

Association of Serum Cortisol Levels with Respiratory Distress Syndrome and Mortality in Premature Babies

Muhammad Sajid,¹ Nousheen Fatima,² Mir Nousharwan,³ Ameer Ahmad⁴

Abstract

Objective: To determine the association of serum cortisol levels with Respiratory distress syndrome and Mortality in premature babies

Method: A descriptive cross sectional study was conducted in Neonatal unit of pediatric medicine 1 of Bahawal Victoria hospital Bahawalpur from Feb 2021 to June 2021. Premature babies (less than 36 weeks gestation by ballard scoring) admitted in Preterm ward on day 1 were enrolled after informed consent and ruling out exclusion criteria (More than 24 hour old, Who have received antenatal steroids for lung maturation, Received any treatment before admission in any other hospital, Patient having Any obvious anomaly). Day 1 sample sent for CRP and cortisol. Data recorded regarding weight, gestational age (ballard scoring), septic risk factors. These patients were followed for development of RDS (on X ray at 24 hour of life). Outcome was documented as expiry, discharged or LAMA. Data analyzed in SPSS 20.

Results: 40 patients were enrolled as per inclusion criteria. 27 (67.5 %) were male and 13 (32.5 %) were female. Gestational age 3 (7.5 %) had less than 28 weeks, 29-30 weeks were 6 (15 %), 31-34 weeks were 31 (77.5 %). Weight less than 1.5 kg were 23 (57.5%), 1.5 to 2 kg were 15 (37.5 %), 2.1-2.5 kg were 2 (5%). Cortisol level low in 4 (10 %), normal in 6 (15 %), high in 30 (75 %). 22 (55 %) discharged, 13 (32 %) expired, and 5 (12.5 %) got LAMA. Cortisol level as compared to outcome has p value 0.002. Twelve (30 %) had RDS. Twenty two (55 %) had clinical evidence of sepsis. 18 (45 %) had CRP more than 6. Cortisol level as compared to RDS presence has P value 0.057 and with sepsis has P value 0.007. Mean cortisol in discharged patients were 19.8, expired 14.2 and LAMA has 22.7. Mean cortisol level in RDS patients were 18.3 and RDS absent had 18.3 also. Mean cortisol level in Sepsis positive patients were 18.6 and sepsis absent were 18.0

Conclusion: Mean cortisol has no significant difference in discharged and expired patients.

Keywords: Cortisol, Respiratory distress syndrome(RDS), Mortality, Premature Babies

How to cite: Sajid M, Fatima N, Nousharwan M, Ahmad A. Association of Serum Cortisol Levels with Respiratory Distress Syndrome and Mortality in Premature Babies. *Esculapio - JSIMS* 2023;19(01):43-46

DOI: <https://doi.org/10.51273/esc23.251919>

Introduction

Pakistan is among the top ten countries where two third premature babies dies every year. An estimated 860,000 babies are born preterm every year and among those almost 11.8 die % due to complications of pre-maturity.¹

Preterm infants have to face lot of complications after birth, respiratory distress syndrome, necrotizing enterocolitis, weekend immune system, retinopathy of prematurity, chronic lung disease, and neuro-logical insult etc.² As prematurity is the most common cause of infant mortality, the respiratory distress syndrome is the leading cause of mortality in premature infants.³ It is an alarming situation and every effort should be made to decrease the morbidity and mortality of preterm infants.

1-3. Department of Pediatrics Quaid-Azam Medical College/Bahawal Victoria Hospital Bahawalpur

Correspondence:

Muhammad Sajid Assistant professor pediatrics Quaid-Azam Medical College/Bahawal Victoria Hospital Bahawalpur.
Email address sajidaimc@gmail.com

Submission Date:	02-02-2023
1st Revision Date:	16-02-2023
Acceptance Date:	12-03-2023

During fetal life adrenals start secreting cortisol at almost 8 weeks of gestation but it is not the main steroid. Dehydroepiandrosterone (DHEA) and its sulphates (DHEAS) are the main steroids during fetal life and act as substrate for placental estrogen production.⁴ Normal development and functioning of adrenal glands is essential not only for fetus but also for neonatal life thereafter. For example, fetal miss programming of the stress axis not only alter fetal cortisol production but may predispose to diseases in later life. If the hypothalamic adrenal axis is not properly activated, it may result in physiological instability which in turn adversely affects the severity of illness, morbidity and mortality.⁵ The preterm newborns are more prone to develop relative adrenal insufficiency because they have limited 3 β -hydroxysteroid dehydrogenase (HSD) and the other enzymes for the synthesis of cortisol. 3 β -HSD is expressed from adrenal neocortex after 23 week of gestation, before that fetus uses progesterone from placenta to produce cortisol.⁶ Antenatal steroids have shown some beneficial effects in prevention of respiratory distress syndrome.⁷ As it is stated above the preterm babies have low cortisol levels and also have relative adrenal insufficiency. If it is proved that the premature babies with low serum cortisol levels have increase morbidity due to RDS and increase mortality, the post natal steroid therapy can help in decreasing the morbidity and mortality of premature babies.

The prophylactic use of steroid in prematures have been a controversy because some trials have suggested that it prophylactic use increase the survival of extreme preterm without broncho pulmonary dysplasia, but on the other hands the steroids have some unaccepted risks like intestinal rupture in prematures.⁸

The rationale of this study is that if we are able to prove that the low serum cortisol levels have association with prevalence and severity of RDS and with mortality of prematures, then we can suggest the prophylactic use of steroids in prematures that will improve their outcome. Although surfactant therapy has definitive role in treatment of RDS, but due to limited resources it is not available in every health care facility dealing with prematures, but steroids are easily available, cheap and if it plays role in prevention of RDS that it will also help in reducing disease burden. Premature babies (less than 36 weeks gestation by ballard scoring admitted in neonatal unit of pediatric department on first day of life. Preterm babies who have received antenatal steroids for lung maturation,

- History of delayed cry or resuscitation required at birth
- Patients having any obvious anomaly
- Patients who received any treatment before admission in any other hospital

Materials and Methods

It was a descriptive, Cross Sectional Study conducted in Department of Pediatrics, Bahawal Victoria hospital, Bahawalpur, from Feb 2021 to June 2021. Total forty premature babies admitted in pediatric department who met the inclusion and exclusion criteria were included in the studies after taking informed consent. Gestational age was determined by using expanded Ballard score. Non-probability consecutive sampling technique was used. After inclusion, patient's demographic, social, personal data, status of respiratory distress syndrome and septic profile was entered on pre-designed proforma. On first day of life (early morning) blood sample were sent for serum cortisol and CRP. Sepsis was labeled on the basis of clinical presentation and raised CRP. All the labs reports were entered on proforma and finally the fate of the patient was also entered.

The data was entered and analyzed by using SPSS version 20. Mean and Median was calculated for numerical data. Frequency, percentages and p-value calculated for serum cortisol, sepsis, RDS status and mortality.

Results

Forty patients were enrolled as per inclusion criteria. 27 (67.5 %) were male and 13 (32.5 %) were female. Three (7.5 %) patients had gestational age less than 28 weeks, 6 (15 %) were of 29-30 weeks gestation, 31-34 weeks were 31 (77.5 %). Patients having weight less than 1.5 kg were 23 (57.5%), 1.5 to 2 kg were 15 (37.5%), and 2.1-2.5 kg were 2 (5%). Serum cortisol levels ranges from 1.1 to 46 IU with mean value of 18.36 IU. Cortisol level were low in 10% of preterm infants, 15% were having normal cortisol levels while it was high in 30 (75 %) of preterm babies. Regarding outcome twenty-two (55 %) discharged, 13 (32 %) expired, and 5 (12.5 %) got LAMA. Cortisol level as compared to outcome has p value 0.002 (Table 1). Twelve (30 %) had RDS. Twenty-two (55 %) had clinical evidence of sepsis. 18 (45 %) had CRP more than 6. Cortisol level as compared to RDS presence has P value 0.06 (Table 2) and with sepsis has P value 0.007. Mean cortisol in discharged patients were 19.8, expired 14.2 and LAMA has 22.7. Mean cortisol in RDS patients were 18.3 and RDS absent had

18.3 also. Mean cortisol in Sepsis positive patients were 18.6 and sepsis absent were 18.

Discussion

In our study 77.5% preterm babies were between 31-34 week gestation and 75% of our preterm babies were having high cortisol level. While in many of the other studies the premature babies were having serum cortisol levels within the reference range for their gestation^{9,10}. However the serum cortisol levels were inversely proportional to the gestational age in our study, similarly Seshagiri, et al concluded in their study that the serum cortisol levels were declined with increasing gestational age in healthy term and preterm babies¹¹. Some studies have concluded that the serum cortisol levels were high in small for gestational age babies as compared to appro-

Table 1: Outcome in relation to serum Cortisol levels

Cortisol Groups	Number of patients	Dis-charged	Died	LAMA
Low (0-2)	4	4	0	0
Normal (2-11)	6	0	6	0
High (12-100)	30	18	7	5
P Value = 0.002				

Table 2: RDS status in relation to Serum Cortisol Levels

Cortisol Groups	Number of patients	RDS Present	RDS Absent
Low (0-2)	4	0	4
Normal (2-11)	6	4	2
High (12-100)	30	8	22
P Value = 0.06			

appropriate for gestational age.⁹ We had included only appropriate for gestational age preterm babies in our study, so we can't comment on serum cortisol levels in small for gestational age babies. Respiratory distress syndrome (RDS) was diagnosed in 30% of our preterm babies included in study. While comparing the serum cortisol levels of those with RDS and without RDS, there was no statistically significant difference in both groups. It means serum cortisol level does not play any significant role in development of RDS in preterm babies. Reynolds JW concluded in his study that adrenal hypo function does not play any role in development of RDS in premature babies.¹² While in 2020 a study conducted in Egypt concluded that that serum cortisol levels has positive correlation with respiratory distress syndrome in preterm babies¹³ that is contrary to our study results. They

have large sample size than ours, so more research and data is needed in future. Similarly results were concluded by a study conducted in turkey.¹⁴ Beverley E. Person Murphy conducted a research in Canada in 2015, in which he said the both the cortisol and cortisone levels were low in cord blood of babies who developed RDS.¹⁵ Elevated serum cortisol has significant effect on pediatric mortality in pediatric intensive care unit (PICU) described by Osama E. Bekhit and colleges in 2015.¹⁶ While talking about effect of serum cortisol and adrenal insufficiency on preterm mortality, Sari F.N concluded that there is no correlation between serum cortisol and mortality in preterm infants.¹⁷ But in our study low serum cortisol levels has significant effect on mortality. In October 2007 a study conducted in Kuopio University Hospital, in this study they have taken cord blood, and serum cortisol and DHEAS concentrations on day one and four of life. It was seen that the low serum cortisol and DHEAS levels in cord blood and first day of life has significant effect on outcome.¹⁸

Conclusion

Serum cortisol was high in 75% of my study population. Low cortisol has good outcome as compared to those having high cortisol level. Cortisol level has no significant relation to the presence of RDS.

Conflict of Interest:

None

Funding Source:

None

References

1. Hanif A, Ashraf T, Waheed K, Sajid MR, Guler N, Perwaiz MK. Prevalence of preterm birth in Pakistan: a systematic review and meta-analysis. *Annals of King Edward Medical University*. 2017 Aug 17;23(2).
2. Khan HS, Khalil S, Akhtar P. Morbidity and Mortality Pattern of Pre-terms. *Journal of Islamabad Medical & Dental College (JIMDC)*. 2016;5(1):77-80.
3. Saboute M, Kashaki M, Bordbar A, Khalessi N, Farahani Z. The incidence of respiratory distress syndrome among preterm infants admitted to neonatal intensive care unit: a retrospective study. *Open Journal of Pediatrics*. 2015;5(04):285.
4. Scott, S., Watterberg, K. Effect of Gestational Age, Postnatal Age, and Illness on Plasma Cortisol Concentrations in Premature Infants. *Pediatr Res* 37, 112– 116 (1995).
5. Ng PC. The fetal and neonatal hypothalamic– pituitary– adrenal axis. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 2000 May 1;82(3):F250-4.

6. Fernandez EF, Watterberg KL. Relative adrenal insufficiency in the preterm and term infant. *Journal of Perinatology*. 2009 May;29(2):S44-9.
7. Hallman M. The story of antenatal steroid therapy before preterm birth. *Neonatology*. 2015;107(4):352-7.
8. Baud O, Maury L, Lebail F, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. *Lancet*. 2016;387(10030):1827–1836.
9. Heckmann M, Wudy SA, Haack D, Pohlandt F. Reference range for serum cortisol in well preterm infants. *Archives of Disease in Childhood-Fetal and Neonatal Edition*. 1999 Nov 1;81(3):F171-4.
10. Bolt RJ, Van Weissenbruch MM, Popp-Snijders C, Sweep FG, Lafeber HN, Delemarre-van de Waal HA. Maturity of the adrenal cortex in very preterm infants is related to gestational age. *Pediatric research*. 2002 Sep;52(3):405-10.
11. KoripaduSeshagiri, Yanamandala Venkata Harischandra. Cortisol levels in healthy term and preterm appropriate for gestation infants. *International Journal of Contemporary Medical Research* 2017;4(8):1659-1664.
12. Reynolds JW. Serum total corticoid and cortisol levels in premature infants with respiratory distress syndrome. *Pediatrics*. 1973 May;51(5):884-90.
13. Arafa AE, ElMeneza SA, Hafeez SA. The Relation between Role of Serum Cortisol Level and Response to Various Respiratory Support Strategies among Preterm Infants. *Open Journal of Pediatrics*. 2020 Sep 11; 10(03): 504.
14. Gunes T, Koklu E, Ozturk MA, Koklu S, Cetin N. Evaluation of serum cortisol levels in a relatively large and mature group of ventilated and nonventilated preterm infants with respiratory distress syndrome. *American journal of perinatology*. 2006 Jul;23(06):335-40.
15. Murphy BE. Cortisol and cortisone levels in the cord blood at delivery of infants with and without the respiratory distress syndrome. *American Journal of Obstetrics and Gynecology*. 1974 Aug 15;119(8):1112-20.
16. Bekhit OE, Mohamed SA, Yousef RM, AbdelRasol HA, Khalaf NA, Salah F. Relation between baseline total serum cortisol level and outcome in pediatric intensive care unit. *Scientific Reports*. 2019 Apr 12;9(1):1-6.
17. Sari FN, Dizdar EA, Oguz SS, Andiran N, Erdeve O, Uras N, Memik R, Dilmen U. Baseline and stimulated cortisol levels in preterm infants: is there any clinical relevance? *Hormone Research in Paediatrics*. 2012; 77(1): 12-8.
18. Nykänen P, Anttila E, Heinonen K, Hallman M, Voutilainen R. Early hypoadrenalism in premature infants at risk for bronchopulmonary dysplasia or death. *Acta Paediatrica*. 2007 Nov;96(11):1600-5.

Authors Contribution

MS: Conceptualization of Project

MN: Data Collection

NF: Literature Search

MS: Statistical Analysis

NF: Drafting, Revision

MS: Writing of Manuscript