

COMPARISON OF SERUM TSH AND T4 LEVELS IN PRETERM AND TERM NEONATES FOR SCREENING OF CONGENITAL HYPOTHYROIDISM

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ABSTRACT

Objective: To Compare Serum TSH and T4 Levels in Preterm and Fullterm Neonates for Screening of Congenital Hypothyroidism.

Material and Methods: A total of 101 neonates aged 3-7 days, both preterm (by Ballard score age from 28 weeks to 37 weeks) and full term were included in the study out of which 52 were preterm and 49 were fullterm respectively. Preterm neonates of gestational age of less than 28 weeks and fullterm neonates with gestational age of more than 42 weeks, severely septicemic babies, hyaline membrane disease, infants of diabetic mothers, dysmorphic and neonates with congenital anomalies were excluded from the study. Venous blood samples of all the babies were taken with sterilized techniques and sent for testing to laboratory of Institute of Radiotherapy and Nuclear Medicine (IRNUM), Peshawar for serum TSH and T4 levels by radioimmunoassay.

Results: There were 101 neonates aged 3-7 days, including 52 preterm and 49 full term babies with mean gestational age of preterm at the time of delivery was 33 weeks ranges from 28 weeks to 36 weeks. Out of 52 preterm neonates, 9 were found to be hypothyroxinemic and 1 fullterm out of 49 was having congenital hypothyroidism. Serum TSH values in preterm infants were not increased in accordance to lower T4 values while in one full term neonate lower T4 level was associated with increased serum TSH levels.

Conclusion: Transient hypothyroxinemia with out hyperthyrotropinemia is relatively common in preterm than in full-term neonates. Combine TSH and T4 screening strategy is more helpful in detecting newborns with congenital hypothyroidism.

Key Words: TSH, T4, Congenital, Hypothyroidism, Fullterm, Preterm, neonates.

INTRODUCTION

Thyroid hormone is known to regulate neurodevelopment probably from early fetal life onward¹. If onset of thyroid hormone deficiency syndrome occur early in development, it can cause long term morbidity in terms of behavior, locomotor ability, cognition and hearing^{2,3}. Detection of congenital hypothyroidism is important as it is relatively common occurring, 1 in 4000 births and one of the few preventable causes of severe hearing difficulties and mental retardation^{4,5}.

Research on the effects of thyroid hormone deficiency early in fetal life is necessary for overt hypothyroidism, but also for more subtle hypothyroxinemia, as found in maternal

hypothyroxinemia during pregnancy^{6,7} and after pre term birth⁸. Hypothyroidism results from deficient production of thyroid hormone or a defect in its receptor activity. The disorder may be congenital or acquired; and is twice as common in girls than in boys^{9,10,11}.

Causes of congenital hypothyroidism may be sporadic or familial, goitrous or nongoitrous e.g. 98% thyroid dysgenesis are sporadic and 2% cases are familial. Thyroid dysgenesis is the most common cause of congenital hypothyroidism, accounts for 85% of cases, 10% are caused by an in born error of thyroid hormone synthesis and 5% are transplacental maternal thyrotropin receptor blocking antibody. Most common cause of goitrous congenital hypothyroidism is iodine deficiency endemic goiter, others are defective synthesis of thyroxin, defect of iodide transport, defects of thyroglobulin synthesis defect in deiodination and thyroid hormone unresponsiveness⁹.

After pre term birth, T4, free T4 and T3 levels remains lower than term infants for the first week. There is an obtunded thyrotropin peak immediately after birth,

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while TSH remains below, 20 μ IU/ml, in the low period of T4 (transient hypothyroxinemia) of pre term infants. It takes three to eight weeks before T4 and T3 levels of preterm infants reach the same level as those in term infants. The earlier an infant is born, the more severe the transient hypothyroxinemia^{12,13}.

Postnatal free thyroid hormone concentration also corresponds with gestational age at birth, being lower in more pre term infants. In infants of less than 30 weeks gestation, bound T4 (total) concentration in first week of life is four times less than term infants¹⁴. Free T4 is two to three times lower in very pre term infants compared with term infants at one week age¹⁵. The objective of the study was to compare serum levels of TSH and T4 in preterm and term neonates presenting to a tertiary care hospital at Peshawar for earlier screening of congenital hypothyroidism.

MATERIAL AND METHODS

This comparative cross sectional study was carried out from April, 2005 to September, 2005 in special care baby unit Khyber Teaching Hospital, Peshawar. A total of 101 neonates aged 3-7 days including 52 preterm babies with gestational age from 28 weeks to 37 weeks and 49 term babies with gestational age from 37 to 42 weeks, were included in the study. Preterm and full term babies with signs of hyaline membrane disease, infants of diabetic mother, dysmorphism or any congenital anomalies or congenital heart disease. Severely septicemic and critically ill babies were excluded from the study.

All the babies were thoroughly examined including their weight, and gestational ages of preterm babies were determined by Ballard scoring system. Blood specimens for TSH and T4 assay's were collected after taking informed consent from parents. Venous blood of 3 ml from premature and 4 ml from full term newborn was taken and collected in sterilized test tubes and then tested in laboratory of IRNUM hospital, Peshawar for serum TSH, T4 and T3 levels by radioimmunoassay. High levels of TSH were defined as more than 20 micro IU/ml in preterm and 4 micro IU/ml in full term neonates. Low levels of T4 were defined as less than 1.2 nanomols/L and less than 60 nanomols/L.

All the newborn babies were divided into two groups i.e. preterm and full term babies then random

Table 2: Mean values and standard deviation of serum T4 and TSH levels in preterm and full-term neonates (n=101)

Category	Test	No. of cases	Minimum	Maximum	Mean	Std. Deviation
Preterm	TSH	52	0.30	60.00	5.8346	9.3980
	T4	52	21.00	213.00	99.0577	44.1585
Full term	TSH	49	0.10	14.00	5.7000	3.7542
	T4	49	49.00	361.00	205.3061	67.9636

sampling was done from each group. Maternal age of all the babies was noted and history of any thyroid disease in mother or family and use of any antithyroid drugs by mother was asked and recorded. All the studied variables were analyzed for comparative statistics. For age, maternal age, serum T4 and TSH levels in preterm and fullterm neonates mean, \pm standard deviation was calculated. The results were expressed/presented through frequency tables or graphs and charts. Chi square test was used to compare the levels of Thyroid function test in both groups. P value was used for significance which was < 0.05. All the study data was analyzed by using computer program SPSS version 12 for windows.

RESULTS

There were 101 neonates aged 3-7 days, including 52 preterm with mean gestational age of preterm at the time of delivery was 33 weeks ranges from 28 weeks to 36 weeks and 49 full term babies. Frequency of normal and abnormal cases in preterm and full term neonates is mentioned in Table 1. Mean values and Standard Deviations (SD) of serum T4 and TSH levels in preterm and fullterm neonates are shown in Table 2. Serum TSH values in preterm infants were not increased in accordance to lower T4 values while in one full term neonate lower T4 level was associated with increased serum TSH levels. Chi-square test was applied on this table and overall $X^2 = 6.591$, $df = 1$, P value = 0.010 which is significant.

Among 9 preterm infants with hypothyroxinemia who were called at later age for follow up, parents of two infants agreed to give specimen of blood for repeat T4 and TSH levels. T4 and TSH levels in both of these infants were normal at 5 months of age showing the transient decreased in T4 levels in preterm neonates during early weeks of life.

Table 1: Frequency of normal and abnormal cases in preterm/fullterm Neonates (n=101)

Status	Preterm (%age)	Fullterm (%age)	Total (%age)
Normal	43 (42.5%)	48 (47.5%)	91 (90.0%)
Abnormal	9 (8.9%)	1 (0.9%)	10 (9.9%)
Total	52 (51.4%)	49 (48.5%)	101 (100%)

DISCUSSION

These data demonstrate that an appreciable number of preterm infants have low postnatal thyroxine (T4) levels without remarkable elevation of serum TSH level during early weeks of life. The data also detect a small number of full-term neonates which are positive for hypothyroidism in the screening test. The hypothyroxinemia in premature and very low birth weight infants during early ages seems to be transient.

The effect of extreme prematurity on postnatal maturation of thyroid function was first reported in 1987¹⁷. The result of that study suggested that there is increasing delay in maturation of the hypothalamic pituitary thyroid control system with increasing prematurity while in our study preterm infant 30-34 weeks of gestation were the common gestation having low T4 level. After preterm birth, T4, free T4 and T3 levels remain lower than in term infants for the first weeks of life. There is obtunded thyrotropin peak immediately after birth, while TSH remains below 20 $\mu\text{U/L}$, the cut off point for congenital hypothyroidism, in the period of low T4.

The period during which T4 (and T3) levels are low is generally referred to as transient hypothyroxinemia of the preterm infants. It takes three to eight weeks before T4 and T3 levels of preterm infants reach the same levels as those in term infants. The earlier the infant is born, the more severe is the transient hypothyroxinemia¹². In our study 9 (20.9%) of pre-term were having transient hypothyroxinemia out of 52 (51.4%). In our study total T4 concentration in preterm infants 30-34 weeks of gestation were about two times less than term babies, while according to one study in infants less than 30 weeks of gestation, T4 concentrations in the first weeks of life were about 60 n mol/L , while in term infants T4 concentration were four times high¹⁴.

In our study thyrotropin levels in hypothyroxinemic preterm babies were less than 20 $\mu\text{U/L}$. In case of severe defect of thyroid hormone synthesis, very preterm infants are able to mount an appropriate TSH response (above 20 $\mu\text{U/L}$) and will be positive in screening. Therefore due to low T4 values normally found in the first postnatal week after preterm birth, screening program should follow a TSH screening strategy or a combined, TSH and T4 screening strategy¹⁹.

Preterm infants are at risk of neurodevelopmental impairment. The more preterm the infant, the higher the risk of impairment. These impairments include speech and language problems cognitive problems, behavioral problems and neuromotor problems (like cerebral palsy). Visual and hearing impairments are also frequent. The combination of the indispensability of thyroid hormones for normal brain development, low serum concentration of thyroid hormones in preterm infants, and high risk of neurodevelopmental impairment in preterm infants supports the hypothesis that low thyroid hormone levels are in part, causal to

neurodevelopmental problems in the preterm infants. Multiple studies support this hypothesis. These studies show an association between low thyroid hormone levels in the first week of life and worse developmental outcome²⁰⁻²³. In a study by Klein et al, 78% of infants with congenital hypothyroidism treated before 3 months of age but 0% treated after 6 months of age had an intelligence quotient (IQ) above 85, the mean IQ of the early treated group being 89, compared with an IQ of 54 in those treated late¹⁶.

According to three randomized double blind trials performed between 1997 and 2003, mortality and morbidity were not significantly influenced by thyroid hormone treatment²⁷⁻²⁹. Hence together, none of these studies provides evidence of need for thyroid hormone supplementation in very preterm infants. Therefore the current advice is not to supplement low thyroid hormone concentration in preterm infants, unless they are accompanied by elevated TSH levels³⁰⁻³². In our study those pre-term infants having only low T4 level and normal TSH level were not given, oral thyroxin.

Although one study done by Van Wassenaer AG and colleagues³³ has shown that T4 supplementation may be beneficial in infants of less than 28-29 weeks of gestation, further randomized trials are required for further investigations.

Serum TSH and free T4 should be measured every 1-2 months in the first 6 months of life and every 3-4 months thereafter. In general, the prognosis of infants detected by screening and started on treatment early is excellent, with IQs similar to sibling or classmate controls. Studies show that a lower neurocognitive outcome may occur in those infants started at a later age (> 30 days of age), on lower l-thyroxine doses than currently recommended, and in those infants with more severe hypothyroidism^{34,35}.

CONCLUSION

Routine screening of the new born is helpful for early detection of infants with congenital hypothyroidism. Screening strategy including determination of serum T4 and TSH levels is more useful than determination of serum T4 level alone.

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