Original Research Article

Congenital hypothyroidism screening by umbilical cord blood: thyroid stimulating hormone

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ABSTRACT

Background: Congenital hypothyroidism (CH) is one of the common preventable cause of intellectual disability. Most cases of CH result from thyroid dysgenesis. CH is often asymptomatic in early infancy, and any delay in treatment can affect the child in terms of delayed cognitive milestones. NSCH (newborn screening for congenital hypothyroidism) has been universally accepted and it is one of the most cost effective screening programs in the field of preventive medicine and public health.

Methods: A cross sectional study was conducted in Sri Venkata Sai Medical College and Hospital from 28th August to 28th February 2019 (1.5 years), this study was done on 73 newborns (70 deliveries, three mothers gave birth to twins). All data was collected prospectively. Mothers with known thyroid disease or on thyroid medication were excluded from the study. Under sterile aseptic conditions blood sample is collected from the umbilical cord soon after delivery.

Results: In the present study Cord blood TSH level of >20 mIU/L was present in 10% (7) of neonates. When the blood TSH levels were repeated (on day 3) among those with high cord blood TSH levels (>20), the blood TSH levels was also high (>20) in 6 (85.7%) neonates and low (<20) in 1 (14.2%). In Neonates with cord blood TSH >20, 6 neonates also had Low T4 (T4<7) levels (85.7%) and 1 neonate (14.2%) had T4 >7. In the present study 6 neonates (85.7%) had Congenital Hypothyroidism. The present study finds that Cord blood TSH as a diagnostic tool has Sensitivity of 100% and Specificity of 98.5% in diagnosing congenital hypothyroidism.

Conclusions: The current study concludes that Cord blood TSH is a sensitive and specific marker to predict the presence of congenital hypothyroidism in neonates.

Keywords: Congenital hypothyroidism, Cord blood thyroid stimulating hormone, Blood thyroid stimulating hormone, Serum T4

INTRODUCTION

Congenital hypothyroidism (CH) is one of the common preventable cause of intellectual disability. Most cases of CH are not hereditary and result from thyroid dysgenesis.

The causes of congenital hypothyroidism can be thyroid dysgenesis (70-80%) or one of the inborn errors of thyroid hormone synthesis (Dyshormogenesis 20-30%).

Most of infants with CH can be detected by newborn screening programs in the first few weeks after birth, before any clinical symptoms and signs develop.1

Any delay in treatment can affect the child in terms of delayed cognitive milestones. However, as CH is often asymptomatic in early infancy, less than a third get diagnosed before 3 months of life. Availability of a simple diagnostic blood test with low cost and easily
available treatment, this makes CH as one of the best condition that can be detected by screening program.

Forty five years after the development of first screening program in Canada, universal newborn screening for congenital hypothyroidism as a means to prevent intellectual disability, by early detection and treatment is a standard of care in all of the developed countries.\textsuperscript{2}

Even as many developing countries like China and Mexico incorporated Newborn Screening (NBS) into public sector healthcare programs, India is still in the contemplating stage for the last few decades.

Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) has recently published clinical practice guidelines, giving clear set of guidelines on screening cut offs, diagnosis, management and follow up of CH.\textsuperscript{3}

The TSH test costs no more than Rs100-200. It can be done at any dependable local lab in a venous sample or sent as a dried blood sample (DBS) on filter paper to one of the screening labs.

It is the responsibility of each individual Pediatrician and Obstetrician, to take initiative and start screening all the babies born under their care, one baby at a time. Screening should be done for every newborn baby using cord blood (soon after birth), if cord blood sample is not taken at birth , peripheral blood sample can be taken at 48-72hrs of age. Neonates with cord blood TSH>20mIu/L serum units, confirm the congenital hypothyroidism by peripheral blood sample taken at 48-72 hrs of age (confirmation by TSH >20mIu/L or T4 <7).\textsuperscript{3}

If neonates (sick babies) not screened for congenital hypothyroidism at birth or not even at 48-72 hrs of age , they should be screened by at least 7th day of age.\textsuperscript{4} The incidence of CH in India varies between 1 in 1172 to as high as 1 in 727 in some southern states. Years after the Indian Council of Medical Research (ICMR) prevalence study (results published 2013) which is supposed to pave the way for universal Government sponsored (newborn screening) NBS, there are no indications of progress, except in Kerala and Goa, where state governments launched newborn screening programs few years ago.\textsuperscript{4}

NSCH (newborn screening for congenital hypothyroidism )has been universally accepted as an essential part of screening for various metabolic disorders. It is successfully implemented in most developed countries and has proven to be one of the most cost effective screening programs in the field of preventive medicine and public health.\textsuperscript{5}

A study done by Ahmad N et al, to test the different types of screening methods to evaluate congenital hypothyroidism.\textsuperscript{6} They concluded that cord blood TSH assay as an initial screening test, had a higher specificity and sensitivity for the diagnosis of primary hypothyroidism.

Olney RS et al, shown an increase in the incidence (birth prevalence) rate of primary congenital hypothyroidism (CH) in the United States, a workshop was held in Atlanta, Georgia, the overall incidence rate was ~1 in 2800 births.\textsuperscript{7}

Medda et al, examined records of 140 Italian newborns with CH and 15 with transient hypothyroidism.\textsuperscript{8} Preterm newborns were more commonly diagnosed with transient hypothyroidism and those with CH.

In a study done by Lakshminarayana S et al, incidence is 3 in 1000 live births and 128 mothers out of 979 had hypertension and 38 mothers had Gestational diabetes.\textsuperscript{9}

In this study incidence is 6 out of 73 newborns, and incidence in Manglik et al, 2 in 1200 , Rasul et al, 1.5 in 1000 from Bangladesh, Urvi Sanghvi et al, 1 in 1000 from India, Ordookhani A et al, with 1 in 914 from Iran.\textsuperscript{10-13}

Aims and objectives of the study was to evaluate the incidence of congenital hypothyroidism among term and preterm babies born at Sri Venkata Sai medical college, Mahbubnagar, to evaluate the effectiveness of Cord Blood TSH screening to detect cases with hypothyroidism and to identify maternal factors effecting the cord blood TSH.

**METHODS**

Source of data was from Sri Venkata Sai Medical College and Hospital. Clinical data is obtained from the case files of the patient. The laboratory data of the subject’s samples is obtained from hospital laboratory records.

This is a Cross sectional study. Prospectively duration of 1.5years (28th August 2017 to 28th February 2019). Study includes 70 deliveries conducted in this hospital during the study period will be a part of the study.

**Inclusion criteria**

- All inborn babies.
- Babies born to mother with no history of thyroid disease.

**Exclusion criteria**

*Mothers on thyroid medications*

A prospective study of 73 delivered newborns which author have personally attended at Sri Venkata Sai Medical College between August 2017 and February 2019 were included in study.
Protocol for collecting the umbilical cord blood samples

- The umbilical cord was doubly clamped and transected 10-30 seconds after the delivery of newborn irrespective of weeks of gestation, after removal of the newborn from the operative field, the free end of the cord should be wiped with betadine to ensure sterility of the collected sample, while the placenta is still in utero, the cord blood is collected by gravity in a plain test tube.
- During caesarean section or multiple births, after the birth of the baby, umbilical cord blood is then collected from the removed placenta outside the operating theatre. Efforts are made to obtain maximum volume from each collection.
- Samples of 5ml are collected in order to know the umbilical cord blood - TSH value and sent to laboratory in sterile conditions.
- The mother’s age, parity, residence, community, blood pressure, diabetes, use of iodine antiseptics on the mother prior to delivery will be recorded.
- At birth, the babies weight, sex, time to first cry, congenital abnormalities, Apgar scores will be noted. TSH will be estimated within 24 hrs by electrochemiluminescence immunoassay ‘ECLIA’ on elecsys 2010 analyser.
- All babies wherein the cord TSH was found to be over 20mIU/L, the babies will be advised to give fresh samples for T4 and TSH between 2-4 day of life.

Statistical analysis

All the data was entered into Microsoft Excel 2007 spreadsheet and analyzed using SPSS software version 13.0. The various clinical parameters like gestational age and birth weight were correlated with the cord blood TSH levels using the Contingency coefficient analysis (Cross tabs procedure). Chi square test and Fisher’s Exact test were used to test the nominal significance at the p value <0.05 level, for high significance at the p value.

RESULTS

A total of 73 newborns were delivered (total 70 deliveries) in Sri Venkata Sai Hospital from August 2017 and February 2019 and all are included in the present study

Maternal age

The presenting age of the mothers ranged from 19 to 36 years with an average age of 25 years (SD =3.88). Out of the 70 mothers, the highest peak i.e. 38 mothers (54%) were aged between 23 to 26 years.

There were 2 mothers aged 19 years who were the youngest and 2 mothers aged 36 years who were the oldest (Figure 1).

Maternal co-morbid factors

Anemia was the most common maternal co-morbidity found in 27 out of 70 mothers (38.5%) followed by gestational diabetes found in 12 out of 70 mothers (17.1%), PIH was present in 10 out of 70 mothers (14.2%) (Table 1).

Table 1: Maternal co-morbid factors.

<table>
<thead>
<tr>
<th>Co-morbid Factor</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational DM</td>
<td>12</td>
<td>17.1%</td>
</tr>
<tr>
<td>Anemia</td>
<td>27</td>
<td>38.5%</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>1</td>
<td>1.42%</td>
</tr>
<tr>
<td>PIH</td>
<td>10</td>
<td>14.2%</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>2</td>
<td>2.85%</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>4</td>
<td>5.71%</td>
</tr>
<tr>
<td>No comorbid factors</td>
<td>36</td>
<td>51.4%</td>
</tr>
</tbody>
</table>

Gestational age

The gestational age of the neonates ranged from 35 to 41 weeks. Majority of the neonates (84.2%) were born at term >37 weeks, while few neonates (14.2%) were preterm, i.e. born before 37 weeks. One of the neonates had a gestational age more than 40 weeks (Figure 2).
Gender of the neonates

There is a slight male preponderance. 40 neonates were males (55%) and 33 (45%) were females. However, among the 6 neonates with congenital hypothyroidism 3 were males and 3 were females. (Figure 3).

Birth weight

Majority of the neonates 75.3% (55) were of normal birth weight (>2.5kgs) as seen in figure 4. However, 24.6% (18) of the neonates were of low birth weight. In the present study none of the neonates had birth weight less than 1.5 Kg (Figure 4).

Cord blood TSH levels

A cut off of 20 mIU/L was used to consider cord blood TSH levels as low (<20) or high (>20). Majority of the neonates that is 90%(66) had cord blood TSH levels of < 20 mIU/L and 10% (7) of neonates had high cord blood TSH levels (> 20 mIU/L) (Figure 5).

When the blood TSH levels were repeated (on day 3) among those with high cord blood TSH levels (>20), the blood TSH levels was also high (>20) in 6 (85.7%) neonates and low (<20) in 1 (14.2%). In Neonates with cord blood TSH >20, 6 neonates also had Low T4 (T4<7) levels (85.7%) and 1 neonate (14.2%) had T4 >7 (Figure.6,7,8).
In the present study in neonates who had cord blood TSH >20 it neonates(85.7%) have Congenital hypothyroidism and 1 neonate (14.2%) was negative for Congenital Hypothyroidism (Figure 8).

**Descriptive statistics**

The mean maternal age was 25.17 years, mean gestational age was 37.98 weeks, mean birth weight was 2.82 kilograms and mean cord blood TSH levels was 11.63 mIU/L (Table 2).

**Cord blood TSH levels of neonates according to gestational age**

Statistically significant difference in cord blood TSH was noted between term (37-41 weeks), and pre-terms (<37 weeks) neonates. Cord Blood TSH is high in 37-41 weeks age group (Table 3).

### Table 2: Descriptive statistics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Median</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>19</td>
<td>36</td>
<td>25.17</td>
<td>25.0</td>
<td>3.88</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>35</td>
<td>41</td>
<td>37.98</td>
<td>38</td>
<td>1.26</td>
</tr>
<tr>
<td>Birth weight (kgs)</td>
<td>1.7</td>
<td>4.2</td>
<td>2.82</td>
<td>2.8</td>
<td>0.48</td>
</tr>
<tr>
<td>Cord blood TSH (mIU/L)</td>
<td>3.07</td>
<td>27.9</td>
<td>11.63</td>
<td>10.37</td>
<td>5.50</td>
</tr>
</tbody>
</table>

N 70 mothers and 73 neonates

### Table 3: Cord blood TSH levels of neonates according to gestational age.

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Frequency</th>
<th>Cord blood TSH Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;37</td>
<td>11</td>
<td>8.8±3.35 (3.88-13.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>37-41</td>
<td>62</td>
<td>12.14±5.67 (3.07-27.9)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4: Cord blood TSH levels of neonates according to gender (*not significant).

<table>
<thead>
<tr>
<th>Gender</th>
<th>Frequency</th>
<th>Cord Blood TSH Mean±SD (Range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40</td>
<td>11.69±5.03 (3.88-27.06)</td>
<td>0.12*</td>
</tr>
<tr>
<td>Female</td>
<td>33</td>
<td>11.56±6.10 (3.07-27.9)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5: Cord blood TSH levels of neonates according to gestational age and gender (*Not significant).

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>n (M/F)</td>
<td>TSH(mIU/L) TSH(mIU/L) Mean±SD (range)</td>
</tr>
<tr>
<td>&lt;37</td>
<td>6/5</td>
<td>8.16±3.2 (3.88-13.98)</td>
</tr>
<tr>
<td>37-41</td>
<td>34/28</td>
<td>12.1±21.5 (0.6-251.7)</td>
</tr>
</tbody>
</table>

**Cord blood TSH levels of neonates according to gender**

This shows that there is no statistically significant difference between cord blood TSH levels in male and female neonates (Table 4).

**Cord blood TSH levels of neonates according to gestational age and gender**

There is no statistically significant difference in cord blood TSH value in male and female neonates <37 weeks of gestational age as well as >37 weeks gestational age (Table 5).

**Cord blood TSH levels of neonates according to birth weight**

It is noted that in present study Cord blood TSH is high in LBW group of neonates and it is statistically significant (Table 6).

**Cord blood TSH levels of neonates according to maternal age**

It is noted that in present study Cord blood TSH was high in maternal age group 29-35 which is statistically significant (Table 7).
Table 6: Cord blood TSH levels of neonates according to birth weight (*statistically significant).

<table>
<thead>
<tr>
<th>Birth weight (kgs)</th>
<th>Number</th>
<th>Cord Blood TSH Mean±SD (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.5 Kg(normal)</td>
<td>55</td>
<td>10.23±5.38 (3.88-27.06)</td>
<td>0.01*</td>
</tr>
<tr>
<td>1.5-2.5Kg (LBW)</td>
<td>18</td>
<td>12.85±5.85 (3.07-27.9)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Cord blood TSH levels of neonates according to maternal age (*statistically significant).

<table>
<thead>
<tr>
<th>Maternal age (years)</th>
<th>Frequency</th>
<th>Cord Blood TSH Mean±SD (range)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-22</td>
<td>22</td>
<td>10.48±6.46 (3.88-27.06)</td>
<td>0.012*</td>
</tr>
<tr>
<td>23-28</td>
<td>40</td>
<td>12.90±6.14 (3.07-26.9)</td>
<td></td>
</tr>
<tr>
<td>29-35</td>
<td>11</td>
<td>15.6±7.7 (6.7-27.9)</td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Sensitivity, specificity, positive predictive value and negative predictive value of cord blood TSH to diagnose congenital hypothyroidism based on serum TSH.

<table>
<thead>
<tr>
<th>Serum TSH &gt;20</th>
<th>Serum TSH &lt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord Blood TSH &gt;20</td>
<td>6</td>
</tr>
<tr>
<td>Cord Blood TSH &lt;20</td>
<td>0</td>
</tr>
</tbody>
</table>

Sensitivity, specificity, positive predictive value and negative predictive value of cord blood TSH to diagnose Congenital Hypothyroidism based on serum TSH

Sensitivity of Cord blood TSH is 100% in regard to Diagnose Congenital Hypothyroidism based on serum TSH. Specificity of Cord blood TSH is 98.5% in regard to Diagnose Congenital Hypothyroidism based on serum TSH. Positive predictive value of Cord blood TSH is 85.7% in regard to Diagnose Congenital Hypothyroidism based on serum TSH. Negative predictive value of Cord blood TSH is 100% in regard to Diagnose Congenital Hypothyroidism based on serum TSH (Table 8).

Sensitivity, specificity, positive predictive value and negative predictive value of cord blood TSH to diagnose Congenital Hypothyroidism based on serum T4 level

Sensitivity of Cord blood TSH is 100% in regard to Diagnose Congenital Hypothyroidism based on serum T4 level. Negative predictive value of Cord blood TSH is 100% in regard to Diagnose Congenital Hypothyroidism based on serum T4 level (Table 9).

Table 9: Sensitivity, specificity, positive predictive value and negative predictive value of cord blood TSH to diagnose congenital hypothyroidism based on serum T4 level.

<table>
<thead>
<tr>
<th>Serum T4 &lt;7</th>
<th>Serum T4 &gt;7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cord Blood TSH &gt;20</td>
<td>6</td>
</tr>
<tr>
<td>Cord Blood TSH &lt;20</td>
<td>0</td>
</tr>
</tbody>
</table>

The prevalence of Congenital Hypothyroidism in the present study is 8.21%.

DISCUSSION

CH was diagnosed if cord blood TSH >20 mIU/L and repeat serum TSH was above and fT4 was below the age appropriate cut off. In the present study, of the 70 deliveries, cord blood was available for 73 infants. Of the 73 infants, 10%(7) infants had cord blood TSH >20 mIU/L and remaining 90%(66) had cord blood TSH levels of <20 mIU/L.

When the blood TSH levels were repeated among those with high cord blood TSH levels (>20), the blood TSH levels was also high (>20) in 6 (85.7%) neonates and low TSH (<20) in 1(14.2%). These neonates also had low T4 levels 6(85.7%) (cord TSH levels >20) neonates have T4 <7.

In the present study in neonates who had cord blood TSH >20, 6 neonates(85.7%) have Congenital hypothyroidism and 1(14.2%) were negative for Congenital Hypothyroidism.

Screening for congenital hypothyroidism remains one of the most cost-effective tools to prevent intellectual disability in the population. Umbilical cord blood thyroid-stimulating hormone (TSH) levels remain an attractive and a practical step for screening for congenital hypothyroidism.

A study done by Ahmad N, et al to test the different types of screening methods to evaluate congenital hypothyroidism. They concluded that cord blood TSH assay as an initial screening test, had a higher specificity and sensitivity for the diagnosis of primary hypothyroidism. In the present study also it is noted that cord blood TSH has high sensitivity and specificity which correlates with study of Ahmad N et al.

Newer TSH assay techniques, such as the enzyme-linked immunoassays, chemiluminescent assays and fluoro-immunoassays offer the advantages of using non-
radioactive labels and greater sensitivity with the potential for better separation between normal and abnormal TSH concentrations.

TSH was estimated by electrochemiluminescence immunoassay ‘ECLIA’ on Elecsys 2010 Analyzer.

Olney RS et al, reported on risk factors in California from 1990 to 1998. The overall incidence rate was ~1 in 2800 births; and reported that newborns with birth weights of <2000 g were at elevated risk. Cord blood TSH is high in low birth weight (<2.5 kg) group of neonates. Finally, Medda et al, examined records of 140 Italian newborns with CH and 15 with transient hypothyroidism compared with those of matched control newborns. Preterm newborns were more commonly diagnosed with transient hypothyroidism and those with CH.

There is a slight male preponderance, 40 neonates were males (55%) and 33(45%) were females. However, among the 6 neonates with congenital hypothyroidism 3 were males and 3 were females. The gestational age of the neonates ranged from 35 to 41 weeks, with an average age of 25 weeks. 37.98% of neonates were born ≥4500g. The mean TSH level (4.24%) in preterm, lbw neonates was higher compared to normal birth weight neonates (<4.0 kg) were statistically significant (p = 0.001) and the prevalence rate of congenital hypothyroidism in the newborns was higher in the group of those weighing 1.5–2.5 kg (4.87%), 2.6–4.0 kg (4.15%), and >4.0 kg (0%); variation was statistically significant (p = 0.001). There was no statistical difference in cord blood TSH according to gestational age in our study (pre-term; term).

In the present study 51.4% (36) mothers had no comorbid factors. Anemia was present in 38.5% (27) mothers, 17.1%(12) mothers had Gestational DM and 14.2%(10) mothers had PIH. In a study done by Lakshminarayana S et al, 128 mothers out of 979 had hypertension and 38 mothers had Gestational diabetes.

In the present study Cord blood TSH was high in LBW neonates (12.85+5.85) as compared to normal birth weight neonates (2.5 kg) (9.16+8.2). In the study done by Lakshminarayana S et al, the prevalence rate of congenital hypothyroidism in the newborns was higher in the group of those weighing 4.0 kg, variation was statistically significant (p = 0.001).

In this study incidence is 6 out of 73 newborns, and incidence in Manglik et al, 2 in 1200 , Rasul et al, 1.5 in 1000 from Bangladesh, Urvi Sanghvi et al, 1 in 1000 from India, Ordookhani A et al, with 1 in 914 from Iran.

CONCLUSION

The present study adds emphasis on the need for continuing screening, one of the important preventable cause of intellectual disability.

Neonates diagnosed with congenital hypothyroidism in the present study had no maternal risk factors.

These infants, had no signs or symptoms suggestive of the disease. In developing countries, incidence is very high, the need for screening programs is the need of the hour.

The study includes the umbilical cord blood TSH done at SVS Medical College Hospital, which is a Tertiary Care Hospital. The congenital thyroid screening is not being performed in any other hospital of the district. In effect, the cases are being missed during infancy, causing irreversible damage to the growing brain.

Deliveries I have personally attended are also included in the study. The initiative prospects of my study to do the screening of congenital hypothyroidism by cord blood TSH have helped in identifying cases and start treatment in the first two weeks of life. Cord blood TSH was effective in screening for congenital hypothyroidism.

In the present study Cord blood TSH was high in term neonates, maternal age group 29-35 years, mothers who were associated with co-morbid factors such as gestational diabetes mellitus, pregnancy induced hypertension(PHI) and anemia which was statistically significant. There is no difference between cord blood TSH levels in male and female neonates.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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