Cortisol Levels in Healthy Term and Preterm Appropriate for Gestation Infants

Koripadu Seshagiri[1], Yanamandala Venkata Harischandra[2]

ABSTRACT

Introduction: Cortisol levels in term and preterm neonates are affected by various factors namely gestational age, postnatal age, sickness and antenatal steroids. There is no normative data on cross-sectional values of serum cortisol levels in preterm babies at various gestations. Previous studies have been on longitudinal data based on postnatal age. Study objective was to study cortisol levels in healthy term and preterm appropriate for gestation infants at various gestations.
Material and Methods: This Prospective observational study was done in Gitam Institute Of Medical Sciences and Research Institute and Omni Rk hospital Visakhapatnam in a level lll neonatal unit. Only appropriate for gestation and healthy Preterm neonates ≥ 30 weeks of gestation and term neonates ≥37 weeks of gestation were included. Babies were stratified in to four groups i) 30-32 weeks (group 1), ii) 33-34 weeks (group 2), iii) 35-36 weeks (group 3) and ≥ 37 weeks were taken in the term category (group 4). Outcomes: The primary outcome measures were mean, median and 10th and 90th centile values of the serum cortisol levels in healthy preterm and term AGA neonates on day 3 and on day 7. Secondary outcome measures were effect of various peripartum factors on cortisol levels.
Results: Of the total 86 babies included, 21 babies were there each in-group 1, 2 and 4, and 23 babies in-group 3 and cortisol estimation was done. The mean cortisol value was lowest on day 3 (295±184 nmol/L) and day 7 (221±155 nmol/L) in term babies as compared to 3 preterm subgroups (303±202 nmol/L, 310±196 nmol/L, 316±274 nmol/L on day 3 and 359±268 nmol/L, 280±210 nmol/L, 228±236 nmol/L on day 7 in group 1,2 and 3 respectively.) In all groups mean and median cortisol levels showed a declining trend from day 3 to day 7 except in group 1 where the mean cortisol level increased from day 3 to day 7 though this increase was not statistically significant. The increase in cortisol level on day7 was also seen in the preterms who received antenatal steroids vs no steroid (291±197 nmol/L and 329±251 nmol/L on day 3 and day 7 vs 362±212 nmol/L and 282±250 nmol/L on day 3 and day 7 respectively).
Conclusions: In neonates the cortisol levels were inversely related to gestational age and showed a progressive decline from day 3 to day 7 however in preterm babies who received antenatal steroid this effect was altered. Amongst perinatal factors, prolonged rupture of membrane had highest cortisol level.

Keywords: Cortisol Levels, Antenatal Steroid

INTRODUCTION

Adrenal steroidogenesis studied extensively in term and preterm infants.[1-5] Normally with increasing gestational age, umbilical cord cortisol levels increases. The serum cortisol concentrations are maximum at the time of birth, and with rapid involution of adrenal glands cortisol levels reach nadir at 24 to 36 hours of life and again increases to attain stable infancy levels by 5 days.[6-10] Study by Jett et al[3] has shown that single random sample of serum cortisol level is representative of serum cortisol level over a prolonged period of time and thus can provide assessment of functional status of adrenal cortex in low birth weight infants. Normative data on cross-sectional values of serum cortisol levels are not available in preterm babies at various gestations. Previous studies have quoted longitudinal cortisol levels in preterm babies who matured to term babies. Cortisol levels were estimated according to post conceptional age. As cortisol levels vary with postnatal age, these levels do not represent the actual cortisol levels for that gestational age in the early neonatal period.

Apart from postnatal age serum cortisol levels are affected by gestational age, sickness and antenatal steroids. Some of the authors have described negative correlation between the basal cortisol levels and gestational age[11-13], where as others have not found any such relationship.[1,15] There are only few studies available regarding the normal cortisol levels in healthy term and preterm infants. Among the available studies there is wide variability in definition of healthy infants, range of normal cortisol levels is wide and also results of various studies are conflicting. Hence we undertook this study to define cortisol levels in various gestational ages on day 3 and day 7.

MATERIAL AND METHODS

Prospective observational study was conducted at Level lll neonatal unit in GIMSR and Omni RK hospital Visakhapatnam from November 2015 to Dec 2016.

Inclusion criteria: Healthy preterm neonates between 30-36 weeks of gestation and term neonates ≥ 37 weeks of gestation were enrolled in the study. Gestational age was assessed by last menstrual period and new Ballard score. Only healthy and appropriate for gestation babies (AGA) were included in the study. AGA was assessed by Lubchenco's intra uterine

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growth chart.

Exclusion Criteria: Babies with major congenital malformations, chromosomal anomalies, suspected or proven endocrine abnormality, babies born by multiple gestation, born to mother who received more than one course of antenatal steroids, Birth asphyxia with APGAR < 6 at 1 min and / or evidence of hypoxic ischemic encephelopathy (HIE) and whose mothers on chronic steroid treatment were excluded.

Secondary exclusion criteria: Among the enrolled babies who developed hypotension (Mean arterial pressure < 2 SD for the gestation), respiratory distress, apneas requiring bag and mask and / or ventilation, congestive cardiac failure, sepsis (screen or culture positive), seizures, IVH grade II or more, metabolic derangement's (hypoglycemia, hyperglycemia, symptomatic polycythemia), anemia requiring blood transfusions, jaundice requiring exchange transfusion and babies requiring steroids for any illness before the cortisol estimation were excluded from the study.

Methods: Babies were stratified in to four groups 30-32 weeks of gestation (group 1),33-34 weeks of gestation (group 2), 35-36 weeks of gestation (group 3) and ≥ 37 weeks were taken in the term category (group 4). The base line information of mothers including detailed maternal history, maternal complications: antepartum hemorrhage, intra uterine growth retardation, pregnancy induced hypertension, eclampsia, diabetes mellitus, anemia, duration of labor, duration of rupture of membranes, antenatal steroids, number of doses, interval between last dose and delivery, fetal distress, mode of delivery and APGAR score at birth were recorded. Neonatal details included birth weight, gestational age, sex and illness. Sample size calculations

In a study by Wiener et al[7] cortisol levels (mean ± SD) in healthy term babies was 6.2 ± 3.8 µg/dL. In our study with the intention of picking the mean whose total width of 95% confidence interval within 3.5 µg/dL, we intend to sample 21 babies in term group. In a study by Rokicki et al[8] cortisol levels (mean SD) in healthy preterm babies was 9.15 ± 7.1 µg/dL. In our study with the intention of picking the mean whose total width of 95% confidence interval within 3.5 µg/dL, we intend to sample 65 babies in preterm group.

Cortisol estimation: The enrolled babies were sampled on third morning of life (48-72 hrs) and on seventh morning of life. One ml of blood was collected by venepuncture in a vial containing 1 drop of heparin and mixed well. The sample was collected between 7 am and 8 am. Cortisol estimation was done by specific Radio immuno assay (RIA) method.[16] The reference range of our assay system had lower minimum of 37 nmol/L and upper limit of 1200 nmol/L and intra and inter assay coefficient of variation of < 8% and cortisol estimation was done with duplicate samples.

Outcome variable: The primary outcome measures were mean, median and 10th and 90th centile values of the serum cortisol levels in healthy preterm and term AGA neonates on day 3 and on day 7. Secondary outcome measures were effect of various peripartum factors like antenatal steroids, duration of labour, duration of rupture of membranes, maternal complications, fetal distress and mode of delivery on serum cortisol levels.

Ethical approval of the study was obtained from the research ethics committee of the PGIMER Hospital. Informed parental consent was obtained for each infant before enrollment.

STATISTICAL ANALYSIS

Continuous numerical variables of demographic characteristics expressed as mean and standard deviation. Cortisol levels of various groups were calculated as mean and standard deviation, range, median and 10th and 90th percentile. The means were compared between 2 groups by students t test, among multiple groups by ANOVA and for skewed data, Kruskal Wallis test was applied. A level of p value < 0.05 accepted as statistically significant.

RESULTS

A total of 125 babies were initially enrolled, 40 babies in-group 1, 32 babies in group 2, 30 babies in group 3 and 23 babies in group 4. After exclusion of babies due to secondary exclusion criteria and inadequate blood samples finally 21 babies each in group 1, group 2 and group 4 and 23 babies in group 3 completed the study. Hence cortisol estimation was done in total of 86 babies on day 3 and day 7. Demographic data of the babies in 4 groups given in

The mean cortisol levels were least in-group 4 and were nearly similar in other 3 preterm groups on day 3 which were statistically not significant. Similarly no statistical significant difference was present in the median day 3 cortisol levels among the various groups (p value 0.991). The term babies had a lesser cortisol levels than preterm babies though it was statistically not significant (Table 2).

On day 7 in-group 1 the mean cortisol was 395 ± 268 nmol/L and the range was from 80 nmol/L to 1050 nmol/L. Median cortisol level was 280 nmol/L and 10th and 90th centiles were 132 nmol/L and 280 nmol/L respectively. Unlike day 3 there was a decreasing trend of mean cortisol levels with increasing gestation. However the declining trend of mean and median cortisol levels with increasing gestation was not statistically significant. In each individual group mean and median cortisol levels showed a declining trend from day 3 to day 7. But in-group 1 the mean cortisol level increased from 303 ± 202 nmol/L to 359 ± 268nmol/L from day 3 to day 7 but this increase was not statistically significant (Table 3).

The babies (≤ 34 weeks) who received antenatal steroids had lower cortisol levels on day 3 as compared to those who did not receive and they showed an increase in cortisol levels on day 7 which is in contrary to the normally decreasing trend of cortisol levels alogwith increasing postnatal age (Table 4). Duration of labor (DOL), maternal complications, fetal distress and Caesarian section had no effect on cortisol levels either on day3 or day 7. The babies who had more than 12 hours of rupture membrane had higher cortisol levels on

	Group 1 (30-32 Wk.) (n=21)	Group 2 (33-34 Wk.) (n=21)	Group 3 (35-36 Wk.) (n=23)	Group 4 (≥ 37 Wk.) (n=21)
Gestation (weeks) (Mean ± SD)	31.86 ± 0.48	33.81 ± 0.4	3530 ± 1.07	38.85 ± 2.46
Birth Weight (grams) (Mean ± SD)	1542 ± 245	1776 ± 237	2099 ± 246	3145 ± 335
Sex ratio (M/F)	1.1 : 1	2.4 : 1	0.9 : 1	1.6 : 1
Duration of labor (hrs) (Mean ± SD)	9 ± 7	10 ± 7	10 ± 6	9 ± 7
Duration of rupture of membranes (hrs) (Mean ± SD)	36 ± 44	11 ±14	8 ± 11	5 ± 4
Maternal Complication	3 (14%)	6 (28%)	4 (17%)	3 (14%)
Antenatal steroids	18 (85%)	15 (71%)	2 (8%)	0
Oxytocin	3 (14%)	2 (8%)	4 (17%)	1 (4%)
Fetal Distress	0	1	1	3
Normal vaginal delivery (%)	23.8	28.5	30.4	66.6
Caesarian (%)	76.2	71.5	69.6	33.3
APGAR (1 min.) Median	8	8	8	8
APGAR (5 min.) Median	9	9	9	9

Table-1: Group wise demographic characteristics

Cortisol levels (nmol/L)	Group 1 (n=21)	Group 2 (n=21)	Group 3 (n=23)	Group 4 (n=21)
Mean ± SD	303 ± 202 *	310 ± 196 *	316 ± 274 *	295 ± 184 *
Range	60-800	68-760	56-1200	36-700
90th centile	744	712	728	576
75th centile	310	390	400	437
50th centile	230	280	220	260
25th centile	197	160	115	120
10th centile	115	89	86	63
* P value 0.991				

Table-2: Cortisol levels (nmol/L) in 4 sub groups on day 3.

Cortisol levels (nmol/L)	Group 1 (n=21)	Group 2 (n=21)	Group 3 (n=23)	Group 4 (n=21)
Mean ± SD	359 ± 268*	280 ± 210*	228 ± 236*	221 ± 155*
Range	80-1050	95-960	37-1140	38-640
90th centile	840	516	532	444
75th centile	580	420	260	330
50th centile	280	200	150	151
25th centile	155	120	107	92
10th centile	132	98	43	58
*P value 0.173				

Table-3: Cortisol levels (nmol/L) in 4 sub groups on day 7

	Antenatal Steroid (n= 33)	No Antenatal Steroid (n=9)	P Value
Gestation (weeks) (mean ± SD)	32.70 ± 1.07	33.33 ± 1.00	0.761
Birth Weight (gms) (mean ± SD)	1645 ± 270	1711 ± 260	0.650
Day 3 Cortisol (nmol/L)	291 ± 197	362 ± 212	0.723
Day 7 Cortisol (nmol/L)	329 ± 251	282 ± 250	0.873

Table-4: Cortisol levels (nmol/L) in babies (≤34 weeks, group 1 and group 2) who received steroids versus no antenatal steroids on day 3 day 7

day 3 than those did not have however on day 7 instead of a normal declining trend in cortisol in the prolonged rupture membrane group.

DISCUSSION

In this study we defined cortisol levels in healthy term and preterm appropriate for gestation infants on day 3 and day 7 (mean, median and range). We also made 10th and 90th centile for cortisol levels in term and preterm babies. We have observed that on day 3 the cortisol levels in term and preterm babies were similar, but on day 7 the preterm babies had higher cortisol levels compared to term babies. The causes for these differences are probably 1) state of immature feed back regulation of cortisol levels in preterm

	Day 3			Day 7		
	Present	Absent	P value	Present	Absent	P value
DOL >12hrs.	256 ± 173 (n=17)	321 ± 224 (n=69)	0.251	262 ± 238 (n=17)	275 ± 224 (n=69)	0.900
DORM >12hrs.	363 ± 273 (n=22)	287 ± 189 (n=64)	0.196	415 ± 306 (n=22)	222 ± 165 (n=64)	0.000*
Maternal complications.	293 ± 182 (n=17)	310 ± 223 (n=69)	0.514	229 ± 260 (n=17)	281 ± 216 (n=69)	0.412
Fetal distress.	328 ± 175 (n=5)	305 ± 218 (n=81)	0.690	347 ± 344 (n=5)	266 ± 217 (n=81)	0.283
Caesarian	338 ± 212 (n=32)	288 ± 216 (n=54)	0.432	259 ± 167 (n=32)	278 ± 254 (n=54)	0.137
P < 0.05 significant						

Table-5: Effect of Various peripartum and antenatal events on cortisol levels in all babies.

infants, which partly recovers by end of 1st week[2,17,18] 2) Decreased tissue sensitivity to cortisol with decreasing gestational age needing higher cortisol concentration for the same physiological functions in the immediate neonatal period[2,17,18] 3) Decreased cortisol degradation with decreasing gestational age 4) Immaturities of enzymes of adrenal cortex like 3β hydroxy steroid dehydrogenase, 11β hydroxylase and 21 β hydroxylase[15,19,20] 5) More stressful adaptation of preterm infants to extrauterine life.

We did not observe the high cortisol levels in preterm babies on day 3 probably because of suppressive effect of antenatal steroids on hypothalamic-pituitary-adrenal axis, resulting in lower levels of cortisol on day 3 which is no longer present by day 7.

Another important observation in our study was that on day 3 cortisol levels were higher compared to day 7 cortisol levels in both term and preterm babies. The causes for this postnatal decrease of cortisol levels from day 3 to day 7 are i) At birth because of stress of labor serum cortisol levels are quite high and these higher levels are necessary for neonatal adaptation to extrauterine life ii) Involution of fetal zone of adrenal gland rapidly after birth results in fall of cortisol levels by half over first 1 to 3 days of life although absolute values may be higher in premature infants.[10,12,13] Sippel WG et al[21] and also observed the similar pattern of changes in cortisol levels from day 3 to day 7 in both term and preterm infants.

In sub group analysis of preterm group babies which was divided in to 3 groups (30-32 weeks) group 1, (33-34 weeks) group 2 and (35-36 weeks) group 3, we observed that the cortisol levels decreased from day 3 to day 7 of life in group 2 and group 3, but in group 1 the cortisol levels increased from day 3 to day 7. The reasons for group 1 having low cortisol on day 3 and not following the postnatal decreasing pattern seen in other groups can be explained by a) Immaturity of HPA axis in this lower gestational age group compared to other groups[2,18] b) Suppressive effect of antenatal corticosteroids on HPA axis.[19,22,23] As the suppressive effect was no longer present on day 7 the cortisol levels rose back to higher baseline levels which are appropriate for that age group. In a study by Scott and Watterberg et al[2] Similar to our observations the cortisol levels decreased from day 4 to day 7 in different gestational age groups. Another important observation in this sub group analysis was inverse relationship of gestation on cortisol levels which was present only on day7, but not on day 3. Scott and Watterberg et al[2] also observed the similar type of inverse correlation of gestational age on cortisol levels from 24 weeks of gestation to 35 weeks of gestation.

Another important observation in our study was that the preterm babies of 34-36 weeks of gestation had higher cortisol levels on day 3 compared to term babies, but on day 7 their cortisol levels were similar to term babies. This implies rapid postnatal adaptation or maturation of HPA axis in this age group of babies. However in babies up to ≤ 34 weeks of gestation on day 7 the cortisol levels remained higher compared to term babies.

In the study by Doerr et al[24], the cortisol levels in babies more than 32 weeks were almost similar to term babies on day 7. However they did not analyze the postnatal changes at each individual gestation unlike our observation. Hence it is quite possible that after 34 weeks of gestation the maturation of HPA axis is rapid.

Like all other organ systems endocrine axis also progresses through stages of maturity during increasing gestation. Premature birth may occur before HPA axis is adequately functional.[18] And delay in maturation of enzymes systems in adrenal cortex and immature response of hypothalamus to stress, delayed cortisol degradation, decreased sensitivity of tissues to cortisol and stress full adaptation to extra uterine life may contribute to this delay in postnatal adaptation in pre term babies.[18]

Another important observation in our study was that antenatal corticosteroid administration to mother (single full course or partial course) associated with HPA axis suppression. In ≤ 34 weeks cortisol levels in babies who received antenatal steroids were lower on day 3 compared to day 7 unlike those who did not receive antenatal corticosteroids whose cortisol levels were higher on day 3 and decreased to lower levels by day 7. This implies that the transient suppression of pituitary and adrenal glands in preterm infants on day 3 who received one or two doses of antenatal corticosteroids which recovered by day 7 of life. In a study by Banks et al[25], plasma cortisol levels at 2 hours of age were less (245 nmol/L) when antenatal steroids (one course) received 1-72 hours before

delivery compared to cortisol levels of 571 nmol/L when steroids received 73-240 hours before the delivery. The results in our study also similar with low cortisol levels on day 3, and suppression of HPA axis is no longer persisting on day 7 of life.In another study by Terrone et al[26], the cortisol levels on day 3 who received no antenatal steroids, one course of antenatal steroids, two or more courses were 229 ± 44.1 nmol/L, 160 ± 38.6 nmol/L and 160 ±24 nmol/L respectively. Similar to our results the cortisol levels were less in babies who received antenatal steroids. Ballard, et al[23], studied the effect of antenatal corticosteroid on HPA axis suppression by estimating the levels of cortisol. In babies who received the antenatal corticosteroids the cortisol levels were lower (104 nmol/L) compared to babies who did not receive (234 nmol/L).

Among the peripartum and antenatal factors which affected the cortisol levels the DORM > 12 hours had statistically significant effect on day 7, but not on day 3. This again can be explained by inspite of being stressed, the cortisol levels were lower on day 3 because of immaturity of HPA axis in preterms and more importantly suppressive effect of antenatal corticosteroids on HPA axis.

CONCLUSION

We defined the cortisol levels of term and preterm (30 weeks to 36 weeks of gestation) appropriate for gestation infants in Indian context on day 3 and day 7. In preterm neonates the cortisol levels were inversely related to gestational age on day 7 but not on day 3. In preterm infants cortisol levels were inversely related to postnatal age. This inverse relation with postnatal age was not present in babies ≤ 32 weeks of gestation. Antenatal steroid administration to mothers resulted in lower cortisol levels on day 3 as compared to day 7 in preterm infants ≤ 34 weeks of gestation, unlike those who did not receive antenatal steroids. We found the maturational effect at ≥ 35 weeks of gestation. Among the antenatal and peripartum factors only duration of rupture of membranes appears to have statistically significant effect on cortisol levels.

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