



THYROID FUNCTION DISORDERS IN LOW BIRTH WEIGHT/ PRETERM NEONATES ADMITTED IN NICU, CHILDREN HOSPITAL COMPLEX MULTAN.

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ABSTRACT... Objectives: Congenital hypothyroidism (CHT) is one of the major endocrine and metabolic disorders in neonates. Delayed diagnosis and treatment of CHT may lead to certain neuro-developmental disorders. **Study Design:** Prospective study. **Setting:** NICU of Children Hospital, Institute of Child Health Multan, Pakistan. **Period:** September 2018 to November 2019. **Material & Methods:** A total of 142 neonates of both gender having birth weight of less than 1500 grams were enrolled in this study. Thyroid function tests, like TSH, free T4 and T4 levels were performed in all these neonates between 1- 5th day, 2nd week and 4th week of life by radioimmunoassay. **Results:** Out of 142 neonates, 76 (53.5%) were male and 66 (46.5%) female. Mean gestational age was 31.41 ± 1.93 weeks while mean birth weight was found to be 1261.53 ± 170.36 grams. Gestational age of < 28 weeks was noted in 9 (6.3%) neonates, 28 to <30 weeks in 59 (40.4%), 30 to 32 weeks in 33 (23.2%) and 41 (28.9%) were above 32 weeks. Thyroid function disorders were noted in 89 (62.7%) neonates while transient hypothyroxinemia was the most common one, found in 65 (45.7%) neonates, transient hyperthyroxinemia in 12 (8.4%) and Congenital hypothyroidism (CHT) in 12 (8.4%). Nasal continuous positive airway pressure (NCPAP) was used for treating respiratory distress syndrome (RDS) in 107 (75.4%) neonates. Surfactant administration was done in 69 (48.6%). Patent ductus arteriosus (PDA) was noted in 27 (19.0%), intraventricular hemorrhage (IVH) in 8 (5.6%) and culture proven sepsis was seen in 18 (12.7%). **Conclusion:** In low birth weight / preterm neonates, thyroid function disorders are quite common. Transient Hypothyroxinemia was noted to be the most common disorder and congenital hypothyroidism was present in 8.4% of neonates.

Key words: Congenital Hypothyroidism, Thyroid Function Disorder, Transient Hypothyroxinemia.

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INTRODUCTION

Congenital hypothyroidism (CHT) is known to be one of the major endocrine and metabolic disorders. Amongst neonates, delay in the diagnosis and treatment of CHT may result in neuro-developmental disorders.¹ Frequency of CHT is noted as 1 per 3500 infants.² In regional findings, CHT was noted to be present in 2% infants.³ Most of the neonates having CHT exhibit very few symptoms, in fact, many stay asymptomatic. In these cases, progression of CHT may take months to become symptomatic.⁴

Proper functioning of thyroid gland is very important for brain to develop normally in infants and in the form of delayed diagnosis, chances

of developing serious mental complications are increased.⁵ Within half an hour to one hour following delivery, surge in serum thyroid stimulating hormone is seen as up to levels of 60 to 80 mU/L, depending upon environmental temperature as well as umbilical cord clamping. These levels fall down to 20 mU/L within 1 day following birth and then goes on to 6 to 8 mU/L during 1st week. The 1st surge in TSH levels result in stimulating secretions of T4 along with exchange of T4 to T3.^{6,7}

In infants those are premature, T4 and free T4 levels are interrelated with birth weight as well as gestational age. As per previous researches, mean T4 serum levels in extremely low birth

weight (ELBW) infants is 5.6 mcg/dL after 2 to 5 days following birth, whereas it was noted as a mean of 6.7 mcg/dL in those infants who were < 30 weeks of gestational age. Mean free T4 levels of 1.2 ng/dL have been noted in infants < 30 weeks of gestational age.^{8,9}

In the post-natal period, it has been observed that levels of TSH, T3 and T4 become quite alike to term infants. In comparison to term neonates, in premature newborns, thyroid hormone levels may fall because of immaturity of the thyroid gland, but these changes may be exacerbated by complications of prematurity. Thyroid metabolism can be affected by exogenous sources of iodine, dopamine infusions, blood transfusion and glucocorticoid treatment.¹⁰

Taking into consideration the abnormalities in some thyroid hormonal levels amongst premature infants, these infants are more prone to thyroid disorders like transient hypothyroxinemia, neonatal hypothyroidism and transient hyperthyroxinemia.¹¹⁻¹³ Our setting being the most common tertiary care center in the south Punjab region, no study has been done to find out the status of thyroid function disorders in neonates admitted in the neonatal intensive care unit (NICU). So, aim of this study was to find out thyroid function disorders in neonates coming to us and admitted in NICU with birth weight < 1500 grams. Neonatal screening can provide early diagnosis and can prevent delays in treatment.

MATERIAL & METHODS

This was a prospective study, conducted at NICU of Children Hospital, Institute of Child Health Multan, Pakistan from September 2018 to November 2019. A total of 142 neonates of both gender and having birth weight of less than 1500 grams were enrolled in this study. All those neonates were not enrolled who had any major congenital abnormality, blood exchange transfusion or mortality in 1st month of life.

Approval from institutional ethical committee was sought for this research. Informed consent was acquired from parents or guardians of all the study participants. Thyroid function tests, like

TSH, free T4 and T4 levels were performed in all these neonate in between 1-5th day, 14th day and 4th week of life with radioimmunoassay. Blood samples of 1 to 1.5 cc were taken from forearms of the study participants and all investigations were analyzed at institutional laboratory. Thyroid function abnormalities were labeled on the bases of figures given in Figure-1 and Figure-2 and according to thyroid dysfunction definitions.^{6,14}

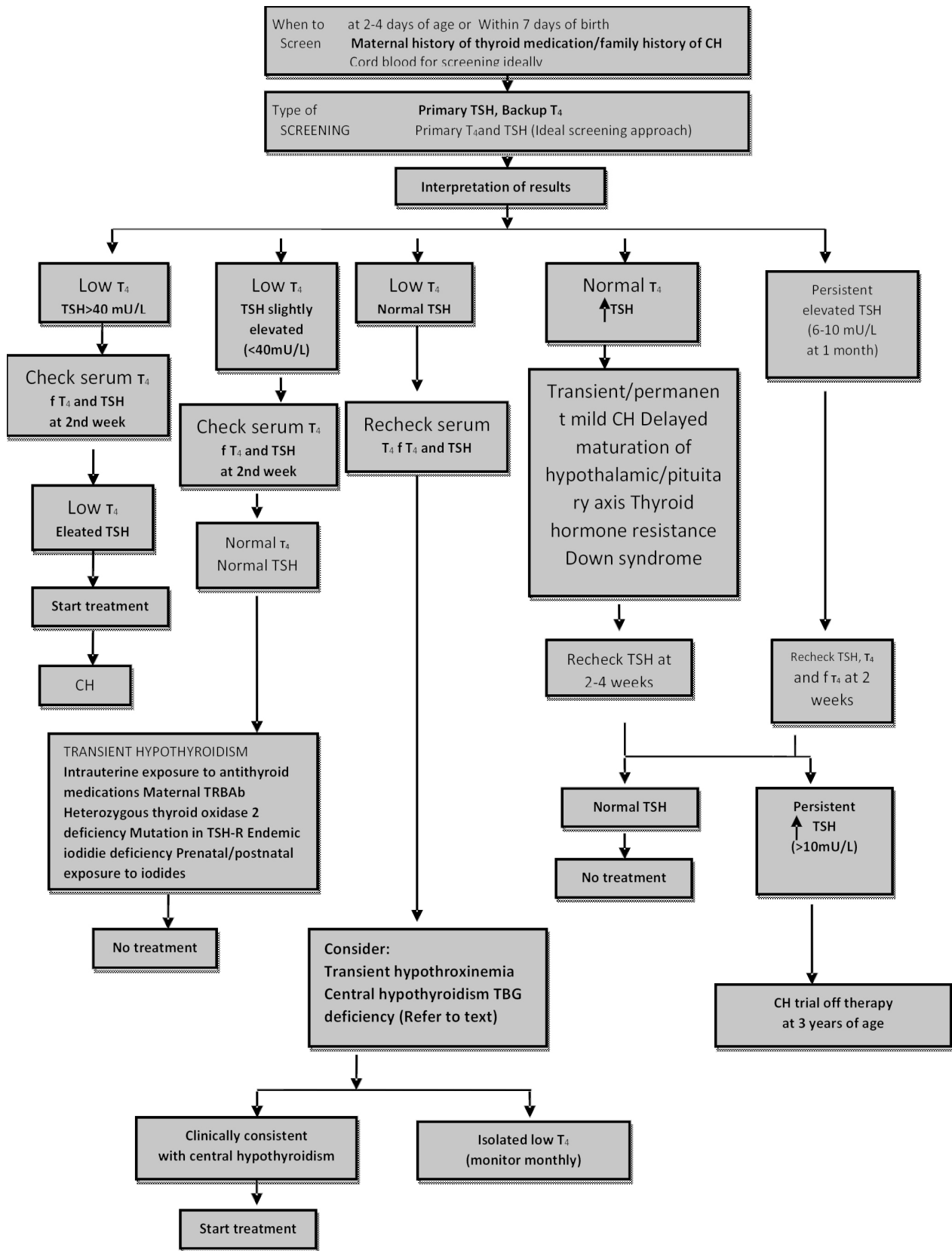
Diagnosis of transient hypothyroxinemia was made as low T4 and free T4 levels as well as normal levels of TSH. Diagnosis as neonatal hypothyroidism was made as raised levels of TSH and decreased free T4 and T4 levels during the neonatal period. Diagnosis as transient primary neonatal hypothyroidism was made as decreased or consistently lowering levels of free T4 while moderate raise of TSH levels. Diagnosis as hyperthyroxinemia was made as raised levels of TSH during neonatal period even if T4 and free T4 levels were found to be normal.^{6,14}

SPSS version 21.0 was used for data handling and analysis. Quantitative variables were presented as mean and standard deviation (SD) while qualitative variables were represented in the shape of frequency and percentages. Chi square test and independent sample t test was used to for comparisons in between neonates, and p value less than or equal to 0.5 was taken as statistically significant.

RESULTS

Out of a total of 142 neonates, 76 (53.5%) were male and 66 (46.5%) female. Mean gestational age was 31.41 ± 1.93 weeks while mean birth weight on 5th day was found to be $1261.53 + 170.36$ grams. Gestational age < 28 weeks was noted in 9 (6.3%) neonates, 28 to 30 in 59 (40.4%), >30 to 32 weeks in 33 (23.2%) and 41 (28.9%) above 32 weeks. Table-I

Some of the cases got excluded because of reasons like lack of compliance and adherence to study protocols. Evaluation of 131 infants was done at 2 weeks and 117 infants got evaluated on 4th week. Ninety eight neonates completed the study at 6 weeks interval of the study.



Algorithm for evaluating congenital hypothyroidism (CH)

Table-II shows that TSH, free T4 and T4 levels increased with increasing gestational age while Table-III is showing mean values of T4, Free T4 and TSH at different study intervals.

Thyroid function disorders were noted in 89 (62.7%) neonates while transient hypothyroxinemia was shown to be the commonest, found in 52 (36.6%), transient primary neonatal hypothyroidism in 13 (9.2%), transient hyperthyrotropinemia in 12 (8.4%) and CHT in 12 (8.4%).

Nasal continuous positive airway pressure

(NCPAP) was used for treating respiratory distress syndrome (RDS) in 107 (75.4%) neonates. Surfactant administration was done in 69 (48.6%). Patent ductus arteriosus (PDA) was noted in 27 (19.0%), intraventricular hemorrhage (IVH) in 8 (5.6%) and clinical sepsis was seen in 18 (12.7%).

Table-IV shows that when neonates having thyroid function disorders were compared with those having no thyroid function disorders for clinical status found, no significance was noted in between the neonates (p value > 0.05).

Age of Specimen	Gestational Age (Weeks)	Free T4 (ng/dl)	T4 (mcg/dl)	TSH (mu/L)
week 1	< 28 weeks	1.29 +/- 0.5	3.8 +/- 1.7	3.3 +/- 2.1
Week 2		1.31 +/- 0.3	4.2 +/- 2.4	4 +/- 2.2
Week 4		1.49 +/- 0.2	5.9 +/- 2.6	3.5 +/- 2.1
week 1	28- <30 Weeks	1.81 +/- 0.6	6.3 +/- 2.1	3.5 +/- 2.2
Week 2		1.62 +/- 0.3	6.6 +/- 2.3	4.8 +/- 10.8
Week 4		1.71 +/- 0.2	7.5 +/- 2.1	3.6 +/- 2.4
week 1	30 - 32 Weeks	2.14 +/- 0.6	9.4 +/- 3.2	3.6 +/- 3.8
Week 2		2.10 +/- 0.4	9.6 +/- 3.6	3.9 +/- 10.1
Week 4		1.88 +/- 0.5	8.9 +/- 2	3.5 +/- 3.4
week 1	>32 Weeks	2.70 +/- 0.6	12.3 +/- 2.1	2.6 +/- 1.6
Week 2		2.05 +/- 0.4	10.6 +/- 1.6	2.5 +/- 1.9
Week 4		1.66 +/- 0.2	9.8 +/- 2.1	1.8 +/- 0.8

Figure-1. Normal ranges of thyroid function tests in premature infants¹⁴

	Gestational Age (weeks)			
	<28 (n=9)	28-<30 (n=59)	30-32 (n=33)	> 32 (n=41)
TSH (Mean±SD)	2.31±0.83	3.72±2.74	4.11±1.31	4.31±2.52
Free T4 (Mean±SD)	1.38±0.32	1.49±0.31	1.53±0.28	1.58±0.35
T4 (Mean±SD)	5.21±2.18	6.03±1.80	7.78±2.57	7.53±1.86

Table-I. TSH, Free T4 and T4 levels with regards to gestational age

	Study Intervals		
	Week 1	Week-2	Week-4
TSH (Mean±SD)	3.55±1.91	4.79±3.02	4.18±1.84
Free T4 (Mean±SD)	1.28±0.24	1.29±0.49	1.31±0.21
T4 (Mean±SD)	6.35±1.80	6.42±1.79	5.92±1.96

Thyroid Function Disorder	Number (%)
CHT	12 (8.5%)
Transient Hypothyroxinemia	65 (45.7%)
Transient Hyperthyroxinemia	12 (8.5%)

Table-III. CHT, Transient hypothyroxinemia and transient hyperthyroxinemia amongst neonates

Clinical Status	Thyroid Function Disorders (n=89)	No Thyroid Function Disorders (n=53)	Total (n=142)	P-Value
RDS	68 (76.4%)	39 (73.6%)	107 (75.4%)	0.706
Surfactant Administration	41 (46.1%)	27 (50.9%)	68 (47.9%)	0.574
NCPAP	68 (76.4%)	39 (73.6%)	107 (75.4%)	0.706
Mechanical Ventilation	3 (3.4%)	2 (3.8%)	5 (3.5%)	0.900
IVH	4 (4.5%)	4 (7.5%)	8 (5.6%)	0.445
PDA	15 (16.9%)	12 (22.6%)	27 (19.0%)	0.395
NEC	5 (5.6%)	2 (3.8%)	7 (4.9%)	0.623
Sepsis	8 (9.0%)	10 (18.9%)	18 (12.7%)	0.87

Table-IV. Distribution of clinical status in between neonates with and without thyroid function disorders

DISCUSSION

Preterm infants are considered to be at increased risk of having thyroid dysfunction. Although, in the last couple of decades, few guidelines have indicated screening regarding CHT in premature neonates but data still lacks regarding best management and outcome in the longer run.¹⁵

In the present study, mean gestational age was found to be 31.41±1.93 weeks while mean birth weight on 5th day was found to be 1261.53 + 170.36 grams. These findings are very near to what was found in another study conducted in Iran⁶ when they noted a mean gestational age of 30.51±2.29 in premature neonates lined up for evaluation of thyroid function disorders. The same study also found mean birth weight to be very closer to our findings (1246.90±193.58 grams).

In our study, gestational age of most neonates (52.1%) were above 30 weeks which is quite similar to Armanian AM et al⁶ where they noted a mean gestational age of 30.51 weeks but our findings were little different from Chung HR et al¹⁶ where they found that to be 28.5 weeks.

In the current study, we noted transient hypothyroxinemia to be the commonest, found in 52 (36.6%) neonates, transient primary neonatal hypothyroidism in 13 (9.2%), transient hyperthyrotropinemia in 12 (8.4%) and CHT in 12 (8.4%). Chung HR et al¹⁶, noted the frequency of CHT as 12% while Armanian AM et al⁶ noted CHT to be present in 6.34% preterms. The difference in terms of frequency of CHT in comparison to

the findings of Chung HR et al¹⁶ could be due to lower mean gestational age found in that study (28.5 weeks). Hashemipour M et al¹⁷ from Iran noted 1 case of CHT amongst 349 live births but that study included term, preterm, and LBW neonates. Researchers from Belgium have reported incidence of CHT in premature neonates as 5 to 18%.¹⁸

Armanian et al⁶ found transient hypothyroidism and hyperthyrotropinemia as 8% and 16% in preterm neonates while these findings are very near to what we found in the present study. Very similar to our results¹⁹, others have also noted transient hypothyroxinemia to be the commonest thyroid function disorder amongst preterm neonates. Seriousness of thyroid function disorders have been observed to be disturbed more with decreasing gestational age previously, we also noted that on the whole, thyroid functions improved with the increase of gestational age in neonates.²⁰ It has been found in the past that transient hypothyroidism contributes more to neuro-developmental disorders while levothyroxine has been found to save these neonates from most common complications.⁶

In the current study, RDS (75.4%), PDA (19.0%), sepsis (12.7%) and IVH (5.6%) were found to be most common clinical status amongst preterm neonates. Chung HR et al,¹⁶ noted RDS, IVH, and NEC to be the commonest findings while our results were well aligned to the findings of Armanian AM et al⁶ where they found RDS and PDA to be the commonest findings amongst preterm neonates.

Our study is the very 1st one in this region to evaluate preterm neonates for thyroid function disorders but as we had a comparatively shorter sample size along with a slim 6 months follow up, more studies involving multi-centers and longer follow ups could further add to the spectrum of thyroid function disorders in these neonates.

CONCLUSION





In LBW preterm neonates, thyroid function disorders are quite common. Transient Hypothyroxinemia was noted to be the commonest disorder while RDS, PDA and sepsis were the most seen clinical findings. Thyroid function tests should be done in all premature neonates.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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3	Ahmed Iqbal Quddusi	Introduction, Results, Discussion.	
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5	Imran Iqbal	Introduction, Results, Discussion.	