ORIGINAL RESEARCH ARTICLE

# Establishing Umbilical Cord Thyroid-stimulating Hormone in Neonates at a Tertiary Care Teaching Hospital for Screening Congenital Hypothyroidism

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## Abstract

**Aim:** To find the normative value of cord thyroid-stimulating hormone (TSH) in neonates in our study group for screening congenital hypothyroidism (CH).

**Objectives:** 1. To establish the cutoff level of cord TSH in full-term and preterm neonates. 2. Correlate cord TSH value with birth weight, gender, and gestational age.

**Materials and methods:** A prospective study was conducted in tertiary care hospital for a period of 1 year from 1st February 2019 to 31st January 2020. Umbilical cord blood (3 mL) collected in sterile vacutainer under aseptic precaution, at the time of delivery from the maternal end of cord and TSH was estimated by chemiluminescent microparticle immunoassay (CMIA) technique. This study was carried out on 1,357 neonates. All data were collected prospectively. Mothers with thyroid illness and/or thyroid medication were excluded from the study.

**Results:** Umbilical cord TSH sample was tested on all 1,357 babies delivered in tertiary hospitals for a period of 1 year. Seven hundred and fifty were males (55.2%) and 607 were females (44.7%). One thousand and sixteen were normal term (74.8%) babies. The mean, median, and standard deviation of cord TSH values were 6.8, 5.5, and 4.5, respectively, in term neonates. Thyroid-stimulating hormone value corresponding to 90th, 95th, and 97th percentile was 16.5, 18.9, and 24.8 percentile in term neonates. Cord TSH values of >20 mIU/L were found in 30 (2.2%) neonates. One neonate had persistently higher TSH on repeat testing. There was no significant correlation of cord TSH between birth weight and gender of neonates but we found a significant correlation of gestational age with cord TSH value ($p$ value $< 0.05$).

**Conclusion:** Incidence of CH was 1 in 1,357 in our study. Umbilical cord TSH is a significant investigation for screening CH and a cutoff of >20 mIU/L can be used for screening CH.

**Keywords:** Chemiluminescent microparticle immunoassay, Congenital hypothyroidism, Neonates, Umbilical cord thyroid-stimulating hormone.

*Indian Journal of Medical Biochemistry* (2021): 10.5005/jp-journals-10054-0190

## Introduction

Congenital hypothyroidism (CH) is the term applied to hypothyroidism that has an etiology present from birth.[1] Congenital hypothyroidism is a major preventable cause of mental retardation.[2] It has an incidence varied between 1 in 248 and 1 in 1,700 as per Indian data.[3,4] For children with untreated CH, the result is a permanent, irreversible cognitive delay, impaired motor function, and growth. This can be prevented by early detection and treatment.[5]

Neonatal screening programs for the detection of CH in the neonatal period are widespread in developed countries for the last three decades and are fast gaining momentum in the developing world as well. In most screening programs, blood samples are collected at 5–6 days of age, but with a large number of babies being discharged early, cord blood samples are being used as well. In our country, it is very difficult to call back babies once discharged. Thus, cord blood remains a very practical alternative for screening purposes, and thus is the practice in some Asian countries.[6]

The clinical manifestations are often subtle or not present at birth. This likely is due to the transplacental passage of some maternal thyroid hormone, while many infants have some thyroid production of their own. Common symptoms include decreased activity and increased sleep, feeding difficulty, constipation, and prolonged jaundice. On examination, common signs include myxedematous facies, large fontanels, macroglossia, a distended abdomen with umbilical hernia, and hypotonia.[7]

According to the Indian Society of Paediatric and Adolescent Endocrinology ISPAE guideline screening should be done 48–72 hours of age using cord blood or postnatal blood. Neonates with thyroid-stimulating hormone (TSH) >20 mIU/L should be recalled for confirmation. For milder elevation, a second screening TSH at 7–10 days of age, should be done. Screening for preterm and low

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**How to cite this article:** Raichurkar AV, Jahagirdar R, Padwal MK, *et al.* Establishing Umbilical Cord Thyroid-stimulating hormone in Neonates at a Tertiary Care Teaching Hospital for Screening Congenital Hypothyroidism. Indian J Med Biochem 2021;25(3):121–124.

**Source of support:** Nil

**Conflict of interest:** None

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birth weight infants at 48–72 hours, and sick babies at 7 days of age should be done.[8]

The diagnosis should be confirmed by finding an elevated serum TSH and low T4 or free T4 level. Other diagnostic tests, such as thyroid radionuclide uptake and scan, thyroid sonography, or serum thyroglobulin determination may help pinpoint the underlying etiology, although treatment may be started without these tests. Levothyroxine is the treatment of choice; the recommended starting dose is 10–15 µg/kg/day.[8]

With the introduction of CH neonatal screening programs, babies affected with this condition are detected before the clinical manifestations are evident and irreversible. Congenital hypothyroidism screening enables timely replacement with thyroxin and efficiently reduces the risk for cognitive defects.[9]

This study was conducted to establish the cutoff value of umbilical cord TSH in term neonates for screening CH and correlate cord TSH with birthweight, gender, and gestational age at our study settings.

## Materials and Methods

This was a prospective study conducted in a biochemistry laboratory tertiary care hospital in collaboration with the Dept. of Paediatrics endocrinology, for a period of 1 year from February 2019 to January 2020, after getting approval from the institutional ethical committee (Cert. no. BVDUMC/IEC/33).

The study was based on the findings from umbilical cord blood samples collected from 1,357 babies born to mothers having no systemic (especially thyroid disorders) and obstetric complications. The mother's gestational age, mode of delivery along with obstetrical history, and history of past illness were properly noted. Babies' birth weight and gender were recorded. Babies born to mothers having hypothyroidism were excluded from study.

Written informed consent was taken from the mother for obtaining cord blood. Three milliliters of umbilical cord blood were collected from the maternal end of the cord in a plain sterile vacutainer. Serum analysis for TSH was carried out. The parameters were measured by chemiluminescent microparticle immunoassay (CMIA) technique on Abbott Architect *i*1000 SR analyzer.

According to ISPAE (Indian Society for Pediatric and Adolescent Endocrinology) guideline, venous confirmatory TSH >20 mIU/L before age of 2 weeks and >10 mIU/L after age 2 weeks, with low T4 (<10 µg/dL) or FT4 (<1.17 ng/dL) indicate primary CH and treatment initiation.

Data were entered in an excel sheet and analyzed using SPSS 26.0 statistical software. Descriptive statistics in the form of proportions (percentages) and mean ± standard deviation were arrived. Chi-square test and Fischer's exact test were used to test the nominal significance. Pearson's correlation was used to determine the correlation between cord TSH with birth weight, gender of neonates, and gestational age of mother and $p$ value <0.05 was considered significant.

## Results

Neonates of all consecutive deliveries conducted in tertiary care hospital from February 2019 to January 2020 were enrolled in the study after informed consent. Total babies 1,374 delivered in this period of study. Detailed antenatal history, medical history, thyroid status, and demographic details were recorded on a predesigned proforma. Some cases were excluded due to incomplete data (7), babies of a mother with a thyroid disorder (10) thus further analysis was carried out on 1,357 neonates.

Neonatal gender: 55% were males (747) and 45% were females (610) with M:F ratio of 1.2:1. Independent *t*-test (Mann–Whitney) revealed that there was no significant difference in gestational age, birthweight, or cord TSH levels between genders.

The mean, median, and standard deviation for the term cohort were 6.8, 5.5, and 4.5, respectively. Cord TSH value ranged between 0.25 and 100 mIU/L. Mean cord TSH value in term neonates corresponding to 90th, 95th, and 97th percentile was 16.5, 18.9, and 24.8, respectively. Table 1 predicts the entire cohort TSH value. Table 2 describes the distribution of cases as per gender, gestation period, and birth weight as per the cutoff value of TSH.

A cutoff of 20 mIU/L was used to consider cord blood TSH levels as low (<20) or high (>20). Majority of the neonates that is 97.7% (1,327) had cord blood TSH levels of <20 mIU/L and 2.2% (30) of neonates had high cord blood TSH levels (>20 mIU/L) (Table 2). The gestational age of the neonates ranged from 24 to 42 weeks. The majority of the neonates 1,016 (74.8%) were born at term >37 weeks, while a few neonates 341 (25.1%) were preterm, i.e., born before 37 weeks.

Table 3 reveals that there was a significant difference ($p < 0.05$) in cord blood TSH value between gestational period premature and normal term babies. Cord TSH was high in 37–42 weeks of gestational age.

Independent sample *t*-test (Mann–Whitney) revealed that there was no significant difference in cord blood TSH value between low birth weight (<2.5 kg) and normal birth weight babies (>2.5 kg) (Table 4).

Out of 1,357 cases, 30 neonates had TSH >20 mIU/L. One baby turned out to be hypothyroid on repeat testing has persistently high TSH value (59.2 mIU/L) and treatment started with L-thyroxine.

## Discussion

Congenital hypothyroidism is one of the major causes of mental retardation in our developing country. It remains a major burden in society. Due to the huge population, it is very difficult to call back neonates for screening on 3–4 days of delivery. So, cord blood TSH investigation remains an effective tool for screening CH due to its easy availability and accessibility. Studies across the world have shown that cord blood remains an effective tool for screening.

In the present study, cord blood was available for 1,357 infants. Among them, term babies were 1,016, preterm were 341, and the majority were falling in normal birth weight (66 %) and low birth weight babies were 34%. Of total infants, 2.21% (30) infants had cord blood TSH >20 mIU/L and remaining 97.79% (1,327) had cord blood TSH levels of <20 mIU/L. One baby turned out to be CH with repeated TSH 59.2 mIU/L and 29 were negative for CH with repeat TSH <10 µIU/L.

The incidence of CH estimated as 1 in 1,357 newborns which is matching with other Indian data varied as between 1 in 248 and 1 in 1,700[3,4] and probably geographic, ethnic (genetic) backgrounds are responsible to access incidence.

Normal cord TSH values show a wide range of 0.25–100 mIU/L and we had used a cutoff of 20 mIU/L which is a widely used cutoff for cord-blood screening programs worldwide. Had we used a cutoff of 30 mIU/L our recall rate would have fallen to 2.5%, and on further increasing the cutoff values to 40 mIU/L the recall rate has fallen to 0.3% which was comparable to Ravi Bhatia study 3 and 2%, respectively.[10]

**Table 1:** Entire cohort TSH value

| | *Cord blood TSH value* | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Gender wise* | | *Gestation wise* | | *Birthweight wise* | | |
| | *Male* | *Female* | *<37 weeks* | *37–42 weeks* | *LBW* | *Normal* | *Total* |
| *n* | 750 | 607 | 341 | 1,016 | 462 | 895 | 1,357 |
| Mean | 6.5 | 6.734 | 5.836 | 6.862 | 6.333 | 6.745 | 6.605 |
| Std. error of mean | 0.156 | 0.192 | 0.232 | 0.142 | 0.2 | 0.153 | 0.122 |
| Median | 5.4 | 5.4 | 4.9 | 5.55 | 5.3 | 5.5 | 5.4 |
| Std. deviation | 4.282 | 4.726 | 4.291 | 4.523 | 4.308 | 4.571 | 4.486 |
| 95th percentile | 14.9 | 17.38 | 11.5 | 16.5 | 14.195 | 16.4 | 15.82 |
| 97th percentile | 16.959 | 19.546 | 14.82 | 18.91 | 18.068 | 18.554 | 18.432 |
| 99th percentile | 24.802 | 25.658 | 27.56 | 24.87 | 24.456 | 25.418 | 25.176 |

**Table 2:** Distribution of cases as per gender, gestation period, and birthweight as per the cutoff value of TSH

| *TSH* | *Total* | *Male* | *Female* | *<37 weeks* | *37–42 weeks* | *LBW* | *Normal weight* |
|---|---|---|---|---|---|---|---|
| Normal (<20 µIU/L) | 1,327 | 737 | 590 | 334 | 993 | 452 | 875 |
| Increased (>20 µIU/L) | 30 | 13 | 17 | 7 | 23 | 10 | 20 |
| Total | 1.357 | 750 | 607 | 341 | 1.016 | 462 | 895 |

**Table 3:** Effect of gestational age on cord blood TSH values

| | *Group* | *N* | *Mean* | *SD* | *SE* | *p value* |
|---|---|---|---|---|---|---|
| Cord blood TSH value | <37 weeks | 341 | 5.836 | 4.291 | 0.232 | 0.0003 |
| | 37–42 weeks | 1,016 | 6.862 | 4.523 | 0.142 | |

**Table 4:** Effect of birth weight on cord blood TSH values

| | *Group* | *N* | *Mean* | *SD* | *SE* |
|---|---|---|---|---|---|
| Cord blood TSH value | LBW | 462 | 6.333 | 4.308 | 0.2 |
| | Normal | 895 | 6.745 | 4.571 | 0.153 |

Both the low CH incidence found, and the high proportion of severely hypothyroid babies identified led to the hypothesis that 20 mIU/L TSH could be a relatively high cutoff for the detection of babies with moderate hypothyroidism. Our figures have shown a comparable trend with the normative data for cord blood values as reported by various workers across the globe.

Our study indicates a possible limitation of using cord-blood (collected at birth) with respect to using heel-blood (collected after 24 hours) while attempting to increase the detection of moderate and mild cases of CH since heel-blood based programs truly achieved such goal by lowering cutoffs from 20 to 10–12 mU/L TSH.[11–13] Nowadays, Hell prick test is commonly used for screening CH. According to González-Irazabal et al., cord testing was superior to heel-stick testing as the recall rate was lower.[14] Our study also prefers cord TSH testing as an early discharge of neonates is the practice.

There is a slight preponderance of male babies (55.04%) than females (44.95%) in our study. There is no correlation of cord TSH with gender. It is comparable with Zion et al.'s study.[15]

We thought of comparing birth weight with cord TSH value in full-term and preterm babies as transient hypothyroidism is prevalent in VLBW (<1.5 kg) babies mainly due to immaturity of the hypothalamic-pituitary-thyroid axis and some affected babies are considered to need treatment. In our study, majority of newborns were having normal weight, i.e., between 2.5 and 2.99 kg. Cord TSH was high in normal birth weight infants than in low birth weight. Olney et al. who reported a high risk in birth weight <2,000 or >4,500 g.[16]

The gestational age of the neonates ranged from 24 to 42 weeks. The majority of the neonates (74.8%) were born at term >37 weeks, while a few neonates (25.1%) were preterm, i.e., born before 37 weeks. There was a significant difference ($p < 0.05$) in cord blood TSH value between gestational period premature and normal term babies. Cord TSH was high in 37–42 weeks of gestational age.

The prevalence of cord TSH value >6.7 mIU/L was 3.5% in term neonates and 2.7% preterm. It was statistically significant ($p < 0.003$). In a study conducted by Lakshminarayana et al., the prevalence rate CB TSH >6.1 µIU/mL was more in neonates belonging to term (4.77%) and preterm (4.24%) neonates, it was statistically significant ($p < 0.01$).[17]

Mean cord TSH values corresponding to 95th, 97th, and 99th percentile were 15.8, 18.4, and 25.1, respectively, which was comparable with studies, Rajkumar Arbind Singh et al. found 95th, 97th, and 99th percentile were 20.055, 21.858, and 29.943

mIU/L, respectively,[1] whereas Manglik et al. found a 97th and 99th percentile of 14.98 and 25.8 mIU/L, respectively.[6]

## Conclusion

Screening of neonates for CH is most important for preventing mental retardation as early as possible. This will reduce the burden of mental retardation in society. In our study, we used a cut-off of >20 mIU/L for screening CH. One neonate was found turning out to be hypothyroid out of 1,357 neonatal screening. There was a significant correlation of gestational age with cord TSH value.

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