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## ACTH and cortisol response to critical illness in term and late preterm newborns

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### Abstract

**Objective**—To determine cortisol and adrenocorticotropin (ACTH) responses to critical illness in term and late preterm newborns and examine the relationship of these values to measures of clinical illness, including markers of cardiovascular dysfunction.

**Study Design**—In this prospective observational study, we measured ACTH, baseline cortisol, and ACTH-stimulated cortisol concentrations in mechanically ventilated infants >34 weeks gestational age and <5 postnatal days. ACTH-stimulated cortisol concentrations were also measured in a comparison group of non-critically ill, non mechanically-ventilated infants. The relationship of these values to measures of severity of illness including SNAP (score for neonatal acute physiology) scores, blood pressure and vasopressor initiation was examined.

**Result**—Concentrations are presented as median [25<sup>th</sup> -75<sup>th</sup> percentile]. Baseline cortisol values in critically ill infants (n=35) were 4.6 mcg/dl [3.0-16.2]; 26 (74%) of these were <15 mcg/dl. ACTH-stimulated cortisol values were not significantly different from the comparison group (41 mcg/dl [30.3-51.8] vs.34.2 mcg/dl [25.2-43.3]). ACTH concentrations in ill infants (n=10) were 12 pg/ml [5.5-19.2]. Neither baseline cortisol, stimulated cortisol nor ACTH increased significantly with increasing severity of illness. 71% of the ill infants received vasopressor therapy for hypotension. Cortisol concentrations in these infants were similar to those infants who did not receive vasopressor therapy.

**Conclusion**—The majority of these critically ill newborns had very low cortisol and ACTH values without the expected increase in response to critical illness; however, their response to exogenous ACTH was normal. These results demonstrate that the inadequate response to critical illness in these newborns does not result from adrenal dysfunction. We therefore hypothesize that this is a secondary insufficiency arising from inadequate stimulation of the adrenal gland.

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There is no potential conflict of interest relevant to this article of any author.

## Keywords

adrenal insufficiency; hypothalamic-pituitary-adrenal axis; cortisol; newborn; critical illness; hypotension

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## Introduction

Relative adrenal insufficiency, a concept which has gained increasing attention in recent years, occurs when cortisol concentrations do not rise appropriately in response to stress or illness. Different investigators, using various definitions, have reported a 5 to 50% incidence of relative adrenal insufficiency (AI), or inappropriately low cortisol values, in children and adults with critical illness.<sup>1-6</sup> Low cortisol values and/or inadequate responses to adrenocorticotrophic hormone (ACTH) stimulation have been found to correlate with increased mortality and morbidity, in particular cardiovascular dysfunction with vasopressor-resistant hypotension.<sup>2,7-14</sup> The etiology of relative AI in critical illness is unknown in most cases but may result from changes in the hypothalamic-pituitary-adrenal (HPA) axis at the central or adrenal level.<sup>14,15</sup> A recently proposed definition for relative AI in critically ill adults is a random cortisol concentration of <15 mcg/dl or an increase of <9 mcg/dl in response to ACTH stimulation.<sup>6,14</sup>

There is scant information regarding occurrence or manifestations of relative AI in the late preterm and term newborn infant. Although several small series have reported a high incidence of low cortisol values in sick term infants, there is no currently accepted definition of relative AI in these infants.<sup>16-20</sup> However, newborn infants may constitute a population uniquely vulnerable to relative AI, as their HPA axis transitions from fetal to extrauterine function. Specifically, the placenta produces large amounts of corticotrophin releasing hormone (CRH) during the latter part of gestation, stimulating the fetal HPA axis.<sup>21-23</sup> We postulate that the sudden loss of this high concentration of CRH at delivery may compromise the ability of the HPA axis to respond to critical illness during the immediate newborn period, leading to relative AI in this population. Therefore, we hypothesize that many acutely ill term and late preterm newborn infants have relative AI, manifested as cardiovascular dysfunction with hypotension. We undertook this prospective cohort study to evaluate cortisol and ACTH concentrations in newborn infants receiving mechanical ventilation, to compare their values to a population of non-critically ill infants, and to investigate the relationship of these values to measures of illness severity, including markers of cardiovascular function.

## Methods

### Patient Population

This study was a single site, prospective, observational study of newborn infants admitted to the University of New Mexico (UNM) Newborn Intensive Care Unit (NICU) between January 2003 and July 2007. The institutional review board of the UNM Health Sciences Center approved the study and informed parental consent was obtained. Eligible ill patients included all infants < 5 days of age with an estimated gestational age (GA)  $\geq$  34 weeks and

who were critically ill as prospectively defined by the initiation of intubation and mechanical ventilation for respiratory failure. A comparison group of non-critically ill infants 34 weeks estimated GA admitted to the NICU was also enrolled, defined as infants who had never been mechanically ventilated or received vasopressors, were enterally fed, who had scores for neonatal acute physiology (SNAP-I) <3 (Richardson 1993), 24 and who were not hypoglycemic at the time of testing.

### Study Procedures

Data collected included infant characteristics, diagnoses, vital signs, fluid intake, ventilator settings and laboratory values; initiation of vasopressors and glucocorticoids for the treatment of hypotension; and days on mechanical ventilation. Clinical severity of illness measures included the lowest recorded mean blood pressure within 24 hours before and 24 hours after the baseline cortisol, initiation of vasopressor or hydrocortisone therapy by the medical care team, days on mechanical ventilation and SNAP scores. Two SNAP scores were obtained; 24 hours before and 24 hours after the baseline cortisol. The highest SNAP score was used for analysis.

Adrenal function studies were performed on the day of study entry. In the group of critically ill infants, blood (1 ml) was drawn for cortisol and ACTH concentrations, after which a low dose (1 mcg/kg) of cosyntropin (1-24 ACTH) was administered intravenously (IV). A second blood specimen (0.5 ml) was drawn 60 minutes later for a stimulated cortisol concentration. Increment cortisol was defined as the difference between the stimulated and baseline cortisol value. In the comparison group of non-critically ill infants, a single specimen was obtained 60 minutes after IV or intramuscular (IM) cosyntropin administration, for a stimulated cortisol concentration. We have previously demonstrated that IM administration of this dose of cosyntropin results in cortisol values similar to IV administration in a newborn population.<sup>25</sup> Baseline cortisol values were not obtained in this group because non-critically ill newborn patients would be expected to have low basal cortisol values in the absence of acute illness<sup>26</sup> and to reduce blood sampling. Cortisol concentrations were measured by radioimmunoassay (Coat-a-count kit, DPC, Los Angeles CA) in the core laboratory of the General Clinical Research Center (GCRC) at UNM. Blood for ACTH testing was placed in a cold EDTA tube, centrifuged cold and frozen at -70°C until analysis by chemiluminescence immunoassay (Immulite 2000 instrument, DPC, Los Angeles CA) in the clinical laboratory of the University Hospital.

### Statistical Analysis

Patient characteristics, cortisol values and measures of severity of illness were compared between groups using the Student t test. Data that were not normally distributed was log transformed prior to analysis. Fisher's exact test was used to compare measures of severity of illness between ill infants with relative AI and those without using 2 different definitions of relative AI. First, we defined relative AI as a random baseline cortisol concentration <15 mcg/dl, based on studies in other populations and on our previous study in critically ill newborns.<sup>16</sup> Second, we evaluated the utility of the median cortisol value in this population as a cutoff for relative AI. Correlations of cortisol and ACTH values with SNAP scores, lowest mean blood pressures, birth weights and gestational ages were analyzed with the

Spearman correlation. Data are presented as mean  $\pm$  standard deviation or as median [25%-75% percentile]. Two infants received a dose of hydrocortisone (1 mg/kg) prior to study: one at 11 hours before testing, and one at 17 hours before testing. The cortisol concentrations in these infants were 3.0 and 11.1 mcg/dl, respectively, and are included in the analyses. The level of significance was set at  $p < 0.05$ . Statistical analysis was performed using NCSS 2007 (Hintze, J. (2006), Kaysville, Utah).

## Results

Of the 183 critically ill infants screened, 102 were ineligible and 46 had parent refusal. Of the 293 comparison infants screened, 113 were ineligible and 155 had parent refusal. Thirty-five critically ill infants and 25 comparison infants were enrolled. Admitting diagnoses in the critically ill infants included meconium aspiration syndrome (MAS) with persistent pulmonary hypertension (PPHN) (40%), suspected pneumonia (23%), persistent pulmonary hypertension of unknown etiology (8.5%), gastroschisis (8.5%), respiratory distress syndrome (RDS) (8.5%), congenital diaphragmatic hernia (8.5%), and non-cardiac, non immune hydrops of unknown etiology (3%). No infant received etomidate or extracorporeal membrane oxygenation and there were no deaths. No infant received any glucocorticoid except hydrocortisone for hemodynamic instability. The comparison group included 22 infants who were  $< 5$  days of age and 3 infants between 8-12 days of age. The mean ACTH-stimulated cortisol value in the 3 infants did not differ from the infants  $< 5$  days of age and were included in the analysis. The admission diagnoses for the comparison group included hypoglycemia secondary to maternal diabetes, transient tachypnea of the newborn, poor feeding, and/or hyperbilirubinemia. Population characteristics are shown in Table 1. The critically ill infants who received vasopressors had significantly higher gestational ages, birth weights and SNAP scores and lower mean blood pressures than those not receiving vasopressors. Those infants receiving vasopressors had a different distribution of disease than those not receiving vasopressors. Eighty-four percent of infants who received vasopressors had MAS and/or PPHN while 70% of those not receiving vasopressors had RDS or pneumonia without documented PPHN. This difference in diagnoses likely accounts for the observed difference in gestational age and birth weight in the two groups.

Baseline cortisol, stimulated cortisol, and ACTH values are shown in Table 2. There was no significant difference in baseline cortisol values between those critically ill infants receiving vasopressors vs. those not. Similarly, when the ill infants who were treated with hydrocortisone (after the cortisol concentrations were obtained) were compared to those not, baseline cortisol values were similar (4.5 mcg/dl [3.6-15.4] vs. 5.6 mcg/dl [2.8-20.4],  $P = 0.8$ ). Overall, the baseline cortisol values were quite low in the critically ill infants: the median value was 4.6 mcg/dl, and 74% of the infants had concentrations  $< 15$  mcg/dl. However, ACTH-stimulated cortisol values in the critically ill patients, despite having a lower median postnatal age than the non-critically ill group (1 day vs. 2 days), were not statistically different from the non-critically ill group ( $P = 0.06$ ) and were not different in infants receiving vs. not receiving vasopressors ( $P = 0.3$ ). All ACTH-stimulated cortisol concentrations were  $> 18$  mcg/dl and all increment cortisol values were  $> 9$  mcg/dl. ACTH values obtained in 10 critically ill patients, all of whom were receiving vasopressors, were a median of 12 pg/ml [5.5-19.2].

There were no significant differences between critically ill infants with cortisol values <15 vs. 15 mcg/dl or < 4.6 vs. 4.6 mcg/dl in SNAP scores, vasopressor initiation, hydrocortisone therapy, or days on mechanical ventilation (Table 3). There was no correlation between SNAP scores and ACTH, baseline or stimulated cortisol values (Figure 1) or between lowest mean blood pressures and baseline cortisol values (Figure 2). No correlation existed between gestational age and baseline ( $\rho=-0.02$ ,  $P=0.9$ ) or stimulated ( $\rho=0.09$ ,  $P=0.7$ ) cortisol values, nor between birth weight and baseline ( $\rho=-0.1$ ,  $P=0.5$ ) or stimulated ( $\rho=-0.2$ ,  $P=0.2$ ) cortisol values.

## Discussion

In this prospective cohort study of cortisol and ACTH response to critical illness in term and late preterm newborn infants, we found that 74% of these infants had cortisol concentrations below the threshold values used to define relative adrenal insufficiency in other populations. 14 Cortisol concentrations in these infants did not increase with increasing severity of illness as measured by the SNAP-I score, and were no higher in infants treated with vasopressor support for hypotension than in those not treated. However, all the infants tested responded appropriately to low-dose ACTH stimulation, achieving cortisol concentrations similar to the non-critically ill, comparison infants in this study and to values previously reported in well term infants ( $38.1 \pm 5$  mcg/dl).<sup>18</sup> In addition, these critically ill infants had ACTH concentrations much lower than those seen in other patients responding appropriately to critical illness.<sup>2,10,27,28</sup> Taken together, these findings indicate that the adrenal glands in these infants have the capacity to secrete cortisol in response to stimulus, but that they are not receiving such stimulus from the pituitary, despite critical illness and evidence of cardiovascular dysfunction.

Studies in adults have led to the proposal that a random cortisol value of <15 mcg/dl is *prima facie* evidence of relative adrenal insufficiency in critically ill patients, and that values between 15 - 25 (or 35) mcg/dl warrant ACTH stimulation to evaluate for its presence.<sup>7,14,<sup>x</sup></sup> In children, Joosten et al reported a median cortisol value of 32 mcg/dl in patients recovering from meningococcal sepsis, compared with 22 mcg/dl in those who died from the disease.<sup>2</sup> These investigators also reported higher ACTH concentrations (median, 49.1 pg/ml) in the surviving patients on admission, and even higher (median, 262 pg/ml) in those that died, compared to our population.

In contrast to other patient populations, there is little published information on adrenal function and its relationship to hypotension and clinical illness severity in term and late preterm infants. Small series have reported a high incidence of low cortisol values in this population. Thomas et al found that 3 of 11 sick term infants had undetectable cortisol values.<sup>29</sup> Pittinger and Sawin reported that 27 of 34 cortisol values in 10 infants with congenital diaphragmatic hernia were <7 mcg/dl.<sup>17</sup> Tantavit and colleagues reported that 6 of 7 critically ill, hypotensive term newborns had cortisol values <15 mcg/dl and responded to dexamethasone with hemodynamic stabilization.<sup>20</sup> Soliman et al reported that 11 of 30 septic term newborns had basal cortisol values < 15 mcg/dl.<sup>18</sup> Of these infants, 4 had an inadequate response to ACTH stimulation defined as a change in cortisol of <20 mcg/dl; these infants had a high mortality rate compared to those infants with significantly higher

basal and ACTH-stimulated cortisol values. We previously reported that 56%, compared to 77% in this current study, of ill term and late preterm infants receiving vasopressor support had cortisol values < 15 mcg/dl and that those infants responded to hydrocortisone therapy.<sup>16</sup>

In this study, there appeared to be no relationship between cortisol values, either basal or stimulated, and severity of illness; however, only 9 of 35 infants had basal concentrations >15mcg/dl and only 3 had values > 25 mcg/dl, the value considered to represent a clearly adequate response to critical illness in adult populations.<sup>14</sup> We did not find that any specific cortisol value defined a population responding appropriately to critical illness. In addition, 8 of the 10 infants in our study had an ACTH concentration <18 pg/ml which is well below the range anticipated in critically ill patients, suggesting that the HPA axis was not responding as expected to critical illness in these infants. <sup>2,10,27,28</sup>

Our findings of low cortisol and low ACTH concentrations, but appropriate response to exogenous ACTH in these infants, demonstrate that the inadequate response to stress observed in these infants is not due to primary dysfunction of the adrenal gland itself. We hypothesize that these infants instead have a secondary adrenal insufficiency. We postulate that the newborn is uniquely susceptible to adrenal insufficiency due to shifts in hormone exposure during transition to extra-uterine life. The human placenta synthesizes large amounts of CRH, which is released into the maternal and fetal circulations, resulting in serum concentrations of CRH far higher than at any other time in life.<sup>23</sup> At parturition, there is an abrupt cessation of CRH delivery from the placenta to the infant. We propose either that the hypothalamus of the newborn is unprepared to secrete CRH or that the pituitary gland, having been exposed prenatally to very high concentrations of CRH, is transiently refractory to the lower concentrations of CRH normally produced by the hypothalamus. We did not measure CRH in these infants, and therefore cannot address these two possibilities. If the newborn is well, this brief refractory period can be well-tolerated; however, if the infant is ill, a state of relative adrenal insufficiency and cardiovascular compromise may ensue.

Limitations of this study include the increasing use of hydrocortisone to treat vasopressor-resistant hypotension during the study period. More than half of our patients received hydrocortisone, which may have confounded our ability to determine the association of cortisol concentrations with measures of illness or outcome. We previously found that infants with cortisol values <15 mcg/dl responded to hydrocortisone treatment with improvement in clinical measures of cardiovascular function, whereas those with cortisol values > 15 mcg/dl did not. A second limitation is that we did not measure cortisol binding globulin in these infants. Although newborns have been reported to have lower cortisol binding globulin concentrations, the modest decrease would not account for differences in cortisol concentrations. One study in adults with critical illness suggested that lower serum binding proteins can account for low total cortisol concentrations and inappropriate diagnoses of relative AI.<sup>30</sup> However, most of the older patients in that study had been ill for a prolonged period of time whereas the patients in our study were all tested in the first five days of life.

In summary, we found that a large majority of the critically ill term and late preterm newborn infants in this cohort had low cortisol concentrations, consistent with a relative adrenal insufficiency. Because they also had low endogenous ACTH concentrations with a normal response to low-dose exogenous ACTH, this appears not to be an insufficiency of the adrenal gland itself, but instead a secondary insufficiency due to inadequate stimulation of the gland. We speculate that these infants experience a transient relative adrenal insufficiency due to withdrawal of placental CRH at the time of delivery. These findings, if validated by randomized clinical trials, suggest that low dose hydrocortisone replacement may be a more appropriate therapy than vasopressors in these infants, treating the etiology rather than the symptom of cardiovascular dysfunction in critically ill newborn infants.

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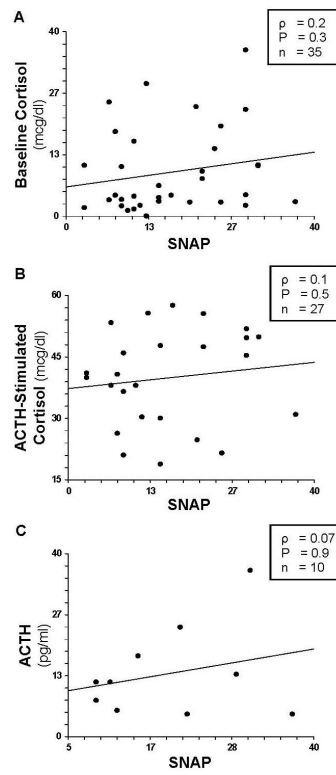
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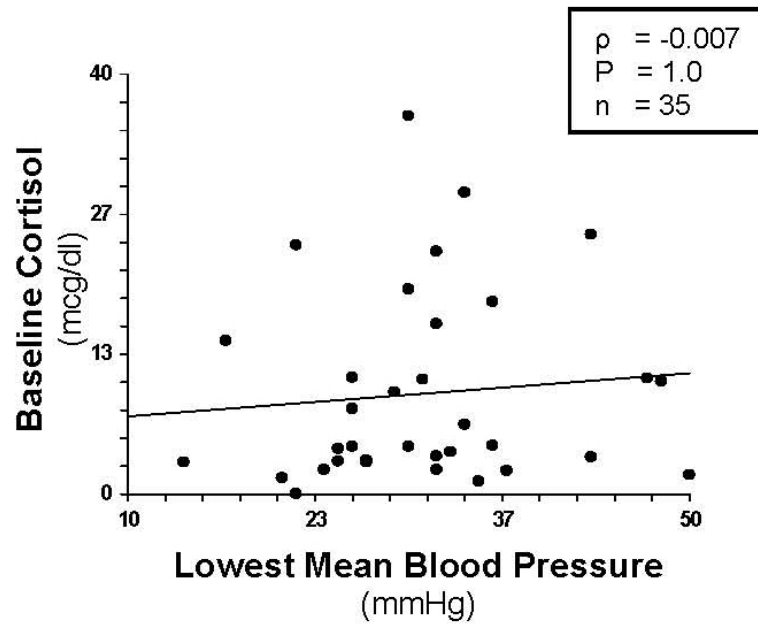
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**Figure 1.**

Critically ill infants. A. SNAP vs. baseline cortisol (1 cortisol value of 99 mcg/dl not shown but included in analysis); B. SNAP vs. ACTH-stimulated cortisol (2 values of 103 and 130 mcg/dl not shown but included in analysis); C. SNAP vs. ACTH. Analyzed with Spearman's correlation ( $\rho$ ).



**Figure 2.** Critically ill infants. Lowest mean blood pressure 24 hours before or 24 hours after baseline cortisol vs. baseline cortisol. Analyzed with Spearman's correlation ( $\rho$ ).

**Table 1**

## Demographic and Clinical Characteristics of the Study Population

<i>Patient Characteristics</i>	<b>Non-critically ill infants (n=25)</b>	<b>Critically ill infants</b>		
		<i>All (n=35)</i>	<i>NOT receiving vasopressors (n=10)</i>	<i>Receiving vasopressors (n=25)</i>
Gestation (weeks)	38.1 ± 1.9	38.1 ± 2.1	36.2 ± 0.9 *	38.8 ± 2.0
Birth weight (g)	3240 ± 737 †	3046 ± 674	2612 ± 573 *	3221 ± 640
Inborn n (%)	19 (79) †	14 (40)	3 (30)	11 (44)
Male n (%)	14 (56)	24 (69)	9 (90)	15 (60)
Postnatal age (days)	2 [1-4] †	1 [0-1]	1 [1-2]	1 [0-1]
SNAP-I score	1 [0-2] †	15 [9-25]	8.5 [6-14] *	21 [12-29]
Lowest mean blood pressure (mmHg)	--	30 [25-35]	40 [33-47] *	27 [24-32]

Mean +/-SD

Median [25%-75% percentile]

\* P&lt;0.05, critically ill infants not receiving vasopressors vs. those receiving vasopressors

† P&lt;0.05, non-critically ill infants vs. all critically ill infants

**Table 2** Cortisol Concentrations Compared Between Non-Critically Ill Infants and Critically Ill Infants and Between Critically Ill Infants not on Vasopressors vs. on Vasopressors

Cortisol Values	Non-critically ill infants	Critically ill infants			P-value
		All	NOT receiving vasopressors	Receiving vasopressors	
Baseline cortisol (mcg/dl)	--	4.6 [3.0-16.2] n=35	10.9 [3.9-19.9] n=10	4.5 [2.7-12.9] n=25	0.4
ACTH-stimulated cortisol (mcg/dl)	34.2 [25.2-43.3] n=25	41.0 [30.3-51.8] n=27	40.9 [37.6-56.1] n=10	45.3 [25.5-49.7] n=17	0.3
Increment cortisol (mcg/dl)	--	28.0 [18.8-42.6] n=27	27.9 [25.0-41.9] n=10	28.0 [18.0-42.8] n=17	0.7
Baseline cortisol < 15 (mcg/dl) (n(%))	--	26 (74)	6 (60)	20 (80)	0.2
Baseline cortisol > 4.6 (mcg/dl) (n(%))	--	18 (51)	4 (40)	14 (56)	0.4

Median [25%-75% percentile]

P-value= critically ill infants not receiving vasopressors vs. those receiving vasopressors

\* = P < 0.05

**Table 3**  
Severity of Illness Measures Compared Between Groups with Different Cutoff Baseline Cortisol Values

Measures of severity of illness	Critically ill infants, Cortisol 15 mcg/dl (n=9)	Critically ill infants, Cortisol 4.6 mcg/dl (n=26)	Critically ill infants Cortisol 4.6 mcg/dl (n=17)	Critically ill infants Cortisol < 4.6 mcg/dl (n=18)	P-value
SNAP score	13 [10-27]	15 [9-24]	21 [10-27]	13 [9-21]	0.4
Received vasopressor(s) n (%)	5 (56)	20 (77)	11 (65)	14 (78)	0.5
Received hydrocortisone n (%)	5 (56)	13 (50)	9 (50)	9 (50)	1.0
Days on mechanical ventilation	7 [3-10]	7 [5-10]	7 [5-11]	7 [3-9]	0.7

Median [25%-75% percentile]

P-value= Critically ill infants with Cortisol 15 vs. < 15 mcg/dl or Cortisol 4.6 vs. < 4.6 mcg/dl