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Association between Serum Cortisol in the 1st and 3rd Days of Life in Neonates with Respiratory Distress Syndrome

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ABSTRACT

Background: Numerous studies have shown that severity of respiratory distress syndrome may affect the endogenous cortisol secretion in preterm infants.

Objective: Is to evaluate the levels of serum 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 during the period from 2019 till 2020. The study included 45 preterm neonates (23 females and 22 males). 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). Group III: Preterm neonates with severe respiratory distress syndrome, were mechanically ventilated (n=15).

Results: In cases received antenatal steroids there was no significant difference between 1st and 3rd day's serum cortisol levels. In cases didn't receive antenatal steroids there was highly significant difference between 1st and 3rd day's serum cortisol levels. There was significant difference between 1st day serum cortisol levels and highly significant difference between 3rd day serum cortisol levels regarding antenatal steroids.

Conclusion: Preterm infants respond to the stress at delivery and cortisol production continues in infants with RDS than those without RDS; may be in order to cope with poor pulmonary function and to enhance lung maturity. Antenatal steroids have effective role in decreasing incidence and severity of RDS.

Keywords: Preterm Infants, Respiratory distress syndrome, Serum cortisol.

INTRODUCTION

Prematurity is a public health problem worldwide. Every year, 15 million infants are born before completing 37 weeks of gestation, accounting for a prevalence of 11% in 184 surveyed countries in 2012 [(1)]. In the last decade, prematurity topped the list of causes of neonatal mortality. Brazil is among the 10 countries with the highest rates of preterm births, which has increased in recent years [(2)]. Infants who survive premature birth have high rates of short and/or long-term postnatal morbidity. Prematurity has repercussions on child development in its various dimensions, causing losses, delays, changes, or even causing impairments [(3)].

Several studies reported that motor, visuospatial and sensory function losses in extremely premature infants at age six, showing that these losses compromised cognitive function and could jeopardize school performance [(4)]. In another study, **Marlow *et al.*** [(5)] showed that extremely premature children at six years of age had the worst results in neurocognitive functions and more disabilities than classmates and in standard normative references. Data from this study shows that 72% had disabilities in the cognitive domain, 24% in the neuromotor domain, 10% presented hearing loss, and 36% visual loss, such that 80% of the sample had some minimal, average or severe disability [(6)].

Respiratory distress syndrome (RDS), also known as hyaline membrane disease, is the commonest respiratory disorder in preterm infants. The clinical diagnosis is made in preterm infants with respiratory difficulty that includes tachypnea, retractions, and grunting respirations. It is a common cause of respiratory distress in a newborn, presenting within hours after birth, most often immediately after delivery [(7)]. RDS primarily affects preterm neonates, and infrequently, term infants. The incidence of RDS is inversely proportional to the gestational age of the infant, with more severe disease in the smaller and more premature neonates. While treatment modalities, including antenatal [(8)].

Preterm infants are liable to various health problems including respiratory distress syndrome (RDS). There is variation in response of preterm infants with the same gestational age to respiratory support, some may respond to oxygen, others may need intubation surfactant extubating (INSURE), continuous positive airway pressure (CPAP) or mechanical ventilator (MV) [(9)]. The cortisol produced by the adrenal cortex changes structurally and functionally along with gestational age and maturation of the adrenocortical gland function. Cortisol increases after late gestation (32 - 36 weeks). However, in preterm infants, the adrenocortical gland secrets cortisol in response to stress [(10)].

RDS develops respiratory distress due to impaired synthesis and secretion of the surfactant and affects mostly preterm infants. Surfactant prevents the alveoli from collapsing during expiration and helps gas exchange [(11)]. Acute illnesses as RDS and infection influence the hypothalamic-pituitary-adrenal axis (HPA axis). Available information on the endogenous cortisol levels of preterm infants and their response to respiratory support strategies in our country is limited [(12)]. So, the aim of this work is to evaluate the levels of

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serum 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 during the period from 2019 till 2020. The study included 45 preterm neonates (23 females and 22 males).

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

Inclusion criteria: included preterm 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).

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), or 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 also excluded.

All patients included in this study were subjected to:

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). Short term outcome during the period of admission were recorded.

Through clinical examination Assessment of gestational age according to Doubowitz score.

Assessment of degree of RDS by Downes score. Neurological, Chest, Heart and Abdominal examination.

The following investigation were done to all groups of the study; Chest X-ray, Laboratory investigations; C-reactive protein and arterial blood gases (before respiratory support).

Serum cortisol levels in: the first and third day of life using the electrochemiluminescence immunoassay "ECLIA" (Elecsys and Cobase Analyzers-1010-Germany).

Specimen collection and preparation: 2 ml of peripheral venous blood were withdrawn and left to clot. Any procedure done to the baby 2 hours before sampling was avoided.

Serum was collected using standard sampling tube, and was centrifuged and kept stable for 5 days at 2-8°C for 3 months at -20°C. It was frozen only once.

Test principle: Competition principle total duration of assay 18 minutes:

1st incubation: 20 µl of sample in incubated with a cortisol-specific biotinylated antibody and a ruthenium complex labeled cortisol derivative. Depending on the concentration of the analyte in the sample and the formation of the respective immune complex, the labeled antibody binding site was occupied in part with sample analyte and in part with ruthenylated hapten. 2nd incubation: after addition of streptavidin-coated micro particles, the complex became bound to the solid phase via interaction of biotin and streptavidin.

The reaction mixture was aspirated into the measuring cell where the micro particles were magnetically captured onto the surface of the electrode. Unbound substances were then removed with proCell. Application of a voltage to the electrode then induced chemiluminescent emission, which was measured by a photomultiplier.

Results were determined via a calibration curve, which was instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Reagents-working solutions: M: Streptavidin-coated microparticles (transparent cap), 1 bottle, 6.5 mL; streptavidin-coated microparticles 0.72 mg/mL; preservative. **R1**: Anti-cortisol-Ab-biotin (gray cap), 1 bottle, 9 mL; Biotinylated polyclonal anti-cortisol antibody (ovine) 90 ng/mL; MES[b] buffer 100 mmol/L, pH 6.7; preservative. **R2:** Cortisol-peptide $\sim Ru(bpy)_3^{2+}$ (black cap), 1 bottle, 9 mL; cortisol derivative (synthetic), labeled with ruthenium complexed 25 ng/mL; danazol 20 µg/mL; MES buffer 100 mmol/L, pH 6.0; preservative.

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 were 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 (X) and standard deviation (SD) and analytic statistics included Student's t-test, Mann-Whitney test (U test). P value<0.05 was considered statistically significant and <0.01 was considered highly significant.

RESULTS

A total of 45 preterm neonates included the study, 23 of them females and 22 were males. Their age ranged from 30 to 36 weeks and their birth weight with a mean value of 1.8 + 0.3 kg (AGA).

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 (**Fig. 1).**

In cases with C.S. there was a significant difference between 1st and 3rd day's serum cortisol levels. In cases with V.D. there was no significant difference between 1st and 3rd day's serum cortisol levels. No significant difference was found between both modes of delivery in all studied groups regarding 1st day and 3rd day serum cortisol **(Table 1 and Fig. 2).**

Table (1): Relation between modes of delivery and mean serum cortisol levels 1st and 3rd day

		1st day serum cortisol (nmol/L)				3rd day serum cortisol (nmol/L)				P value
		Min	Max	X	SD	Min	Max	X	SD	
Mode of delivery	Cesarean section	188	411	301	77	134	989	403	193	0.012*
	Vaginal delivery	192	439	358	90	150	400	300	100	0.249
P value		0.98				0.49				

X mean SD Standard deviation * Significant

In cases who didn't receive antenatal steroids there was highly significant difference between 1st and 3rd day's serum cortisol levels. There was **a** significant difference between 1st day serum cortisol levels regarding antenatal steroids. There was a highly significant between 3rd day serum cortisol levels regarding antenatal steroids **(Table 2 and Fig. 3).**

Table (2): Relation between antenatal steroids and serum cortisol levels 1st and 3rd day in all studied groups

		1st day serum cortisol (nmol/L)				3rd day serum cortisol (nmol/L)				P value
		Min	Max	X	SD	Min	Max	X	SD	
Antenatal Steroids	Didn't receive	196	411	323	69	136	989	455	159	0.001**
	received	188	376	247	69	134	530	229	138	0.717
P value		0.022*				<0.001**				

* Significant at level of 0.05. ** Highly significant at level of 0.01.

There was no significant difference in both sexes regarding serum cortisol levels (1st and 3rd days) **(Table 3 and Fig. 4).**

Table (3): Serum cortisol level among males and females cases regarding

		1st Day Serum Cortisol (nmol/L)				3rd Day Serum Cortisol (nmol/L)				P-value
		Min	Max	X	SD	Min	Max	X	SD	
Sex	Female	188	410	282	75	149	582	390	155	0.18
	male	194	411	320	75	134	989	389	213	0.143
P value		0.09				0.59				

There was no significant difference in both (single and twin pregnancy) regarding serum cortisol levels (1st and 3rd days) **(Table 4 and Fig. 5).**

Table (4): Comparison between 1st day and 3rd day levels of serum cortisol regarding to multiplicity of pregnancy

		1st day serum cortisol (nmol/L)				3rd day serum cortisol (nmol/L)				P value
		Min	Max	X	SD	Min	Max	X	SD	
Multiple Pregnancy	Single	190	411	312	76	134	620	391	157	0.079
	Twin	188	378	276	75	149	989	386	240	0.065
P value		0.14				0.94				

Regarding 3rd day serum cortisol level cases with pathological findings had significantly higher levels than

control group. In a significant way, cases with pathological findings have higher 3rd day serum cortisol level than their 1st day serum cortisol level but control group has lower one on 3rd day. **(Table 5 and Fig. 6).**

Table (5): Comparison between cases with different X-ray findings regarding serum cortisol levels

		1st day serum cortisol (nmol/L)				3rd day serum cortisol (nmol/L)				P value
		Min	Max	X	SD	Min	Max	X	SD	
X-ray	Control	191	400	299	80	134	182	162	17	<0.001**
	Ground glass	188	411	317	79	411	989	511	123	0.004**
	Air bronchogram	211	399	286	66	419	481	451	30	<0.001**
	White lung	196	338	265	70	490	620	540	57	0.002**
P value		0.55				<0.001**				

** Highly significant.

In significant way 3rd day serum cortisol was negatively correlated with pH, PO_2 and HCO_3 and positively correlated with PCO_2 and Downes score (severity of RDS) (**Table 6).**

Table (6): Correlation between cortisol levels of all studied cases and other quantitative data

		1st day serum cortisol (nmol/L)	3rd day serum cortisol (nmol/L)
Birth Weight (kg)	Pearson Correlation	-0.481	-0.008
	Sig. (2-tailed)	0.069	0.959
Down score	Spearman Correlation	0.013	0.929**
	Sig. (2-tailed)	0.932	<0.001**
Hb (g/dl)	Pearson Correlation	0.162	0.011
	Sig. (2-tailed)	0.563	0.94
RBCs (x1,000,000 cells/mm3)	Pearson Correlation	0.162	0.011
	Sig. (2-tailed)	0.563	0.94
WBCs (x1,000 cells/mm3)	Pearson Correlation	0.292	-0.07
	Sig. (2-tailed)	0.291	0.636
Platelet count (x1,000 cells/mm3	Pearson Correlation	0.116	0.060
	Sig. (2-tailed)	0.681	0.697
pH	Pearson Correlation	0.430	-0.683**
	Sig. (2-tailed)	0.110	<0.001**
PO_2 (mmHg)	Pearson Correlation	0.050	-0.671**
	Sig. (2-tailed)	0.860	<0.001**
PCO_2 (mmHg)	Pearson Correlation	-0.203	0.364*
	Sig. (2-tailed)	0.468	0.014*
HCO_3 (mEq/L)	Pearson Correlation	0.337	-0.347*
	Sig. (2-tailed)	0.220	0.020*
1st day serum cortisol (nmol/L)	Spearman Correlation	-	-0.07
	Sig. (2-tailed)	-	0.642
3rd day serum cortisol (nmol/L)	Spearman Correlation	-0.071	-
	Sig. (2-tailed)	0.642	-

* Significant. ** Highly significant.

Regarding 1st day serum cortisol level, the table shows that there was no significant difference between studied groups however, regarding 3rd day serum cortisol level groups with less favorable prognosis had significantly higher levels than control group. Groups with less favorable prognosis had higher 3rd day serum cortisol level than their 1st day serum cortisol level but control group had lower one on 3rd day **(Table 7).**

Table (7): Comparison between different cases' prognosis regarding serum cortisol levels

		1st day serum cortisol (nmol/L)		3rd day serum cortisol (nmol/L)		P value
		Mean	SD	Mean	SD	
Prognosis	Control	299	80	162	17	<0.001**
	BPD	346	50	506	28	<0.001**
	Died	284	77	506	65	0.006**
	Improvement	299	80	501	139	<0.001**
P value		0.54		<0.001**		

** Highly significant

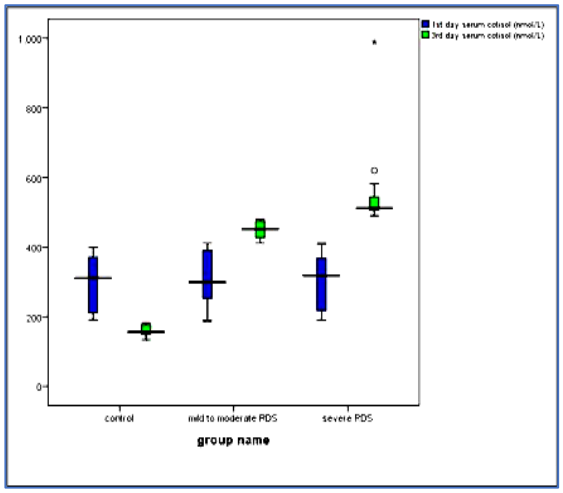


Fig. (1): Comparison between all studied groups regarding serum cortisol levels 1st and 3rd day

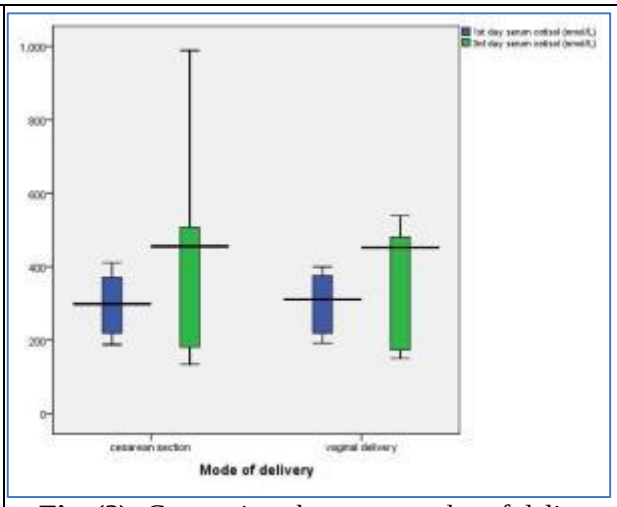


Fig. (2): Comparison between modes of delivery regarding mean serum cortisol levels 1st and 3rd day

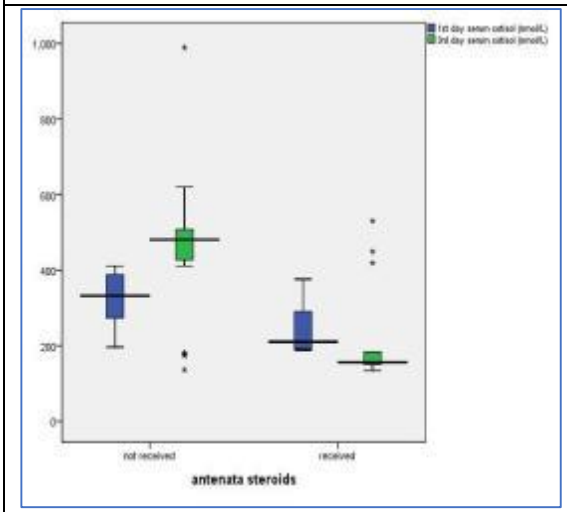


Fig. (3): Comparison between antenatal steroid, regarding serum cortisol levels 1st and 3rd day in all studied groups.

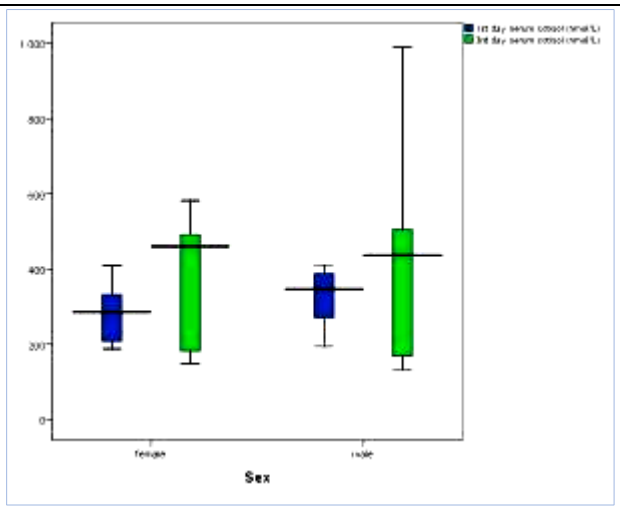


Fig. (4): Comparison between male and female cases regarding serum cortisol level.

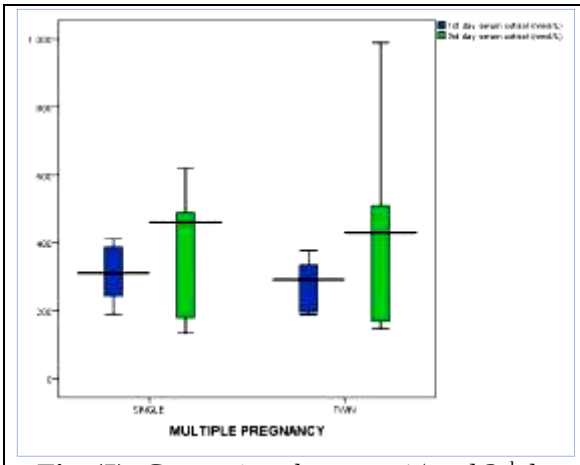


Fig. (5): Comparison between 1st and 3rd day levels of serum cortisol regarding to multiplicity of pregnancy.

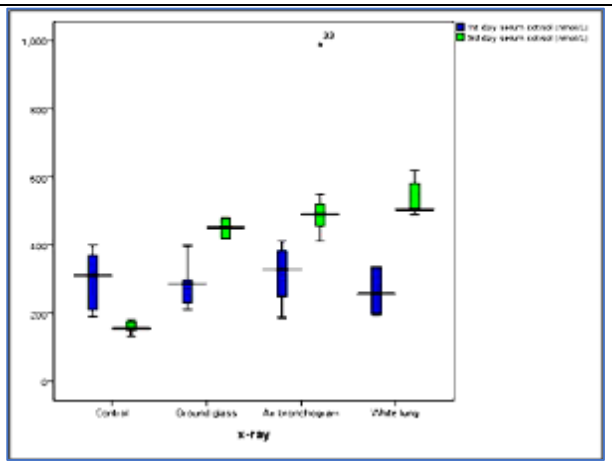
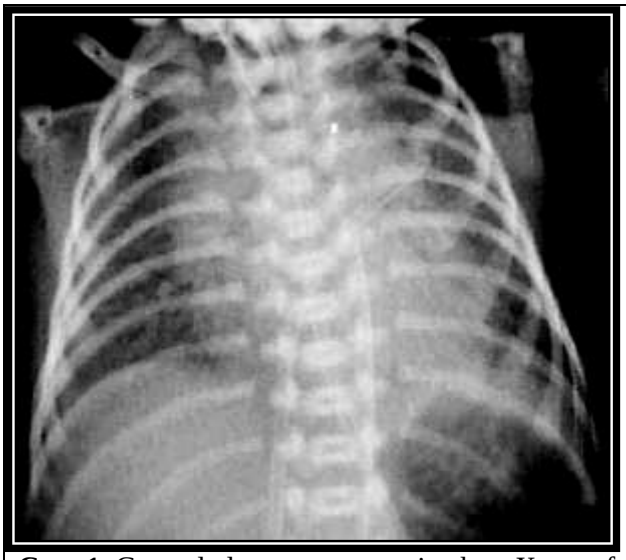
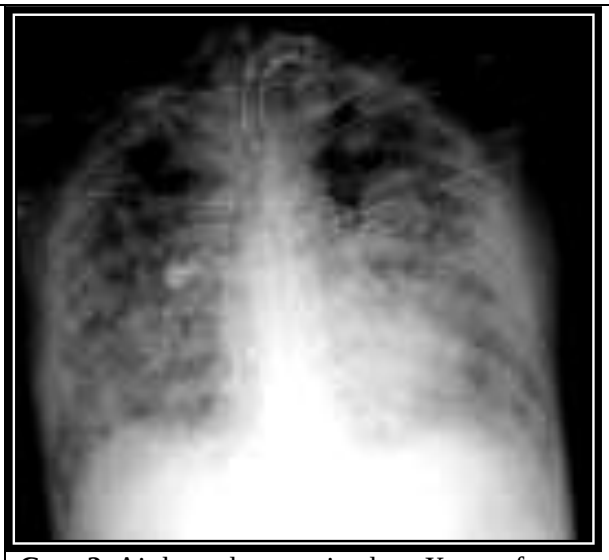


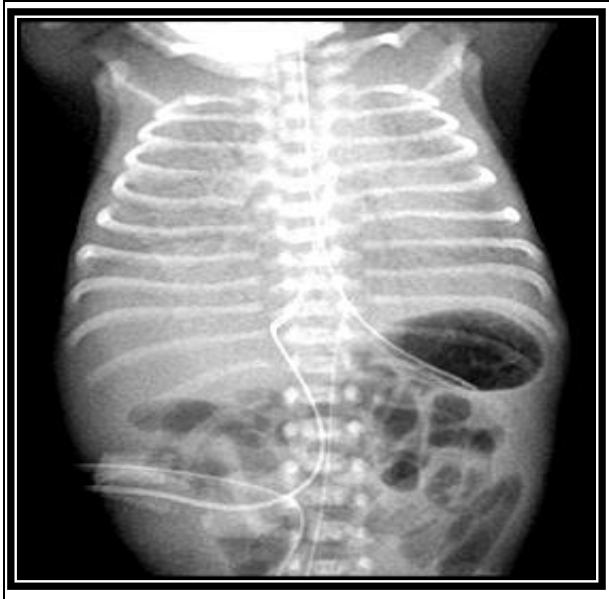
Fig. (6): Comparison between cases with different X-ray findings regarding serum cortisol levels.



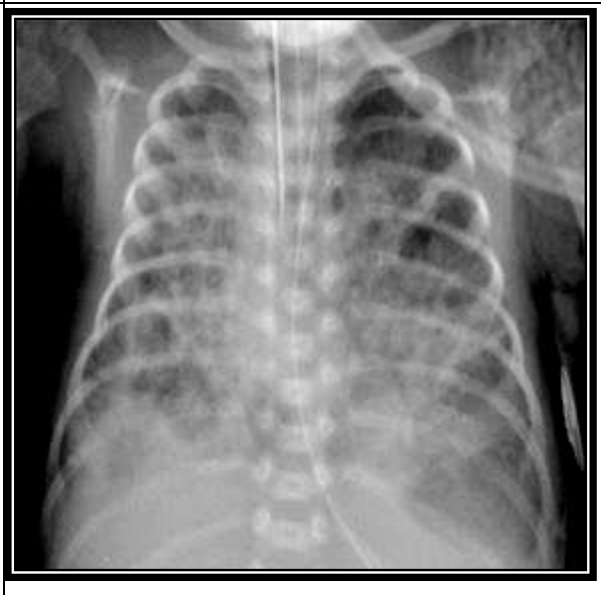
Case 1. Ground glass appearance in chest X-ray of case no. 17 in group II.



Case 2. Air bronchogram in chest X-ray of case no. 40 in group III.



Case 3. White lung in chest X-ray of case no. 45 in group III.



Case 4. Chest X-ray of case no. 31 in group II aged 28 day (postnatal age) complicated with bronchopulmonary dysplasia.

DISCUSSION

As regards the serum cortisol levels in the studied groups, we noticed that group (I) showed mean levels serum cortisol in the 1st day of life of (299 + 80 nmol/L) and in 3rd day of (162 + 17 nmol/L), with significant higher 1st day levels than 3rd day levels. While, in group II, mean levels of serum cortisol in 1st day were (308 + 76 nmol/L) and 3rd day mean levels of cortisol of the same group was (450 + 26 nmol/L), with statistically significant increase in third day than first day. In group III mean levels of serum cortisol in 1st day was (296 + 78 nmol/L) and 3rd day mean levels of cortisol of the same group was (557 + 125 nmol/L), with statistically significant increase in third day than first day. 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 **(13).**

While, comparison between 3rd day mean levels of serum cortisol between group II and III, showed that group III had significant higher levels than group II. This elevation in 3rd day serum cortisol in cases of mild to moderate RDS could indicate that endogenous cortisol is an important physiological stimulus to fetal lung maturation **(14)**.

Elevated serum cortisol levels in ventilated preterm infants (group III) than other groups in our study may suggest that infants with RDS release more cortisol than healthy one in order to cope with poor pulmonary function, preterm infants respond to the stress at delivery and cortisol production continues, these finding could be the result of severe stress associated with respiratory distress and positive pressure ventilation. So, our study does not provide any support for the hypothesis that early supplementation with physiologic doses of hydrocortisone may benefit preterm infants older than gestational age of 30 weeks, which was recommended by **Ng *et al.* (15).**

Our findings were in agreement with the results of **Gunes *et al.* (16) and Tan *et al.* (17)** who found high serum cortisol levels in all preterm infants regardless their respiratory distress within 1st day of life. Also, our study has a support from **Bolt *et al.* (18)** who studied the maturity of adrenal cortex in preterm infants and found that preterm born less than 30 weeks had lower cortisol levels and cortisol 17 hydroxy progesterone ratio compared with those born between 30 – 36 weeks (regardless their clinical status) suggesting that adrenal cortex function closely related to gestational age. Our study differed than this study by performance of our study on certain age group (30-36 weeks) regarding respiratory distress syndrome. On the other hand, **Huysman *et al.* (19)** who studied the adrenal function in sick preterm infants (less than 30 weeks) by measuring basal cortisol level and cortisol after ACTH stimulation test; found that mean baseline cortisol level was significantly lower in ventilated than non-ventilated indicating adrenal insufficiency in sick newborn infants.

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 (P-value = 0.54), 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 **Aucott *et al.* (20)** 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 **Nykänen *et al.* (21)**, 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 (22)** in contrast with our study, found that developing BPD was related to lower cortisol secretion in response to ACTH hormone. While the study, which was done by **Gunes *et al.* (16)** 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 respond to the stress at delivery and cortisol production continues in infants with RDS than those without RDS; may be in order to cope with poor pulmonary function and to enhance lung maturity. Moreover, 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. 1st day serum cortisol level was affected by perinatal events as the use of antenatal steroids and mode of delivery. 3rd day cortisol level increased by increasing the severity of RDS, and its elevations may reflect consequent poor prognosis. Also, 3rd day serum cortisol shows a predictive value in the prognosis of RDS.

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Author contribution: Authors contributed equally in the study.

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