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Antenatal Steroid in Preterm Infants with Respiratory Distress Syndrome

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ABSTRACT

Background: Respiratory distress syndrome (RDS) remains the most important determinant of increasing neonatal morbidity in preterm infants**.** A low secretory capacity of the adrenal cortex may cause a diminished stress response during the acute illness in preterm infants and could lead to increased morbidity in these infants.

Objective: To evaluate the levels of antenatal steroid (cortisol) in the 1st and 3rd days of life in preterm neonates with respiratory distress syndrome.

Patients and methods: This study was carried out in neonatal intensive care unit (NICU) of Benha University Hospital from June, 2020 to January, 2022. The study included 45 preterm neonates (23 females and 22 males), with gestational age ranged from 30 to 36 weeks, and their weights ranged between 1.100 kg to 2.700 kg (all of them were appropriate for gestational age (AGA) with mean weight 1.800 ± 0.300 kg).

Results: In the current study, in ROC curve and area under the curve shows that 3rd day serum cortisol significantly could be used as a predictive measure in cases prognosis with probability of 71% that the assay result for a randomly chosen positive case will exceed the result for a randomly chosen negative case. Among respiratory distress groups (2 and 3) 3rd day serum cortisol level of 485.5 (nmol/l) was chosen as a cutoff point below which cases with respiratory distress tend to show improvement in prognosis with sensitivity of 80% and specificity of 80%.

Conclusion: Preterm infants with severe RDS (mechanically ventilated) release more cortisol, which could be the result of severe stress associated with respiratory distress and positive pressure ventilation. Increased incidence and severity of RDS were noticed more in cesarean section (CS) than in vaginal delivery (VD). Antenatal steroids have effective role in decreasing incidence and severity of RDS.

Keywords: Preterm Infants, Respiratory Distress Syndrome, Serum Cortisol.

INTRODUCTION

Respiratory distress syndrome (RDS) remains the most important determinant of increasing neonatal morbidity in preterm infants **[1].** A low secretory capacity of the adrenal cortex may cause a diminished stress response during the acute illness in preterm infants and could lead to increased morbidity in these infants **[2].** The function of the adrenal cortex in the neonatal period was related to many factors such as respiratory distress, gestational age, birth weight and arterial hypotension **[3].** Higher incidence of hronchopulmonary dysplasia (BPD) in patients with an insufficient cortisol response to adrenocorticotropic hormone (ACTH) has been found **[4]**.

During the final prenatal period of fetal lung development in humans, important maturation processes occur, including the production of surfactant, which is necessary to decrease surface tension at the air-liquid interface of the alveoli **[5].** During early gestation, the glucocorticoid receptor is expressed in the fetal lung, and glucocorticoid stimulate the production of surfactant-associated proteins and increase phospholipids synthesis by enhancing the activity of phosphatidylcholine. Other glucocorticoid-induced effect may include stimulation of cell maturation and differentiation, inhibition of DNA synthesis, changes in interstitial tissue components, stimulation of antioxidant enzymes, and regulation of pulmonary fluid metabolism **[6].**

Recently, it was suggested that glucocorticoids are also important in postnatal pulmonary development, and may be related to the development of neonatal lung disease in preterm infants. It has been suggested that preterm infants may have developmental immaturity of the hypothalamic-pituitary-adrenal axis, and that decrease cortisol response to stress and increases risk of chronic lung disease secondary to inflammatory lung injury **[7].**

Adrenal function in very low birth weight preterm infants has received increasing attention during recent years, small studies have recently suggested that these patients may exhibit a relative adrenal insufficiency in the face of critical illness **[8]**.

The aim of this work is to evaluate the levels of serum cortisol in the 1st and 3rd days of life in preterm neonates with respiratory distress syndrome. Also, to study the correlation of serum cortisol levels in early days of life with clinical status and prognosis for assessment of its predictive value of short-term outcome.

PATIENTS AND METHODS

This study was carried out in neonatal intensive care unit (NICU) of Benha University Hospital from June, 2020 to January, 2022. The study included 45 preterm neonates (23 females and 22 males), with gestational age ranged from 30 to 36 weeks, and their weights ranged between 1.100 kg to 2.700 kg (all of them were AGA with mean weight 1.800 ± 0.300 kg).

The neonates included in the study were divided into three groups: **Group I:** Preterm neonates without RDS as control (n =15). **Group II:** Preterm neonates with mild to moderate respiratory distress syndrome, were on continuous positive airway pressure (CPAP) (n =15).

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Group III: Preterm neonates with severe respiratory distress syndrome, were mechanically ventilated (n=15).

Exclusion criteria at admission: Neonates with apparent congenital anomalies, asphyxiated at birth, persistent hypoglycemia, death within 3 days of life and hypotension (defined as blood pressure less than 2 standard deviation normal for gestational age), large and small for gestational ages babies were excluded. Also, infants with maternal history of hypertension, diabetes, and thyroid disorder. Premature rapture of membrane (PROM), or severe infections were excluded.

Collection of Data:

Full history taking: Prenatal history (maternal illness, antenatal steroids). Natal history (mode of delivery, birth asphyxia, and trauma). Postnatal history (oxygen therapy and history of any invasive procedures that were done to the baby after delivery including resuscitation and incubation). Short term and outcome during the period of admission were recorded.

Full clinical examination Assessment of gestational age according to Doubowitz score. Assessment of degree of RDS by Downes score [9]. Neurological, Chest, Heart and Abdominal examination.

The following investigation were done to all groups of the study; Chest X-ray, Laboratory investigations; CBC: Complete blood count, CRP: C-reactive protein, ABG: Arterial blood gases (before respiratory support). **Serum cortisol levels in:** the first day of life and the third day of life by using the electrochemiluminescence immunoassay "ECLIA" (Elecsys and Cobase Analyzers-1010-Germany). Method of measurement of serum cortisol level.

Ethical consent:

An approval of the study was obtained from Benha University Academic and Ethical Committee. Every patient's legal guardian signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data collected throughout history, basic clinical examination, and outcome measures were coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 25.0) (Armonk, NY: IBM Corp, 2018). Descriptive statistics included percentage (%), mean and standard deviation (SD) and analytic statistics included chi-square test (χ^2), Student's t-test,. P value<0.05 was considered statistically significant.

RESULTS

In the current study, there were no significant differences in frequencies of cases among all studied groups regarding sex, birth weight, mode of delivery, and multiplicity of pregnancy. While, there was a highly significant difference in frequencies of cases among all studied groups regarding antenatal steroids **(Table 1).**

Table (1): Comparison between all studied groups regarding sex, weight, mode of delivery, antenatal steroids, and multiple pregnancy

		Group name						P value
		Group (I) Control		Group (II) Mild to Moderate RDS		Group (III) Severe RDS		
		No.	%	No.	%	No.	%	
Sex	Female	7	46.7%	8	53.3%	8	53.3%	0.915
	Male	8	53.3%	7	46.7%	7	46.7%	
Weight	Mean ±SD	1.8±0.3		1.8±0.3		1.8±0.4		0.913
	Range	1.5-2.7		1.3-2.6		1.1-2.4		
Mode of delivery	Cesarean section	10	66.7%	10	66.7%	12	80%	0.649
	Vaginal delivery	5	33.3%	5	33.3%	3	20%	
Antenatal steroids	Didn't Receive	5	33.3%	13	86.7%	14	93.3%	<0.001*
	Received	10	66.7%	2	13.3%	1	6.7%	
Multiple Pregnancy	Single	9	60%	13	86.7%	9	60%	0.190
	Twin	6	40%	2	13.3%	6	40%	

*Significant

In the current study, there were no significant difference between all studied groups regarding CRP, hemoglobin percent, RBCs count, WBCs count and platelets count **(Table 2).**

Table (2): Comparison between all studied groups regarding CRP, hemoglobin percent, RBCs count, WBCs count and platelets count

		Group name						P value
		Group (I) Control		Group (II) Mild to Moderate RDS		Group (III) Severe RDS		
		No.	%	No.	%	No.	%	
CRP (mg/L)	Negative	15	100%	13	86.7%	7	46.7%	0.915
	Positive	0	100%	2	13.3%	8	53.3%	
Hemoglobin % (g/dL)	Mean ±SD	13.8±2.7		14.7±2.7		13.4±2.2		0.37
RBCs (mcL)	Mean± SD	4.9± 1		5.2±1		4.8±0.8		0.37
WBCs (mcL)	Mean± SD	7.8±1.6		8.8±2.3		6.9±2.3		0.24
Platelets count (mcL)	Mean± SD	118±5		122±9		115±53		0.94

In the current study, there were highly significant difference between all studied groups regarding pH, PO_2, PCO_2 and HCO_3 **(Table 3).**

Table (3): Comparison between all studied groups regarding vital signs

		Group name						P value
		Group (I) Control		Group (II) Mild to Moderate RDS		Group (III) Severe RDS		
		No.	%	No.	%	No.	%	
pH	Mean± SD	7.38±0.03		7.17±0.09		7.11±0.11		<0.001**
PO_2	Mean± SD	89±5		78±5		78±5		<0.001**
PCO_2	Mean± SD	37±2		41±6		46±5		0.04*
HCO_3	Mean± SD	22±5.12		8±1.61		5±1.1		0.01**

* Significant, ** Highly significant

In group I, serum cortisol level in 3rd day was highly significantly lower than in 1st day. In group II and III serum cortisol level in 3rd day was highly significantly higher than in 1st day. There was highly significant difference between all studied groups regarding 3rd day serum cortisol **(Table 4).**

Table (4): Serum cortisol levels at 1st and 3rd day among all studied groups

		1st day serum cortisol (nmol/L)	3rd day serum cortisol (nmol/L)	P value
		Mean ±SD	Mean ±SD	
Group Name	Group (I) Control	299±80	162±17	<0.001**
	Group (II) Mild to Moderate RDS	308±76	450±26	<0.001**
	Group (III) Severe RDS	296±78	557±125	<0.001**
P value		0.89	<0.001**	

** Highly significant

In the current study, ROC curve and area under the curve show that 3rd day serum cortisol significantly could be used as a predictive measure in cases' prognosis with probability of 71%; that the assay result for a randomly chosen positive case will exceed the result for a randomly chosen negative case. Among respiratory distress groups (2 and 3) 3rd day serum cortisol level of 485.5 nmol/l was chosen as a cutoff point below which cases with respiratory distress tend to show improvement in prognosis with sensitivity of 80% and specificity of 80% **(Table 5, Fig. 1).**

Table (5): Area under the curve for serum cortisol levels at 1st and 3rd day

Area Under the Curve					
Test Result Variable (s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
1st day serum cortisol (nmol/L)	0.569	0.108	0.520	0.357	0.781
3rd day serum cortisol (nmol/L)	0.711	0.104	0.049	0.508	0.915

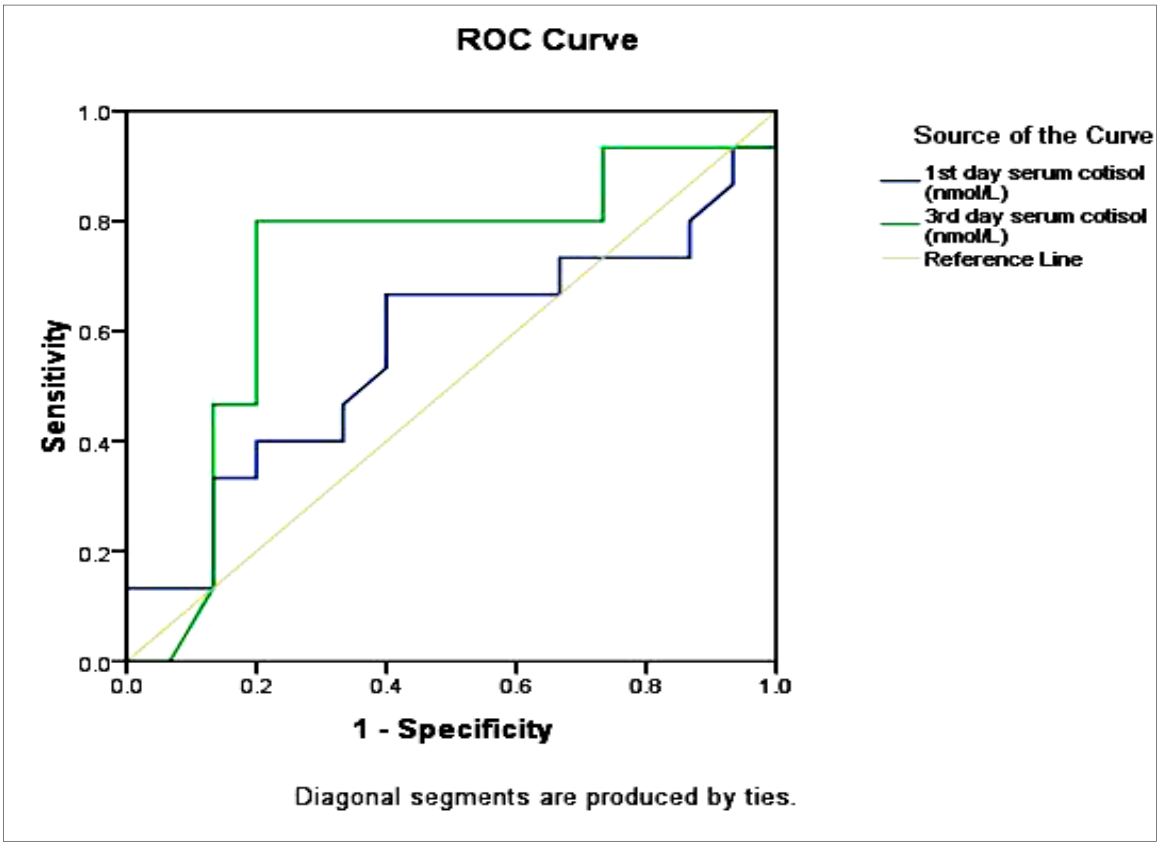

Fig. (1): ROC curve for serum cortisol levels at 1st and 3rd day

DISCUSSION

We found that the mean of maternal age in our study was (30 ± 5) years in all studied groups with no statistically significant difference in comparison between the three groups. Also there was no statistically significant correlation of mean serum cortisol levels (1st and 3rd day) with maternal age in the studied groups. This suggests no correlation between severity of respiratory distress syndrome and maternal age. Our findings are in disagreement with the study performed by **Beydoun *et al.*** [10] who stated that in many developed and developing countries maternal age at first child birth above 25 years is an independent risk factor for low birth weight but not for preterm delivery and respiratory morbidity.

The present study reported that male patients represented (46.7%) of cases (group II and III), while female patients represented (53.3%) of cases (group II and III), while in the control group (I) males represented (53.3%) and female represented (46.7%) with no statistical significant difference between males and females in the cases and control and there was no statistical significant correlation between serum cortisol levels in 1st day and sex distribution and also no statistical significant correlation between serum cortisol level in 3rd day of life and sex distribution. On the other hand, study performed by **Townsend *et al.*** [11] on 3356 boys and 3382 girls of very low birth weight showed relative difference in short term morbidity and mortality persist between both sexes, boys have pulmonary morbidity predominated.

In the present study, all our cases and control had appropriate weight for gestational age by blotting on centile charts. The range of birth weight was from 1100 to 2700 gm with gestational age ranging from 30 to 36 weeks. We found no statistically significant correlation between birth weight and serum cortisol levels in 1st day and 3rd day suggesting there is no relation between birth weight and severity of respiratory distress syndrome in the previously mentioned gestational age. While **Manabe *et al.*** [12] stated that in neonate whose birth weight was less than 2000 gm, there was a negative correlation between cortisol levels in umbilical vein and birth weight but there was no correlation between cortisol levels in umbilical vein and gestational age.

In this study by comparison between the three groups as regard to mean value of CBC, it showed that hemoglobin (Hb) levels were (13.8 ± 2.7, 14.7 ± 2.7 and 13.4 ± 2.2), RBCs counts were (4.9 ± 1, 5.2 ± 1 and 4.8 ± 0.8), WBCs counts were (7.8 ± 2.6, 8.8 ± 33 and 6.9 ± 2.3), and platelets counts were (118 ± 50, 122 ± 49 and 115 ± 53) in groups I, II and III respectively. There was no significant difference between the three groups as regard to CBC, and there was no significant statistical correlation between the levels of serum cortisol in 1st day and CBC. Also there was no significant statistical correlation between the three groups and 3rd day serum cortisol. However, our results were consistent with the results was performed by **Fares *et al.*** [13] that stated no correlation between severity of respiratory distress syndrome in preterm infants and CBC findings in early postnatal age.

Our study showed that there was statistical significant reduction in arterial blood gases parameters

among cases of RDS (group II and III) as follow: mean values of pH (7.17 ± 0.09 and 7.11 ± 0.11), PO_2 (7.8 ± 5 and 7.8 ± 5), PCO_2 (41 ± 6 and 46 + 15) and HCO_3 (19 ± 8 and 16 ± 8) respectively compared with that of group I, mean values of pH (7.38 ± 0.03), PO_2 (89 ± 5), PCO_2 (37 ± 2) and HCO_3 (24 ± 2). This showed the importance of measuring the arterial blood gases as a diagnostic procedure for diagnosis of RDS. Our study also showed high statistically significant negative correlations between 3rd day serum cortisol and pH, PO_2 and HCO_3 and positive correlation between 3rd day serum cortisol and PCO_2 in all cases of the study (group II and III). Our results were in agreement with the following: **Victor and Upadhyay [14]** indicated that umbilical cord pH was related to subsequent adverse outcome events for infants delivered preterm. **Chauhan *et al.* [15]** indicated that among newborns at > or = 34 weeks, pH < or = 6.92 is the threshold linked with neonatal organ dysfunction. **Shiao and Ou [16]** stated that the safety limits for pulse oximeters were higher and narrower in neonates (75 – 95%) than in adults, and clinical guidelines for neonates may require modification.

The study revealed that 1st day mean levels of serum cortisol in the three groups were elevated and showed no significant difference between the three groups, that could be explained by the association between the birth process and the large increase in the fetal stress hormones such as cortisol and catecholamine, which began in decreasing to reach the normal range within 48 hours of birth **[17].**

In this work we noticed the outcome of our cases through one month and we found that group II (mild to moderate RDS) had 6.7% of cases complicated with BPD, 13.3% of cases died and 80% had improvement on discharge. However, group III (severe RDS) had 26.7% of cases complicated with BPD, 53.3%, of cases died and 20% had improvement on discharge. As regards prognosis, our results indicated that regarding 1st day serum cortisol levels there were no significant difference between the studied groups, however regarding 3rd day serum cortisol levels, showed that groups with less favorable prognosis tend to have significantly higher levels than control group and cases which showed improvement.

These results are consistent with those of **Ng [18]** who stated that low cortisol concentrations were not predictive of adverse short-term outcomes, but high cortisol concentrations were associated with morbidity and death. Our findings were in contrast with **Baraldi *et al.* [19]**, who found that low cord and 1st day serum cortisol and DEHAS (dehydroepiandrosterone sulphate) levels associated with poor outcome in preterm infants, which suggest general relative adrenocortical insufficiency in some premature newborns. **Watterberg [20]** in contrast with our study, found that developing BPD was related to lower cortisol secretion in response to ACTH hormone. While in the study was done by **Gunes *et al.* [21]** on preterm infants with gestational age (30 – 36 weeks) with respiratory distress syndrome goes with our results in elevation of cortisol levels in severe and (mild to moderate) RDS infants significantly raised than their corresponding in 1st day, but these results were different from our study in that the cortisol level on 3rd day of life were not significantly different in infants with poor outcome compared with infants with better outcome.

CONCLUSION

Preterm infants with severe RDS (mechanically ventilated) release more cortisol, which could be the result of severe stress associated with respiratory distress and positive pressure ventilation. Increased incidence and severity of RDS were noticed more in CS than in VD. Antenatal steroids have effective role in decreasing incidence and severity of RDS. Chest X-ray and ABG measurement are the most reliable diagnostic procedures in RDS.

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Author contribution: Authors contributed equally in the study.

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