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Thyroid Function in Preterm Infants during 5 Weeks of Life

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Abstract--- *In preterm infants, delayed secretion of the thyroid stimulating hormone hinders the diagnosis of congenital hypothyroidism. Therefore, this study was conducted to assess thyroid tests in preterm infants for five weeks to detect infants with congenital hypothyroidism manifesting with a delay for further treatment. This retrospective study was conducted in 186 preterm infants below 37 weeks' gestation hospitalized in Imam Ali and Kamali hospitals in 2016-2017. Peripheral blood samples were collected from the infants 3-5 days, 2-3 weeks, and 5 weeks after delivery, and the results of TSH and T4 levels were available in their hospital records. The data were collected into data collection forms and analyzed using SPSS version 18. The TSH and T4 levels were compared between these three measurement times. The TSH level was significantly lower at 3-5 days of age compared to 3-5 weeks of age (p=0.016). Moreover, the serum level of TSH at 3-4 weeks of age showed a small decrease compared to 2-3 weeks of age, but no significant difference was observed in the TSH level between 3-4 and 4-5 weeks of age (p=0.82). Since thyroid function tests may be normal at birth, they can be used for disease diagnosis. Therefore, it is necessary to repeat thyroid and screening tests with a delay and their parents should receive the proper training in this regard.*

Keywords--- *Hypothyroidism, Preterm, Infant, Screening.*

I. INTRODUCTION

Congenital hypothyroidism is the most common preventable cause of mental retardation. This disease has a global prevalence of 1:1600 to 1:2800 live births [1-4]. Congenital hypothyroidism is more common in preterm versus term infants. Incomplete development of the hypothalamus-pituitary axis in preterm infants causes a delay in increased secretion of thyroid stimulating hormone, making the diagnosis of congenital hypothyroidism a challenge [5, 6].

The prevalence of hypothyroidism is 2 in 1000 live births in Iran and the highest prevalence is reported in Markazi Province. Screening for hypothyroidism is done at 3-5 days of age via a heel-prick blood test. If the TSH level is above 5 µg/dl, thyroid hormones are rechecked [7-10].

It is estimated that the TSH level increases with a delay in about 12% of the preterm infants [11, 12]. Although this time frame may vary, the most common time is between 2-5 weeks after birth. The reason for this delay is complicated and multifactorial, but iodine deficiency is probably the most important factor. The daily iodine requirement of preterm infants is more than twice that of term infants [13-16]. Several studies found that most of the preterm infants were iodine deficient [17, 18]. The prevalence of hypothyroidism is higher in preterm versus term

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infants; however, only one third of them are diagnosed in screening tests [19-23]. Many studies suggest that very low birth weight infants should be re-screened while many other studies recommend and lower cut-off point for TSH in these infants [24]. Measurement of the TSH concentration is the best screening test for congenital hypothyroidism [25, 26]. A diagnosis of congenital hypothyroidism depends of the TSH cut-off point, which is different in the available guidelines [27-30].

Considering the above, since hypothyroidism screening is performed at 3-5 days of age for all infants and preterm infants born before 37 weeks' gestation may have normal thyroid tests at this time because the TSH level may rise with a delay of 2-7 weeks, the results of many studies in this regard are contradictory [31, 32].

There is no consensus about repeating thyroid tests in preterm infants; however, considering the improved care and survival of preterm infants and the resulting higher prevalence of hypothyroidism in this population, more accurate screening and diagnostic tests are recommended [33]. Since hypothyroidism screening is performed at 3-5 days of age for all infants and preterm infants born before 37 weeks' gestation may have normal thyroid tests at this time because the TSH level may rise with a delay of 2-7 weeks, this study was conducted to evaluate thyroid tests in preterm infants in Alborz Province for 5 weeks to detect the cases of congenital hypothyroidism diagnosed with a delay for further treatment [34-37].

II. MATERIALS AND METHODS

This retrospective study was conducted in 186 preterm infants below 37 weeks' gestation hospitalized in Imam Ali and Kamali hospitals of Alborz province. Peripheral blood samples were collected from the infants at 3-5 days, 2-3 weeks, and 5 weeks of age. The preterm infants who underwent thyroid tests at 3-5 days, 2 weeks, and 5 weeks of age were included in the study. The results of thyroid function tests, including TSH and T4, were available in the infants' hospital records. The data were collected into checklists and data collection forms and analyzed using SPSS version 18, and the levels of TSH and T4 were compared between the three measurement times. Paired t-test was used to investigate any difference in TSH and T4 levels and independent t-test was used to examine any inter-gender difference. The McNemar's test was also administered to study the prevalence of hypothyroidism at different times. Convenience sampling was used in this study and the sample size was determined according toa study by Torkaman et al. Assuming a prevalence of 13% for congenital hypothyroidism in preterm infants and a 95% confidence interval, the number of samples was calculated using the following formula and finally 186 infants were enrolled in the study considering attrition.

Ethical Considerations

This study was approved by the Ethics Committee of Alborz University of Medical Sciences. Confidentiality was maintained in all stages of the study, including sample selection, data collection and analysis, and presentation of the results.

III. RESULTS

A total of 186 preterm infants were evaluated in this study, of whom 86 (46.2%) were girls and 100 (53.8%) were boys. The characteristics of the infants are presented in Table 1. The mean gestational age was 29.94±2.4 years in girls and 29.45±2.43 in boys.

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The TSH level was significantly lower at 3-5 days of age compared to 3-5 weeks of age (p=0.016). Moreover, the serum level of TSH at 3-4 weeks of age showed a small decrease compared to 2-3 weeks of age, but no significant difference was observed in the TSH level between 3-4 and 4-5 weeks of age (p=0.82) (Table 1).

Table 1: TSH Level at Three Measurement Times

Measurement time	***(μg/dL)TSH (Mean±SD)***	***P value****
3-5 days of age	4.39±3.72	0.016
2-3 weeks of age	5.24±3.96	0.82
4-5 weeks of age	5.18±3.86	

*independent T-test

The prevalence of hypothyroidism was 32.3%, 41.9%, and 44.6% in preterm infants aged 3-5 days, 2-3 weeks, and 4-5 weeks, respectively. There was a significant difference in the prevalence of hypothyroidism between the first and the second and also between the second and the third measurements (p<0.001) (Table 2). The prevalence of hypothyroidism was similar between male and female infants in the first and second measurements, while its prevalence was significantly higher in female infants 4-5 weeks of age (56.6% versus 43.4%, p=0.012).

Table 2: Comparison of Prevalence of Hypothyroidism between Three Measurement Times

Measurement time	***Prevalence***	****P value***
3-5 days of age	32.3%	P<0.001
2-3 weeks of age	41.9%	P<0.001
4-5 weeks of age	44.6%	

* McNemar's test

Pearson's correlation analysis showed no significant correlation between birth weight and TSH level in the three measurement times. Moreover, in this study, in addition to TSH that is routinely used for screening, T4 was also measured to diagnose hypothyroidism. The prevalence of hypothyroidism at three measurement times according to TSH and T4 is presented in Table 3. The prevalence of hypothyroidism was 8.5%, 13.5%, and 11.1% in the first, second, and third measurement time, respectively. The difference in the prevalence of hypothyroidism was not significant between the first (3-5 days of age) and second measurement (2-3 weeks of age) while the difference between the second and the third measurement was significant (Table 3).

Table 3: Prevalence of Hypothyroidism based on TSH and T4

Measurement time	***Prevalence***	***P value****
3-5 days of age	8.5%	0.154
2-3 weeks of age	13.5%	<0.0001
4-5 weeks of age	11.1%	

* McNemar's test

IV. DISCUSSION

The results of the present study showed no correlation between sex and serum TSH level. However, the highest prevalence of hypothyroidism was seen at the third measurement time (4-5 weeks of age), which had a significant correlation with female sex. Rezaeian et al found a significant correlation between the prevalence of hypothyroidism

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and female sex with a ratio of 1.1:2 [38, 39].

One study investigated the relationship between several factors like sex, birth season, delivery mode, and birth weight on the incidence of hypothyroidism. The results showed that birth season was effective in developing hypothyroidism while sex and birth weight had no significant correlation with the prevalence of hypothyroidism. A study reported a relationship between low birth weight and prevalence of hypothyroidism [40-43].

Another study found a significant correlation between hypothyroidism and delayed TSH elevation pattern in very low birth weight infants (below 1500 g), which was not in line with our results [44].

In the present study, the mean serum TSH level was significantly lower at the first measurement time (3-5 days of age) compared to other measurements while no significant reduction in the TSH level was observed between the second and third measurements. The prevalence of hypothyroidism was higher in the third measurement compared to the second measurement and in the second measurement compared to the first measurement. Thus, the prevalence of hypothyroidism increased over time. Torkman et al found that a lower gestational age at birth was associated with more changes in the T4 level; therefore, the authors suggested that screening tests should be repeated [45-47]. Evaluation of the pattern of transient hypothyroidism in preterm infants, which manifests itself with elevated TSH and normal T4 levels, showed the necessity of repeating important lab tests with an interval, which was consistent with our findings [48]. Scratch et al measured the T4 level at 2 and 6 weeks of age. The results of their follow-up in preschool children showed that the lower the T4 level, the less the mental development at 7 years of age. In their study, the T4 level was 9.9-14 Pmol/L between the 1^{st} day and the 6^{th} week, while the T4 level was 5.4-12.6 µmol/dl in our study [49]. The difference is due to different measurement units and the values obtained in our study were within the lower normal range. However, the subjects did not reach the school age to investigate learning disorders [50, 51]. Therefore, studies with longer follow-up periods are required to assess the infants' growth, development, and learning abilities at higher ages [52, 53]. TSH is used for decision-making in the national screening program; however, in the study, the results of T4 and TSH were also rather similar. Screening is done at 3-5 days of age in Iran and since the results of thyroid function tests may be normal at birth in preterm infants and cannot be used for diagnosis and decision-making, it is very important that they be repeated at a timely interval. The parents of preterm infants should be supported before discharge and receive training about the care of their baby; moreover, they should also be informed of the importance of repeating thyroid screening tests [54, 55]. This study had a retrospective design and therefore it was not possible to investigate other causes of hypothyroidism like infantile respiratory distress syndrome, surgery, exposure to iodine disinfectants, etc. using hospital records. It is recommended to design prospective studies with larger sample sizes and longer follow-up periods to investigate these factors.

As a limitation of this study, since thyroid function tests in preterm infants are performed at the physician's request, it was possible that the tests were not repeated at the three measurement times, resulting in a reduction in the sample size.

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V. CONCLUSION

According to the national guideline, thyroid diseases are screened at 3-5 days of age in Iran. Since the results of thyroid function tests may be normal at birth in preterm infants and cannot be used for decision-making, it is important that screening and thyroid test be repeated at a timely interval.

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