Scott SM, Watterberg KL, Rodgers C, Hartenberger C, Merker L, Gifford K** 1998 Positive relationship of cortisol concentrations and oral nutrition to epidermal growth factor concentrations in preterm infants. Biol Neonate 74:259–265
20. **Ng PC, Lam CWK, Lee CH, Ma KC, Fok TF, Chan IH, Wong E** 2002 Reference ranges and factors affecting the human corticotropin-releasing hormone test in preterm, very low birth weight infants. J Clin Endocrinol Metab 87:4621–4628
21. **Lamberts SWJ, Bruining HA, de Jong FH** 1997 Corticosteroid therapy in severe illness. N Engl J Med 337:1285–1292

22. **Cooper MS, Stewart PM** 2003 Corticosteroid insufficiency in acutely ill patients. N Engl J Med 348:727–734
23. **Joosten KFM, De Kleijn ED, Westerterp M, De Hoog M, Eijck FCV, Hop WCJ, Voort EVD, Hazelzet JA, Hokken-Koelega ACS** 2000 Endocrine and metabolic responses in children with meningococcal sepsis: striking differences between survivors and nonsurvivors. J Clin Endocrinol Metab 85:3746–3753
24. **Annane D, Sebille V, Charpentier C, Bollaert PE, Francois B, Korach JM, Capellier G, Cohen Y, Azoulay E, Troche G, Chaumet-Riffaut P, Bellissant E** 2002 Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288:862–871
25. **Mesiano S, Jaffe RB** 1997 Developmental and functional biology of the primate fetal adrenal cortex. Endocr Rev 18:378–403

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

Erratum

The article by Illig *et al*., "Significant Association of the Interleukin-6 Gene Polymorphisms C-174G and A-598G With Type 2 Diabetes" (*J Clin Endocrinol Metab* 89:5053–5058, 2004) contains partially incorrect genotyping data that affect the described association of the *IL-6* SNPs C-174G and A-598G with type 2 diabetes. The assignment of sample ID and sample location on the test plates used for the genotyping was incorrect for some study participants. This led to altered genotypes in 222 of the 650 subjects for the SNP *IL-6 G-174C* and 180 of 607 subjects for the SNP *IL-6 A-598G*. The correction and completion of the database, which now also includes 46 additional subjects for whom at least one of the genotypes was missing in the first report, attenuated the association of the −174G and −598G alleles with type 2 diabetes. Both −174G and −598G alleles do exhibit a positive trend towards association with type 2 diabetes, but no significant associations remained. With the reference category of −174C/C, conditional logistic regression now yielded an odds ratio (OR) of 1.24 with a 95% confidence interval (CI) of 0.94–1.63 ($P = 0.14$) for the association with diabetes (original results: 1.35; 1.02–1.79; $P = 0.037$). The additional consideration of body mass index (BMI) as covariable did not alter the degree of association (OR, 1.25; CI. 0.92–1.70; $P = 0.16$). Subanalyses for men and women or for lean and more overweight subjects showed no significant differences between the groups. A corrected Table 2 is shown *below*.

For Tables 3, 4, and 5, which were also based on statistical analyses with the genotype data, only minor differences to the printed manuscript were detected. In Table 3, the impact of the C-174G SNP on BMI is not significant.

The authors regret the error and apologize for any inconvenience that this may have caused.

TABLE 1. Association of the C-174G SNP with type 2 diabetes: conditional logistic regression on type 2 diabetes patients and controls (subgroup analysis)

Model	Covariables	Subgroup	Odds ratio	CI	*P*
Additive			1.24	0.94–1.63	0.14
Additive		Men	1.25	0.87–1.79	0.23
Additive		Women	1.22	0.79–1.88	0.38
Additive	BMI		1.25	0.92–1.70	0.16
Additive		BMI ≤ 28.7	1.27	0.85–1.91	0.24
Additive		BMI > 28.7	1.24	0.80–1.90	0.34
Additive	BMI, physical activity		1.25	0.92–1.72	0.16
C/G *vs.* C/C			1.66	0.98–2.81	0.058
G/G *vs.* C/C			1.64	0.93–2.91	0.090
C/G *vs.* C/C		Men	1.78	0.89–3.59	0.11
G/G *vs.* C/C			1.72	0.81–3.63	0.16
C/G *vs.* C/C		Women	1.52	0.69–3.36	0.30
G/G *vs.* C/C			1.55	0.64–3.76	0.34
C/G *vs.* C/C	BMI		1.58	0.88–2.85	0.13
G/G *vs.* C/C			1.66	0.88–3.15	0.12
C/G *vs.* C/C		BMI ≤ 28.7	1.77	0.80–3.94	0.16
G/G *vs.* C/C			1.77	0.76–4.16	0.19
C/G *vs.* C/C		BMI > 28.7	1.67	0.77–3.62	0.20
G/G *vs.* C/C			1.63	0.69–3.85	0.26
C/G *vs.* C/C	BMI,		1.63	0.90–2.96	0.11
G/G *vs.* C/C	physical activity		1.69	0.89–3.22	0.11

Considered are models with an additive allele effect (*upper half*) as well as models with individual estimates for −174C/G and −174G/G genotypes *vs.* the −174C/C genotype.