Relationship between Serum Free T4 and Thyroid Stimulating Hormone Levels in Preterm Neonates and Respiratory Distress Syndrome

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Abstract: Background and objectives: Worldwide 15 million babies are born preterm every year. Preterm birth is one of the leading causes of neonatal morbidity and mortality worldwide. Respiratory distress syndrome (RDS) is one of the most common respiratory complications of prematurity and its incidence inversely proportional to gestational age and birth weight. Despite the proven efficacy of antenatal corticosteroids in preventing RDS, they are not effective at preventing all cases of RDS and are limited by the time required to exert an effect on lung maturation and surfactant production before preterm birth. So the use of thyroid hormones has the potential to stimulate surfactant release and reduce respiratory morbidity in preterm infants with RDS. **Methods:** In This In case control study we measure the serum free thyroxin (FT4), and thyroid stimulating hormone (TSH) in 60 preterm neonates in Al-Azhar University Hospital in New Damietta during 1st postnatal 24 hours to demonstrate the relationship between their levels and RDS. **Results:** We found in this study that there was no relation between TSH serum levels and both the occurrence and the severity of RDS, however; there was a significant negative correlation between FT4 serum levels and both the occurrence and the severity of RDS. The study also revealed significant decrease in FT4 in the RDS subgroup with lower gestational age compared to the RDS subgroup with higher gestational age. **Conclusion:** There is significant negative correlation between the occurrence and severity of RDS and the serum level of free thyroxin (FT4) but there is no correlation between the occurrence and severity of RDS and the serum level of thyroid stimulating hormone (TSH) in preterm neonates.

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Key words: Prematurity, respiratory distress syndrome (RDS), free thyroxin (FT4), thyroid stimulating hormone (TSH).

1. Introduction

Preterm, as defined by the WHO 1999 is a newborn who is delivered before 37 completed weeks of gestation[1]. Worldwide 15 million babies are born preterm every year[2]. Preterm birth is one of the leading causes of neonatal morbidity and mortality worldwide. Recent reduction in infant mortality rates have been primarily occurred through more effective treatment of prematurely born infants[3].

Premature baby is the baby born during the fetal period where the organs are present, but not yet fully functional and are still undergoing further development. The early weeks of gestation are devoted to growth, while the final weeks are devoted to maturity and finishing off the finer details[4].

Respiratory distress syndrome (RDS) is the most common cause of respiratory distress in newborn. It occurs almost primarily in preterm infants and its incidence inversely proportional to gestational age and birth weight. It occurs due to deficiency, inactivation or dysfunction of pulmonary surfactant[5]. It occurs in 60-80% of infants less than 28 week of gestational age, in 15-30% of those between 32 and 36 weeks, in about 5% beyond 37 weeks[6].

The diagnosis of RDS is based on a combination of the clinical features (tachypnea, subcostal, intercostal retractions, nasal flaring and cyanosis, on auscultation air movement is diminished despite vigorous respiratory effort, evidence of prematurity) with exclusion of other causes of respiratory distress. Also the characteristic radiographic appearance helps RDS diagnosis. The typical radiographic features consist of a diffuse reticulogranular pattern, giving the classic ground-glass appearance, in both lung fields with super-imposed air bronchograms[7].

Variety of hormones affects surfactant synthesis and lung development hence affects the occurrence and severity of RDS in neonate. Among these hormones are glucocorticoids and thyroid hormones[8].

In preterm infants, values for serum T4 and free T4 (FT4) in the first days after birth vary directly with gestation. However, unlike term infants, the concentrations of T4 and FT4 reach a nadir between day 10 and 14 after birth that is more severe at lower

gestations and birth weights. Thyroid hormone levels then tend to return to its normal levels after three weeks, but continue to increase up to six to eight weeks after birth. This period of low thyroid hormone levels in infants born prematurely has been termed "transient hypothyroxinaemia of prematurity"[9].

Risk factors for transient hypothyroxinaemia reported in observational studies have included lower gestational age, maternal pre-eclampsia with placental insufficiency, fetal growth restriction, perinatal asphyxia, respiratory distress syndrome, more severe respiratory disease, mechanical ventilation, and low diastolic blood pressure and dopamine infusions. Adverse neonatal outcomes associated with transient hypothyroxinaemia have included intraventricularhaemorrhage, chronic lung disease and death[9].

Despite the proven efficacy of antenatal corticosteroids in preventing RDS, they are not effective at preventing all cases of RDS and are limited by the time required to exert an effect on lung maturation and surfactant production before preterm birth. So the use of thyroid hormones has the potential to stimulate surfactant release and reduce respiratory morbidity in preterm infants with RDS[10].

2. Patients and method

This study was carried out in Al-Azhar University Hospital in New Damietta. This case control study was conducted on 60 preterm neonates. They were classified into 30 cases (group 1) with respiratory distress syndrome and 30 control preterm neonates (group 2) who don`t have respiratory distress.

Each group is further subdivided into 2 categories according to gestational ages; group 1A (15 cases of with RDS with gestational age ≤ 32 wks), group 1B (15 cases with RDS with gestational age from >32 wks to <37wks), group 2A (10 control preterm without RD with gestational age ≤ 32wks) and group 2B (20 control preterm without RD with gestational age from >32 wks to <37 wks).

Inclusion Criteria:

1) Preterm neonates with RDS (Cases) and healthy preterm neonates (Control) whose gestational age range from (28 wks to <37 wks).

2) Both sexes.3) Age: at the first day of life.

Exclusion Criteria:

1) Apparent major malformations (CNS, CVS, respiratory system) e.g. obvious congenital anomalies as congenitalcyanotic heart diseas, hydrocephalus, spina bifida, etc.

2) Apparent signs suggesting chromosomal abnormalities.

3) Infants of mothers with history of thyroid disease or on thyroid medications.

4) Infant of diabetic mother.

5) Infant of mothers with history of chronic diseases as chronic renal failure, SLE, etc,.

6) Suspected congenital infections.

7) ABO and Rh incompatibility.

8) Prenatal asphyxia.

In this study we measured the serum free thyroxin (FT4), and thyroid stimulating hormone (TSH) by ELISA test in preterm neonates within the 1st day after delivery to demonstrate the relationship between their levels and RDS.

Each neonate in this study was subjected to the following:

1) History taking: Prenatal, Natal, Postnatal and Family history

2) Clinical examination: - Apgar score at 1 and at 5 minute after birth[11].

- Examination of general condition, CNS, CVS, respiratory system, abdomen and genitalia.

- Estimation of GA using Modified Ballard Score[12].

- Anthropometric measures (birth wt., length and head circ. at birth) and plotted on growth charts to detect SGA, LGA and AGA[13].

3) Investigations:

A. Laboratory:

1- CBC 2- Serum free T4 3- Serum TSH 4- CRP 5- ABG (for cases)

B. Radiological: Chest X-ray.

C. Oxygen Saturation: By pulse oximetry.

3. Results:

Table 1: Demographic data for all studied neonates

Characteristics		No.	%	Mean ± SD
Gender	Male	36	60.0%	
	Female	24	40.0%	
GA (wks)	≤ 32	25	41.7%	
	>32 - <37	35	58.3%	32.85 ± 2.51
Maternal age (yrs)	<20	10	16.7%	
	20 - 30	40	66.7%	
	>30	10	16.7%	24.5 ± 4.5
Weight (kg)	Range (0.68 - 3.6)			1.9 ± 0.74

Table 2: Risk factors for RDS in case and control groups

Risk factors for RD		Group				MCP
		Group 1 (Cases) No.=30		Group 2 (Controls) No.=30		
		No.	%	No.	%	
GA (Wks)	≤ 32 wks	15	25%	10	16.7%	0.295
	>32 - <37 wks	15	25%	20	33.3%	
Weight (Kg)	<1.5	12	40.0%	10	33.3%	0.181
	1.5-2.4	14	46.7%	10	33.3%	
	2.5+	4	13.3%	10	33.3%	
Maternal medical disorders during pregnancy	1- No observed disorder	13	43.3%	12	40%	0.951
	2- Intrauterine fetal distress	1	3.3%	1	3.3%	
	3- Pre eclampsia	3	10.0%	2	6.7%	
	4- Vaginal bleeding	2	6.7%	3	10.0%	
	5- PROM	8	26.6%	5	16.7%	
	3,4	0	0.0%	1	3.3%	
	3,5	2	6.7%	5	16.7%	
	4,5	1	3.3%	1	3.3%	
Mode of delivery	N.V.D	10	33.3%	16	53.3%	0.118
	C.S	20	66.7%	14	46.7%	
Apgar score at 1 min	3-6	15	50.0%	1	3.3%	0.001*
	7-9	15	50.0%	29	96.7%	
Apgar score at 5 min	3-6	4	13.3%	0	0.0%	0.028*
	7-10	26	86.7%	30	100.0%	
Mode of resuscitation	1- Tactile stimulation	2	6.7%	11	36.7%	0.001*
	2- O2 supply	0	0.0%	0	0.0%	
	3- Ambu mask	0	0.0%	0	0.0%	
	4- ETT	9	30.0%	0	0.0%	
	1,2	14	46.7%	18	60.0%	
	1,3	1	3.3%	1	3.3%	
	1,4	4	13.3%	0	0.0%	

MCP: Mont Carlo exact probability * P < 0.05 (significant)

Table 3: Some laboratory investigations in case and control groups

Lab investigations		Group		t (P)
		1 (Cases) No=30	2 (Controls) No=30	
Hb (g/dL)	Mean ± SD	15.91 ± 3.24	15.45 ± 3.60	0.51 (0.610)
Hct (%)	Mean ± SD	46.23 ± 9.29	43.86 ± 7.56	0.92 (0.360)
WBC (billion /L)	Mean ± SD	11.21 ± 5.10	12.27 ± 5.98	0.74 (0.460)
Plt (billion/L)	Mean ± SD	205.70 ± 108.93	273.37 ± 147.77	2.1 (0.048)*
TSH (µIU/ml)	Range	0.31 – 52.76	0.51 – 13.54	U=0.37 (0.712)
	Mean ± SD	6.10 ± 10.89	3.79 ± 3.03	
	Median	26.55	7.025	
FT4 (pmol/L)	Range	11.35 – 25.80	12.21 – 28.59	2.5 (0.015)*
	Mean ± SD	18.61 ± 3.71	20.90 ± 3.40	

t: independent samples t-test U: Mann-Whitney test * P < 0.05 (significant)

Table 4: Risk factors for RDS among case subgroups

Risk factors for RDS		Group 1 (Cases)				*P*
		Subgroup 1ANo.=15		Subgroup 1BNo.=15		
		No	%	No	%	
Weight (Kg)	<1.5	10	66.7%	2	13.3%	0.004*
	1.5-2.5	5	33.3%	9	60%	
	>2.5	0	0.0%	4	26.7%	
Maternal medical disorders during pregnancy	1- No observed disorder	6	40.0%	7	46.7%	0.389
	2- Intrauterine fetal distress	0	0.0%	1	6.7%	
	3- Pre eclampsia	0	0.0%	3	20%	
	4- Vaginal bleeding	1	6.7%	1	6.7%	
	5- PROM	5	33.3%	2	13.3%	
	2,5	1	6.7%	0	0.0%	
	3,4	0	0.0%	0	0.0%	
	3,5	1	6.7%	1	6.7%	
	4,5	1	6.7%	0	0.0%	
Mode of delivery	N.V.D.	6	40%	4	26.7%	0.439
	C.S.	9	60%	11	73.3%	
Apgar score at 1 min	3-6	7	46.7%	8	53.3%	0.715
	7-10	8	53.3%	7	46.7%	
Apgar score at 5 min	3-6	1	6.7%	2	13.3%	1.000
	7-10	14	93.3%	13	86.7%	
Mode of resuscitation	1- Tactile stimulation	0	0.0%	2	13.3%	0.096
	2- O2 supply	0	0.0%	0	0.0%	
	3- Ambu bag	0	0.0%	0	0.0%	
	4- ETT	4	26.7%	5	33.3%	
	1,2	6	46.7%	8	53.3%	
	1,3	1	6.7%	0	0.0%	
	1,4	4	26.7%	0	0.0%	

MCP: Mont Carlo exact probability * P < 0.05 (significant)

Table 5: Clinical data for RDS among case subgroups

Clinical data		Group 1 (Cases)				FEP
		Subgroup 1A No.=15		Subgroup 1B No.=15		
		No	%	No	%	
Down score	3-6	13	86.7%	12	80.0%	0.624
	>6	2	13.3%	3	20.0%	
Silverman Anderson Index	3-6	7	46.7%	10	66.7%	0.269
	>6	8	53.3%	5	33.3%	

FEP: Fisher exact probability * P < 0.05 (significant)

Table 6: Some laboratory investigations among case subgroups

Lab investigations	Group 1 (Cases)				t (P)
	Subgroup 1A No.=15		Subgroup 1B No.=15		
	Mean	SD	Mean	SD	
Hb (g/dL)	16.39	3.53	15.43	2.96	0.81 (0.427)
Hct (%)	47.62	10.29	44.83	8.29	0.82 (0.421)
WBC (billion cells/L)	10.96	4.51	11.45	5.78	0.23 (0.798)
Plt (billion/L)	199.80	138.74	211.60	72.48	0.29 (0.772)
TSH (µIU/ml)	4.18	1.72	8.02	15.32	U=0.96 (0.315)
FT4(pmol/L)	17.21	3.74	20.00	3.21	2.2 (0.037)*

t: independent samples t-test U: Mann-Whitney test * P < 0.05 (significant)

Table 7: Some laboratory investigations among control subgroups

Lab investigations	Group 2 (Controls)				t (P)
	Subgroup 2A No=10		Subgroup 2B No=20		
	Mean	SD	Mean	SD	
Hb (g/dL)	16.41	2.77	14.98	3.93	1.0 (0.312)
Hct (%)	45.84	8.83	42.87	11.41	0.72 (0.477)
WBC (billion cells/L)	10.61	3.83	13.10	6.74	1.1 (0.289)
Plt (billion /L)	235.00	139.56	292.55	151.47	1.0 (0.323)
TSH (µIU/ml)	3.75	1.70	3.81	3.56	U=0.04 (0.867)
FT4 (pmol/L)	20.28	3.62	21.20	3.33	0.69 (0.495)

t: independent samples t-test U: Mann-Whitney test * P < 0.05 (significant)

Table 8: Thyroid hormones in case and control groups

Lab	Group 1 (case) No.=30	Group 2 (control) No.=30	MCP
	No. (%)	No. (%)	
TSH (1.99-28 µIU/ml)			0.279
▪ Low	7 (23.33%)	10 (33.33 %)	
▪ Normal	21 (70.0%)	20 (66.67%)	
▪ High	2 (6.67%)	0 (0.0%)	
FT4 (20.4-68.4 pmol/L)			0.288
▪ Low	21 (70.0%)	16 (53.33%)	
▪ Normal	9 (30.0%)	14 (46.67%)	

MCP: Mont Carlo exact probability

Table 9: Comparison of thyroid hormones between subgroup 1A and 2A

Lab	Subgroup 1A No.=15	Subgroup 2A No.=10	*P*
	No. (%)	No. (%)	
TSH (1.99-28 µIU/ml)			^{FE}p = 1.000
▪ Low	2 (13.3%)	2 (20.0%)	
▪ Normal	13 (86.7%)	8 (80.0%)	
▪ High	0 (0.0%)	0 (0.0%)	
Mean ± SD	4.2 ± 1.7	3.8 ± 1.7	t (p)= 0.613 (0.546)
FT4 (20.4-68.4 pmol/L)			^{FE} p= 0.378
▪ Low	12 (80.0%)	6 (60.0%)	
▪ Normal	3 (20.0%)	4 (40.0%)	
Mean ± SD	17.2 ± 3.7	20.2 ± 3.6	t (p)= 2.038 (0.053)

FE: Fisher Exact for Chi square test ^{t}p: ^{t}p value for Student t-test

Table 10: Comparison of thyroid hormones between subgroup 1B and 2B

Lab	Subgroup 1B No.=15	Subgroup 2B No.=20	*P*
	No. (%)	No. (%)	
TSH (1.99-28 µIU/ml)			^{MC}p= 0.341
▪ Low	5 (33.3%)	8 (40.0%)	
▪ Normal	8 (53.3%)	12 (60.0%)	
▪ High	2 (13.3%)	0 (0.0%)	
Mean ± SD	8.0 ± 15.3	3.8 ± 3.6	U=142.0p=0.790
FT4 (20.4-68.4 pmol/L)			0.557
▪ Low	9 (60.0%)	10 (50.0%)	
▪ Normal	6 (40.0%)	10 (50.0%)	
Mean ± SD	20.0 ± 3.2	21.2 ± 3.3	t=1.072p=0.291

MC: Monte Carlo for Chi square test ^{t}p: ^{t}p value for Student t-test U: Mann-Whitney test

Table 11: Comparison of thyroid hormones between subgroup 1A and1B

Lab	Group 1 (Cases)		*MCP*
	Subgroup 1A No.=15	Subgroup 1B No.=15	
	No. (%)	No. (%)	
TSH (1.99-28 µIU/ml)			
▪ Low	2 (13.3%)	5 (33.3%)	0.107
▪ Normal	13 (86.7%)	8 (53.3%)	
▪ High	0 (0.0%)	2 (13.3%)	
FT4 (20.4-68.4 pmol/L)			
▪ Low	12 (80.0%)	9 (60.0%)	0.232
▪ Normal	3 (20.0%)	6 (40.0%)	

MCP: Mont Carlo exact probability

Table 12: Comparison of thyroid hormones between subgroups 2A & 2B

Lab	Group 2 (Controls)		*MCP*
	Subgroup 2A No.=10	Subgroup 2B No.=20	
	No. (%)	No. (%)	
TSH (1.99-28 µIU/ml)			
▪ Low	2(20.0%)	8 (40.0%)	0.273
▪ Normal	8 (80.0%)	12 (60.0%)	
▪ High	0 (0.0%)	0 (0.0%)	
FT4 (20.4-68.4 pmol/L)			
▪ Low	6 (60.0%)	10 (50.0%)	0.605
▪ Normal	4 (40.0%)	10 (50.0%)	

MCP: Mont Carlo exact probability

Table 13: Correlation between Thyroid hormones (TSH & FT4) in all studied groups

Thyroid hormones	TSH	
	R	P
FT4	0.128	0.331

R= Correlation Coefficient * P < 0.05 (significant) **P < 0.01 (highly significant)

Table 14: Correlation between Thyroid hormones (TSH & FT4) and respiratory clinical data

Clinical data	TSH		FT4	
	R	P	R	P
Down score	0.107	0.416	-0.280	0.030*
Silverman Anderson Index	0.123	0.349	-0.331	0.009*

R= Correlation Coefficient * P < 0.05 (significant) **P < 0.01 (highly significant)

4. Discussion

Respiratory distress syndrome (RDS) is the most common cause of respiratory distress in newborn. It occurs almost primarily in preterm infants and its incidence inversely proportional to gestational age and birth weight. It occurs due to deficiency, inactivation or dysfunction of pulmonary surfactant[5]. It occurs in 60-80% of infants less than 28 week of gestational age, in 15-30% of those between 32 and 36 weeks, in about 5% beyond 37 weeks[6].

The diagnosis of RDS is based on a combination of the clinical features (tachypnea, subcostal, intercostal retractions, nasal flaring and cyanosis; on auscultation air movement is diminished despite vigorous respiratory effort), evidence of prematurity, exclusion of other causes of respiratory distress[7].

Also the characteristic radiographic appearance helps in RDS diagnosis. The typical radiographic features consist of a diffuse reticulogranular pattern, giving the classic ground-glass appearance, in both lung fields with super-imposed air bronchograms[7].

Variety of hormones affects surfactant synthesis and lung development hence affects the occurrence and severity of RDS in neonate. Among these hormones are glucocorticoids and thyroid hormones[8].

Significant advances made in the management of RDS include prevention of the disease by antenatal administration of glucocorticoids, advances in respiratory support, and surfactant replacement therapy. As a result, the mortality from RDS has decreased. Despite the proven efficacy of antenatal corticosteroids in preventing RDS, they are not effective at preventing all cases of RDS and are limited by the time required to exert an effect on lung maturation and surfactant production before preterm birth[14.]

The thyroid hormones are steroid hormones released from follicular cells of the thyroid gland under the effect of TSH released from pituitary gland. They are iodinated thyronines, primarily tetraiodothyronine (thyroxin or T4) and a lesser quantity of triiodothyronine (T3). Triiodothyronine (T3) is produced by outer ring deiodination (ORD) of T4 in peripheral tissues. Majority of both hormones circulate in blood bound to plasma proteins[15.]

The relationship between RDS and thyroid hormones levels was a subject of debate. This study explores the relationship between FT4 & TSH and RDS in preterm infants during 1st postnatal 24 hours. Many other studies were done to explore the relationship between RDS and thyroid hormones levels in cord blood or during postnatal days (Cuestas and Engel 1979[16], Stahnke N et al, 1986[17], Mercado M et al, 1988[18], Kim S et al, 2001[19], Simpson et al, 2005[20], Tanaka K et al, 2007[21], Dilli D et al, 2010[22]).

The study comprised of 60 preterm neonates (36 males and 24 females) with mean gestational age 32.85 ± 2.51 wks and mean weight of 1.9 ± 0.74 kg (ranging from 0.68 kg to 3.6 kg). They were classified into 30 cases (group 1) with respiratory distress syndrome and 30 control preterm neonates (group 2) who didn`t have respiratory distress.

Each group was further subdivided into 2 categories according to gestational ages; group 1A (15 cases of with RDS with gestational age ≤ 32 wks), group 1B (15 cases with RDS with gestational age from >32 to <37wks), group 2A (10 control preterm without RD with gestational age ≤ 32wks) and group 2B (20 control preterm without RD with gestational age from >32 to <37wks).

The present study revealed no significant difference between normal & RDS preterm newborns for birth weight (P = 0.181). This finding was in accordance with the study done by Su et al, 2008 on infants with RDS categorized as very preterm, moderately preterm, late preterm and term, reported no correlation between RDS severity and birth weight (p value <0.01).

Contrary to our result, a study done by Chandrasekhar et al, 2016[23] on 100 consecutive born neonates with respiratory distress reported that birth weight less than 2.5Kg was associated with severe respiratory distress in newborns. Also, the study done by Liu and Tong, 2015[24] on 99 preterm infants (69 infants were diagnosed with TTN and 30 were diagnosed with RDS) with mean gestational age (31.9 ± 2.2) weeks and birth weight (1661 ± 501 g) showed that preterm infants with RDS are characterized by younger gestational age and lower birth weight.

The present study revealed no significant difference between normal & RDS preterm newborns for history of maternal medical disorders in pregnancy as (maternal diabetes, hypertension or chorioamnionitis) (P = 0.951).

In agreement with our study, Clair et al, 2007[25] on a sample of 210 mother-neonate pairs revealed that neither maternal diabetes nor hypertension affects incidence of RDS (p value 0.23, 0.60 respectively). However Shimoya et al, 2000[26] said that chorioamnionitis promotes fetal lung maturation by inducing SP-A (surfactant protein- A) synthesis, thereby decreasing the incidence of RDS in the preterm neonates, and the study done by Lahraet al, 2009[27] on infants <30 weeks' gestation revealed that chorioamnionitis was associated with a significant reduction in RDS, but pregnancy-induced hypertension was one of factors associated with increased RDS.

The difference between the present study and these studies as regards effect of mother's condition on incidence of RDS may be due to small number of mothers having diabetes, hypertension or chorioamnionitis in our sample and also the differences in gestational ages may contribute to this difference.

The present study revealed no significant difference between normal & RDS preterm newborns for mode of delivery (P = 0.118). This finding agreed with the study done by Liu and Tong, 2015[24] on 99 preterm infants (69 infants were diagnosed with TTN and 30 were diagnosed with RDS), revealing no significant difference of caesarean section between the RDs and normal group (P = 0.025).

Contrary to our results, the study done by Correia C et al, 2016[28] on 498 newborns, 44 (8.83%) of them with RDS showed that caesarean section was independent risk factors for respiratory morbidity, and the study done by Chandrasekhar et al, 2016[23] on 100

consecutive born neonates with respiratory distress reported that cesarean delivered newborns were associated with severe respiratory distress in newborns. Also, the study done by Sun H et al, 2013[5] on infants with RDS categorized as very preterm, moderately preterm, late preterm and term, reported that caesarean section was significantly associated with RDS in term and late preterm infants ($P < 0.001$).

The difference between the present study and others as regards the effect of mode of delivery on incidence of RDS appears because most of our caesarean sections are not elective and on the other hand most of our vaginal deliveries are complicated.

The present study revealed that RDS preterm newborns had lower Apgar score at both 1 min and 5 min than the normal preterm newborns ($p = 0.001$, 0.028 respectively). This is agreement with the study done by Chandrasekhar et al, 2016[23] on 100 consecutive born neonates with respiratory distress which showed that 1 min Apgar score less than 7 is a risk factor for RDS. Another study done by Liu and Tong, 2015[24] on 99 preterm infants (69 infants were diagnosed with TTN and 30 were diagnosed with RDS) with mean gestational age (31.9 ± 2.2) weeks and birth weight (1 661 ± 501) g, revealed lower Apgar score in RDS group (9 cases in the RDS group had Apgar score ≤ 7 while 4 cases in the TTN group had Apgar score ≤ 7) ($P = 0.001$).

Also, the study done by Tanaka et al, 2007[21] on 449 preterm infants, who were born at 22 – 36 weeks of gestation reported that the incidence of RDS was found to have significant negative correlation with Apgar score (p value =0.0006). Lahra et al, 2009[27] on a sample of infants <30 weeks' gestation revealed that an Apgar score <4 at 1 minute was one of factors associated with increased RDS frequency.

On the contrary, Dani et al, 1999[29] on a sample of 63,537 live infants (734 infants suffer from RDS) revealed that the Apgar score at the 1st minute was <4 in 32.3% (237/734) of affected newborns, 4-6 in 37.2% (273/734) and>7 in 30.5% (224/734). The controversy between this study and ours may be due to significant difference in sample size or presence of associated other risk factors.

The present study revealed that RDS preterm newborns had a significantly higher need for resuscitation, endotracheal intubation and oxygen therapy ($p = 0.001$).

This finding was in accordance with the study done by Correia C et al, 2016[28] on 498 newborns, 44 (8.83%) of them with RDS. It revealed that RDS newborns had a significantly higher need for resuscitation, endotracheal intubation, oxygen therapy and early invasive ventilation ($p = 0.002$).

The results of our study revealed that platelet count is significantly lower in the RDS preterm than normal ones, especially that the RDS group contains more number of low gestational age cases (50%) than the normal group (33.33%). However, there was no difference in hemoglobin, hematocrit and white blood cell count. The obtained results may indicate immaturity of thrombopoiesis in preterm newborns.

This finding was in accordance with many previous reports. The study done by Tirupathi et al, 2017[30] on 200 neonates with thrombocytopenia were divided into three groups based on severity of thrombocytopenia, revealed that preterm and low birth weight babies had severe thrombocytopenia. Another study done by Wasiluk et al, 2016[31] on 58 preterm newborns and 71 full term newborns demonstrated a decreased count of blood platelets (249×109/L) as compared to FTN (295×109/L), $p < 0.001$. The obtained results indicate immaturity of thrombopoiesis in preterm newborns and decrease in platelet count in more preterm newborns.

The study done by Canpolat et al, 2009[32] on 44 preterm infants who developed RDS and received surfactant in the first 6 h of life and of 39 preterm infants who did not develop RDS, agreed with our study in that there were no statistically significant differences in Hemoglobin, hematocrit, White blood cell count first day, however, it revealed that platelet counts were similar in the first day of life for both groups ($P= 0.5$). This difference may be attributed to different gestational ages in both studied groups compared to ours.

The present study revealed significant difference between the two subgroups of RDS preterm newborns for birth weight. Lower gestational ages showed lower birth weights ($P =0.004$). This finding was in accordance with the study done by Chandrasekhar et al, 2016[23] reported that birth weight less than 2.5Kg was associated with severe respiratory distress in newborns. Also, Liu and Tong[24], 2015 showed that preterm infants with RDS are characterized by younger gestational age and lower birth weight.

The study done by Luerti et al, 1993[33] on 131 newborns with RDS agreed with our study in that the risk of RDS markedly increased with decreasing birth weight. Likewise, compared to babies born between the 35th and the 37th week of gestation, the RR of RDS was 3.3 and 21.5 in those born between the 31st to 34th or before the 31st week of gestation.

The results in the present study revealed significant difference between the two subgroups of RDS preterm newborns for maternal medical disorders during pregnancy, mode of delivery, Apgar at 1 & 5 min and mode of resuscitation.

The difference between the present study and others as regards the comparison of risk factors for RDS between the two subgroups of RDS preterm newborns may be due to small number of preterm

infants included in our study and also differences in gestational ages may contribute to this difference.

The results in the present study revealed no significant difference between the two subgroups of RDS preterm newborns for the clinical grading of RDS severity using Down score and Silverman Anderson score (P = 0.624, 0.269 respectively).

Down score and Silverman Anderson score are commonly used for quick diagnosis of distress and assessment of its severity which is crucial in decision making for further management including mechanical ventilation for severe distress; however, Down score is used for assessment of both term and preterm newborns whereas Silverman Anderson score has been validated only in preterm babies but both used interchangeably in preterm newborns and that severity of RDS inversely related to gestational age[34].

This difference in our study as regards assessment of clinical severity of RDS subgroups may be due to small number of preterm infants included in our study and the differences in gestational ages. Also, the fact that RDS has multifactorial risk factors may contribute to this difference.

The results in the present study revealed no significant difference between the two subgroups of RDS preterm newborns and the two subgroups of the healthy preterm newborns for hemoglobin, hematocrit, white blood cell count and platelet count.

The study done by Canpolat et al, 2009[32] agreed with our study in that there were no statistically significant differences in hemoglobin, hematocrit, white blood cell and platelet counts in the first day for both groups (44 preterm infants group who developed RDS and received surfactant in the first 6 h of life and of 39 preterm infants group who did not develop RDS) (P= 0.5).

The results in the present study revealed no significant difference between normal & RDS preterm neonates for TSH during 1st postnatal day but the FT4, was significantly decreased in RDS preterm neonates more than that in healthy normal ones ($p < 0.050$).

In spite that the RDS preterm group showed higher percentage (70%) of low FT4 compared to the normal preterm group (53.33%), the study showed no significant difference between the two groups for low, normal and high values of both TSH and FT4 according to their normal ranges (1.99-28 uIU/ml, 20.4-68.4 pmol/L respectively).

As well, the results of our study revealed that there was no significant correlation between TSH and the severity of RDS (respiratory clinical picture based on Down score and Silverman Anderson Index) (P = 0.416, 0.349 respectively) but there was significant negative correlation between FT4 and Down score (P = 0.030) and significant negative correlation between FT4 and Silverman Anderson index (P = 0.009).

In our study, comparing between RDS & control subgroups of newborns having GA ≤ 32 wks, revealed no significant differences in TSH and FT4 (P = 0.546, 0.053 respectively). Although that the RDS subgroup with lower gestational age showed higher percentage (80%) of low FT4 compared to the control subgroup with lower gestational age (60%), the study showed no significant difference between the two lower gestational age subgroups for low, normal and high values of both TSH and FT4 according to their normal ranges (1.99-28 uIU/ml, 20.4-68.4 pmol/L respectively).

Also, our study in comparing between RDS & control subgroups of newborns having GA > 32 wks, revealed no significant differences in TSH and FT4 (P = 0.790, 0.291 respectively). Although that the RDS subgroup with lower gestational age showed higher percentage (60%) of low FT4 compared to the control subgroup with lower gestational age (50%), the study showed no significant difference between the two higher gestational age subgroups for low, normal and high values of both TSH and FT4 according to their normal ranges (1.99-28 uIU/ml, 20.4-68.4 pmol/L respectively).

These finding were in accordance with many previous reports. The study done by Cuestas and Engel 1979[16] on premature infants 30 to 35 weeks GA (gestational age) with severe RDS compared to healthy control subjects of similar GA revealed that the infants with RDS had significantly lower serum level of FT4. Stahnke N et al, 1986[17] measured indices of thyroid function in 97 preterm infants several days after birth. Infants developing respiratory distress syndrome had significantly lower thyroxine, free thyroxine, and triiodothyronine values at 5 days of age; while thyroid stimulating hormone values remained normal. This alteration in thyroid functions was interpreted as being secondary to respiratory distress syndrome.

Thyroid function was measured in 108 infants born at 23–31 weeks gestation, after birth, at 24 and 72 h, and at 1, 3, 4, 5 and 6 weeks of age by Mercado M et al, 1988[18]. He found that infants who had hyaline membrane disease (HMD) had significantly lower T4, FT4 and FTI values compared to those without HMD for up to 3 weeks of age but normal TSH.

Simpson et al, 2005[20] in his study on 441 preterm infants 23-34 week of gestation tried to relate severity of illness like RDS at 1, 7, 14, 28 postnatal days to the corresponding sera levels of FT4, T3, T4 and TSH. The results displayed that FT4, T4 and T3 were substantially reduced in infants with severe illness like RDS, irrespective of gestational age, yet TSH remains unchanged.

In keeping with our study, the study done by Dilli D et al, 2010[22] - on 200 infants (26–32 wk gestation) admitted to neonatal intensive care units (NICU) - when adjusted for age, THOP (transient hypothyroxinemia of prematurity) was associated with need for mechanical ventilation (P=0.03) and for having respiratory distress syndrome (RDS)

Contrary to our results, a study done by Stahnke N et al, 1986[17] on 35 premature infants with RDS and 43 well prematures, matched for gestational age, and revealed no significant differences in cord blood TSH, T3, T4, TBG values. Kim S et al, 2001[19] did a study on 57 premature infants divided into 3 groups according to their respiratory disease: the healthy premature group (A), the RDS without BPD group (B), and the BPD group (C) and revealed no differences in thyroid function between the healthy premature infants and the infants with RDS who did not develop BPD later.

The study done by Rabin et al, 2004[35] on a sample of 114 infants less than 1500 g revealed that there was no difference in the incidence of RDS between the infants with and without low FT4 values. Another study done by Tanaka et al, 2007[21] on 449 preterm infants, who were born at 22 – 36 weeks of gestation, revealed that the levels of serum FT4 and TSH showed no significant effect on the incidence of RDS (p values 0.110 and 0.070 respectively).

Our study revealed the relationship between FT4 & TSH levels and RDS in preterm infants during 1st postnatal day which is in accordance with the fact that thyroid hormones play a role in surfactant synthesis and this does support the idea that deficiency of thyroid hormones leads to occurrence of RDS. It also supports the idea that hypoxia from RDS affects hypothalamo-pituitary-thyroid axis and hence lowers thyroid hormones levels.

The results in the present study revealed no significant difference between the two subgroups of the RDS group in TSH (P = 0.315) but there is significant decrease in FT4 the subgroup of the lower gestational age (p = 0.037). These results support the idea of "nonthyroidal illness" (the "sick euthyroid syndrome") reflecting the infant's response to severe illness like RDS.

In spite that the RDS subgroup with lower gestational age showed higher percentage (80%) of low FT4 compared to the RDS subgroup with higher gestational age (60%), the study showed no significant difference between the two RDS subgroups for low, normal and high values of both TSH and FT4 according to their normal ranges for their age groups (1.99-28 uIU/ml, 20.4-68.4 pmol/L respectively).

The results in the present study revealed also no significant difference between the two subgroups of control group for both TSH and FT4 (P = 0.867, 0.495 respectively).

In spite that the control subgroup with lower gestational age showed higher percentage (60%) of low FT4 compared to the control subgroup with higher gestational age (50%), the study showed no significant difference between the two control subgroups for low, normal and high values of both TSH and FT4 according to their normal ranges for their age groups (1.99-28 uIU/ml, 20.4-68.4 pmol/L respectively).

Conclusion

- The results in the present study revealed that there was significant negative correlation between the occurrence and severity of RDS and the serum level of free thyroxin (FT4).
- There is no correlation between the occurrence and severity of RDS and the serum level of thyroid stimulating hormone (TSH) in preterm neonates.

Recommendations

- We recommend to measure free thyroxin (FT4), and thyroid stimulating hormone (TSH) in preterm neonates during 1st postnatal 24 hours to explore whether thyroid hormones affect the occurrence of RDS or not and also after the 2nd postnatal day to explore whether hypoxia from RDS affects thyroid hormones level or not.
- The relationship between respiratory distress syndrome (RDS) and thyroid hormones must be explored on a larger scale to give more insight on it.

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