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Relation of Cord Cortisol Level and Respiratory Distress Syndrome in Preterm

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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. **Aim of the Work:** assess the relationship between Cortisol level in umbilical cord in first and third day after delivery & Respiratory distress syndrome in preterm. **Patients and Methods:** a case control study that includes 90 preterm infant. Each included infant was submitted to history taking, complete clinical examination and laboratory investigations including complete blood count, arterial blood gases, level of cortisol in day one and day three. **Results:** in the present work, there was no significant difference between cases and controls as regard age, gender, weight, gestational age, as regards the serum cortisol levels in the studied groups,this study revealed that mean level of serum cortisol in 1stday of life among the three groups showed elevation and showed no significant statistical difference between the three groups (P-value = 0.107) Regarding mean level of serum cortisol in 3rd day of life showed high significant difference between the three groups (P-value = 0.001). group I (without RDS) marked lower than both groups II&III (with RDS), and comparison between group II and III regarding the same value, showed that group III had significant higher level than group II (P-value = 0.001). **Conclusion:** preterm infants respond to the stress at delivery and cortisol production continues in infants with RDS than those without RDS.

Keywords: Cord Cortisol, Preterm, Respiratory Distress, Stress Response.

INTRODUCTION

A preterm birth is defined as live birth at < 36 weeks' gestation and a lower cutoff defined in some countries as 20 or 22 weeks' gestation. This group is further trichotomized as late preterm (>32 weeks), very preterm (28–<32 weeks) and extremely preterm (<28weeks) [(1)]. Approximately 11% of births in the United States occur before 37 completed weeks of gestation, which is considered premature, or preterm, birth [(2)]. Respiratory distress syndrome (RDS) is a breathing disorder that affects preterm babies due to surfactant deficiency. Surfactant is a liquid that coats the inside of the lungs. It helps keep them open, so that infants can breathe in air once they are born [(3)]. 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[(4)]. Researchers have long measured cortisol as a marker of both acute and chronic stress, whether collected from serum, blood, saliva, or urine[(5)].

AIM OF THE WORK

The aim of this study is to assess the relationship between Cortisol level in umbilical cord in first and third day after delivery & Respiratory distress syndrome (RDS) in preterm.

PATIENTS AND METHODS

This is a prospective cohort study done in Damnhour Teaching hospital and Hospital at new Damitte (Al-AzharUniversity) during period from October 2016 to January 2018. **Subject:** 90 preterm newborns were included into the study, divided in 2 groups: **Patient groups:** consist of 60 Preterm infant diagnosed with Respiratory distress syndrome which divided in 2 subgroups. Mild to Moderate Respiratory distress syndrome. Severe Respiratory distress syndrome. **Control group:** consist of 30 of healthy Preterm infant, healthy status was determined through examination and investigation. **Inclusion criteria:** born preterm babies (gestational age 30-37 weeks), any mode of delivery, both genders, birth weight. (>1000gm). **Exclusion criteria:** Neonatal sepsis, birth asphyxia or any complication during birth, congenital anomalies, meconium stained amniotic fluid, any complication arising during the hospital stay, antenatal steroid intake, maternal disease or any type of stress during pregnancy, all the newborns in this study were subjected to the following: **1- Comprehensive history taking including:** antenatal history: maternal age, maternal disease (diabetes or immune disease) and drug intake, natal history: Gestational age, sex, mode of delivery, birth trauma, family history: consanguinity, congenital anomalies, respiratory distress in previous sibling and endocrinal disease. **2- Clinical examination for neonates:** Recording apgar score at 1 and 5 minutes, gestational age by new ballard score, Anthropometric measures, general examination, cardiac, chest, abdominal and

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neurological examination. **3-Laboratory investigation:** C-reactive protein, arterial blood gases, cord cortisol level (on 1st and 3rd day). **Method of measurement of Serum cortisol level: Sampling of blood:** at First day: 2ml of cord blood were collected in sterile vacutainer tube, at Third day: 2ml of venous blood were collected in sterile vacutainer tube, the collected blood was left to clot then centrifugated at 3000 r.p.m. The serum was separated and stored at -20 C° till the time of assay. **Test principle of cortisol:** serum Cortisol level was assayed using an automated chemiluminscene. Immunoassay by Immulite instrument (Diagnostic products corporation, Los Angeles, CA 90045 USA). **Statistical analysis of data:** Statistical presentation and analysis of the present study was done using SPSS V20.0 conducted using the mean, standard deviation, student t- test, ANOVA, Chi square test and roc curve. Description of quantitative variables by mean, SD and range and description of qualitative variables by numbers and percentage. Un paired student t-test was used to compare between groubs in quantitative data. Linear correlation coefficient was used for detection of correlation between two quantitative variables in one group. ***Ethical and approval considerations***: A complete set of templates for participant information and consent forms have been done. The study was approved by the Ethics Board of Al-Azhar University.

RESULTS

The results of this study are represented in the following tables and figures.

Table (1): Comparison between the studied control and patients groups regarding sex.

Sex / Groups	Total	Control group "n=30"		Patients group			
				Mild to moderate RDS "n=30"		Sever RDS "n=30"	
		No.	%	No.	%	No.	%
Male	43	13	43.3	16	53.3	14	46.7
Female	47	17	56.7	14	46.7	16	53.3
X^2		0.623					
P		0.732					

Table (1), show the comparison between the studied control and patients groups regarding sex, it was found that there was no statistical significant difference between the three groups regarding sex ($p > 0.05$).

Table (2): Comparison between the studied control and patients groups regarding gestational age and birth weight.

GA/Birth Weight / Groups	Control group "n=30"	Patients group	
		Mild to moderate RDS "n=30"	Sever RDS "n=30"
GA(weeks)			
Mean	35.6	34.02	33.2
S.D.	8.36	8.65	8.42
ANOVA	2.36		
p-value	0.136		
birth weight(kg)			
Mean	2.06	2.00	1.89
S.D.	0.46	0.39	0.43
ANOVA	0.25		
P	0.748		

Table (2) shows Comparison between the studied control and patients groups regarding gestational age and birth weight, it was found that there was no significant difference between the three studied groups regarding gestational age and birth weight ($p > 0.05$).

Table (3): Comparison between the studied control and patients groups regarding hemodynamic data.

Hemodynamic data / Groups	Control group "n=30"	Patients group		ANOVA	p
		Mild to moderate RDS "n=30"	Sever RDS "n=30"		
pH					
Mean	7.37	7.19	7.13		0.001*
S.D.	1.8	1.7	1.6		
PO2					
Mean	92.0	79.5	74.6	18.2	0.001*
S.D.	23	19.8	18.6		
PCO2					
Mean	38.6	40.3	43.2	4.26	0.039*
S.D.	9.6	10.1	10.8		
HCO3	26.2	19.8	17.2	5.69	0.029*
Mean	6.55	4.9	4.3		
S.D.					

Table (3), show the comparison between the studied control and patients groups regarding hemodynamic data, the pH, PO2, PCO2 and HCO3 show a significant difference between the three studied groups ($p < 0.05$).

Table (4): Comparison between the studied control and patients groups regarding X-ray findings.

x-ray findings / Groups	Total	Control group "n=30"		Patients group: Mild to moderate RDS "n=30"		Patients group: Sever RDS "n=30"	
		No.	%	No.	%	No.	%
Free	30	30	100.0	0	0.0	0	0.0
Ground glass	17	0	0.0	15	50.0	2	6.7
Air bronchogam	30	0	0.0	15	50.0	15	50.0
White lung	13	0	0.0	0	0.0	13	43.3
X^2		35.65					
P		0.001*					

Table (4), show the comparison between the studied control and patients groups regarding X-ray findings, the control cases mild to moderate group show that 50.0% of cases had ground glass, while the other 50.0% show air bronchogam, the cases with severe RDS, only 2 cases (6.7%) had ground glass, 50.0% of the cases had air bronchogam and 43.3% had white lung, there was a significant difference between the three groups regarding the X-ray findings.

Table (5): Comparison between the studied control and patients groups regarding blood picture.

Blood picture / Groups	Control group "n=30"	Patients group: Mild to moderate RDS "n=30"	Patients group: Sever RDS "n=30"	ANOVA	p
Hemoglobin level (g/dl)					
Mean	14.25	13.8	14.01	1.26	0.365
S.D.	3.56	3.45	3.52		
RBCs (10^{-3}) / µl)					
Mean	4.89	4.72	4.36		
S.D.	0.95	0.72	0.425	1.09	0.421
WBCs (10^{-3}) / µl)					
Mean	8.01	9.06	8.22		
S.D.	2.33	2.65	2.74	2.07	0.163
Platelet (10^{-3})/ µl)					
Mean	185.2	182.6	186.5		
S.D.	26.2	25.6	26.6	1.22	0.32

Table (5), show the comparison between the studied control and patients groups regarding blood picture, the hemoglobin level, RBCs, WBCs and platelet show no significant difference between the three studied groups ($p > 0.05$).

Table (6): Comparison between the studied control and patients groups regarding prognosis.

Prognosis / Groups	Total	Control group "n=30"		Patients group: Mild to moderate RDS "n=30"		Patients group: Sever RDS "n=30"	
		No.	%	No.	%	No.	%
Control	30	30	100.0	0	0.0	0	0.0
Improved	40	0	0.0	28	93.3	12	40.0
Died	20	0	0.0	2	6.7	18	60.0
X^2		19.8					
P		0.001*					

Table (6), show the comparison between the studied control and patients groups regarding prognosis, there was a significantly increase in mortality in severe RDS group (60.0%) of the neonates was die, ($p < 0.01$).

Table (7): Comparison between the studied control and patients groups regarding cortisol level at 1st and 3rd day.

Cortisol level(nmol) / Groups	Control group "n=30"	Patients group: Mild to moderate RDS "n=30"	Patients group: Sever RDS "n=30"	ANOVA	P
At 1st day					
Mean	211.66	220.5	233.03	3.01	0.107
S.D.	46.1	60.9	77.02		
At 3nd day					
Mean	192.4	428.7	597.86	62.65	0.001*
S.D.	49.4	97.8	160.29		
T	1.98	4.65	16.52		
P	0.041*	0.01*	0.001*		

In group I, highly significant difference between 1st and 3rd days serum cortisol levels (in 3rd day lower level than in 1st day). In group II, highly significant difference between 1st and 3rd days serum cortisol levels (in 3rd day higher level than in 1st day). In group III, highly significant difference between 1st and 3rd days serum cortisol levels (in 3rd day higher level than in 1st day). No significant difference between all studied groups regarding 1st day serum cortisol. Highly significant difference between all studied groups regarding 3rd day serum cortisol.

Table (8): Relation between the level of cortisol at 1st and 3rd day and prognosis.

Cortisol level / Groups	Control	Improved	Die	ANOVA	P
At 1st day					
Mean	211.66	220.5	235.4		
S.D.	46.1	81.1	70.1	3.12	0.064
At 2nd day					
Mean	192.4	456.5	626.9		
S.D.	49.5	93.3	104.7	19.3	0.001*

Table (8), show the relation between the level of cortisol at 1st show no significant between the different out come. at 3rd day, it was found that there was a significant increase in cortisol level in die neonatal more than the improved cases ($p < 0.05$).

DISCUSSION

Respiratory distress syndrome (RDS) is a breathing disorder that affects preterm babies due to surfactant deficiency. Surfactant is a liquid that coats the inside of the lungs. It helps keep them open, so that infants can breathe in air once they are born [(3)]. Preterm infant try to response to this stressful condition with multiple mechanism. The hypothalamic-pituitary-adrenal (HPA) axis plays an important role in the host stress response. During stress, stimulation of the HPA axis increases corticotropin release and enhances adrenal secretory activity and increase release of cortisol [(6)]. This prospective was carried out to evaluate the levels of serum cortisol in the 1st and 3rd days of life in preterm neonates with respiratory distress syndrome. The current study was carried out in NICU of DamietteFaculty of Medicine (Al-azharUniversity) and Damnhour medical Teaching Institute during the period of October 2016 to January 2018 on 90 preterm babies, with gestational age ranged from 30 to 36 weeks, were classified into; preterm neonates without RDS(group I, n=30) as control, preterm neonates with mild to moderate RDS, were on CPAP (group II, n=30), and preterm neonates with severe RDS, were mechanically ventilated (group III, n=30). All neonates were subjected to full history taking (maternal drug history, prenatal, natal and postnatal history), clinical examination was performed by assessment of APGAR score, vital signs, birth weight and gestational age by Ballard score. The diagnosis of RDS was established by physical examination shows usually Chest wall retraction and cyanosis on room air, compatible x-ray demonstrating diffuse alveolar atelectasis and arterial blood gases demonstrating metabolic acidosis, hypoxemia and hypercapnia. The present study reported that, percentage of male patients was (53.3%) versus(46.7%) to female patients among cases with moderate RDS (groups II) while in cases with severe RDS male patients was (46.7) versus (53.3%) to female patients (group III)while in cases without RDS (group I), males were (43.3%) versus (56.7%) to females. With no statistical significant difference between males and females in all groubs (P= 0.732). These data are similar to results of **Marttila*et al.*** [(7)]who study the incidence and risk factors of RDS and concluded that, there are no significant difference in RDS risk regarding gender. In our study, concerning gestational age (GA), gastational age ranged from 32 to less than 37 week in group I, from 30-37 week in group II and from 31 to 36 week in group III, with no statistically significant difference between the studied groups regarding gestational age (p-value =0.136), which indicating the compatibility of the three groups for comparison. As regards, X-ray findings in our study, showed that cases (groups II and III) had more pathological X-ray findings than control (group I).Our results noticed a highly statistical significant difference between the studied groups regarding X-ray findings (p-value =0.001). Our study showed that there was no statistically significant difference between the studied groups regarding CBC findings. **In the present study, as regards the serum cortisol levels in the studied groups,** we noticed that group (I) showed mean level serum cortisol in the 1st day of life was (201.53 $\pm$59.7nmol/L), and in 3rd day of life was (192.4 $\pm$49.4 nmol/L), with highly significant statistical difference between both values (P-value =. 042). While, in group II, mean level of serum cortisol in 1st day of life was (220.5$\pm$60.9 nmol/L),and in the 3rd day was 428.7$\pm$ 97.8 nmol/L), with highly significant statistical difference between both values (P-value = 0.01). In group III mean level of serum cortisol in 1st day of life was (233.03$\pm$77.02 nmol/L), and in 3rd day was (597.86$\pm$160.29 nmol/L) (P-value = 0.002), with statistical significant higher in third day than first day (P-value = 0.001). On other hand, this study revealed that mean level of serum cortisol in 1stday of life

among the three groups showed elevation and showed no significant statistical difference between the three groups (P-value = 0.107). Regarding mean level of serum cortisol in 3rd day of life showed high significant difference between the three groups (P-value = 0.001). group I (without RDS) marked lower than both groups II&III (with RDS), and comparison between group II and III regarding the same value, showed that group III had significant higher level than group II (P-value = 0.001). Our finding concerning the elevation of 1stday serum cortisol explained by **Mesiano and Jaffe** [8]who clarified the association between the birth process and the large increase in the fetal stress hormones such as cortisol and catecholamine which began in decreasing after 24 of birth to reach the normal range within one week. Our findings are in agreement with the results of **Kouppila*et al.*** [9]who found high serum cortisol levels in all preterm infants regardless their respiratory distress within 1st day of life. So, in our study, the decrease in 3rd day serum cortisol in cases didn't suffer from RDS may be considered as a normal physiological changes in cortisol levels. Regarding the elevation in 3rd day serum cortisol in cases suffered from RDS (groups II &III),these findings are similar to those of **Mesiano and Jaffe**[8]who concluded that the severity of RDS and mechanical ventilation were related to serum cortisol levels of preterm infants, suggesting that large and mature preterm infants who are ventilated and\or more severely ill release more cortisol than those less severely ill. A further possible explanation clarified by **Bolt*et al.*** [4] who reported that preterm infants with RDS showed high serum cortisol levels, could indicate that endogenous cortisol is an important physiological stimulus to postnatal lung maturation. This finding were also in agreement with the result of **Grofer*et al.*** [10]that there is a positive association between illness severity and cortisol production rates (CPR) in preterm infants with a gestational age between 30 and 36 weeks. Another study done by **Bagnoli *et al.*** [11] demonstrated that the pituitary–adrenal axis is completely mature only at the end of gestation, the secretion of cortisol and ACTH increased in a progressive linear way from the lowest gestational ages up to the end of gestation. Also **Chung** [12] reported that fetal cortisol levels in the human are low relative to normal cortisol levels until about 30 weeks gestation.

CONCLUSION

Preterm infants respond to the stress at delivery and cortisol production continues in infants with RDS than those without RDS. Moreover, infants with severe RDS (mechanically ventilated) release more cortisol which could be the result of severe stress associated with respiratory distress. Early prevention of RDS as a very important cause of neonatal morbidity &mortality by decreasing the perinatal risk of preterm labor. Using of 3rd day serum cortisol as a simple test for prediction of the short –term outcome of cases with RDS, further studies are required to determine the bioactivity of endogenous cortisol in those patients and study the relation between neonatal cortisol concentrations in different morbidities and both short and long- term outcome.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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