RESEARCH PAPER

# Cord Blood Thyroid Stimulating Hormone Level – Interpretation in Light of Perinatal Factors

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**Objectives:** To study the influence of perinatal factors on cord blood TSH (CB TSH) levels.

**Design:** Cross-sectional study.

**Setting:** Tertiary care private hospital.

**Methods:** CB TSH levels were measured in 952 live-born infants using electrochemiluminescence immunoassay. The effect of perinatal factors on the CB TSH levels was analyzed statistically.

**Results**: The median CB-TSH was 8.75 microIU/mL (IQR = 6.475 – 12.82) with 11.5% neonates having values more than 20. CB TSH was significantly raised in first order neonates (*P* <0.01) and in babies delivered by assisted vaginal delivery and normal delivery (*P* <0.01). Neonates who had fetal distress or non-progress of labour had significantly higher CB TSH than those who were delivered by elective caesarean section. Requirement of resuscitation beyond the initial steps and low Apgar scores at 1 minute also resulted in significantly raised CB TSH (both *P* <0.01). Maternal hypothyroidism, maternal hypertension and neonates' weight appropriateness for gestation, gestational age and birth weight did not have significant effect.

**Conclusions**: The incidence of high cord blood TSH (>20 microU/mL) is 11.45%. On multivariate analysis, requirement of resuscitation, mode of delivery and fetal distress as indication for LSCS were significant factors affecting CB TSH values. Hence, these values need to be interpreted in light of perinatal factors.

**Keywords**: *Cord blood, Newborn screening, Perinatal factors, Thyroid stimulating hormone.*

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Congenital Hypothyroidism is the most common preventable cause of mental retardation with an incidence of 1:2500 to 1:2800 live births in India [1, 2]. Clinical diagnosis is difficult at birth and the time of initiation of therapy is a critical determinant of outcome. In view of paramount importance of early diagnosis and treatment, various screening programs were initiated [3,4]. In India, ICMR introduced congenital hypothyroidism screening program in neonates at various centers in 2007 [5,6]. Neonatal screening methods measure Thyroid Stimulating Hormone level in either cord blood sample or that obtained from heel prick sample at 3 to 4 days of life. When cord blood Thyroid Stimulating Hormone (CB TSH) is measured for congenital hypothyroidism screening, it has a high sensitivity but with a high false positive rates [7].

Various maternal and perinatal factors are known to affect the CB TSH levels [8]. There is a scarcity of Indian data on the effects of various factors on CB TSH levels. This study presents an analysis of various maternal and perinatal factors on CB TSH level.

## METHODS

This cross-sectional study was conducted in the neonatology unit of department of pediatrics at Fortis Escorts hospital, Faridabad, a tertiary-care hospital in Delhi NCR region. Priori calculation of sample size to study 10 factors in multiple regression model with a small (0.02) effect size and type 1 error of 5% (*P*<0.05) and power of 80% yielded a minimum sample size of 818. The study was planned to include consecutive 1000 live born neonates delivered at our hospital from July 2009 onwards to account for a maximum 20% drop out/ consent withdrawal or sample processing issues. We planned to include all live births in the hospital from July 2009 onwards. Exclusion criteria were: neonates with major life threatening malformations; those with antenatally detected central nervous system malformations; and neonates whose mothers were on any antithyroid drugs.

An informed consent was obtained from either of the parents. Antenatal and intra-partum information was noted from mother's medical record. Blood samples were drawn for blood group and TSH assay as per unit's

protocol, through a 5 mL syringe from the maternal end of the cord immediately after the cord was cut. The sample thus collected was kept at room temperature of around 25°C and was transported to laboratory within one hour. Neonates whose blood samples were not processed for technical reasons were excluded from final analysis (commonly due to inadequate amount hemolyzed sample). The sample was analyzed within 3 hours using electrochemiluminescence immunoassay on Cobas e 411 analyser with functional sensitivity of 0.014 microIU/mL All neonates who had CB TSH values more than 20 were advised repeat TSH assessment within 14 days of life.

The data were entered in Excel sheet and percentages of various outcome measures were calculated using SPSS for Windows version 12. The effect of various perinatal factors on the CB TSH levels was analyzed using independent Kruskal Wallis and Mann Whitney tests to define differences between groups and a *P* value of <0.05 was defined as significant. The relationship between variables was first analyzed using univariate analysis and all the variables were then taken to multivariate regression along with demographic factors. The study was approved by the hospital ethics committee.

## RESULTS

Of 1000 newborns enrolled, one was excluded on clinical grounds (mother on anti thyroid dugs) while another 47 cord blood samples could not be processed. Thus the study population comprised of 952 subjects (***Table* I**). The CB-TSH values ranged between 1.01- 63.74 microIU/mL with median at 8.75 (IQR = 6.475-12.82). 109 out of 952 neonates (11.45%) had CB-TSH values >20 microIU/mL and 44 (4.6%) had values >30. CB TSH values were found to be significantly raised in neonates delivered as first order compared to multiparous mothers (higher order births) (*P*=0.005) and in babies delivered by assisted vaginal delivery and normal delivery compared to caesarean section (*P*<0.001). Also, neonates who had fetal distress or non-progress of labour had significantly higher CB TSH than those who were delivered by elective caesarean section; (*P*<0.001). Requirement of resuscitation beyond the initial steps and low Apgar scores of <7 at 1 minute also resulted in significantly raised CB TSH (*P*<0.001). Male neonates had slightly increased CB TSH than their female counterparts (*P* =0.031). It was noticed that maternal hypothyroidism, maternal hypertension and neonates' weight appropriateness for gestation do not significantly affect the CB TSH value (***Table* II**). No correlation was found between CB TSH, gestational age (r= -0.009) (***Fig.* 1**) and birth weight (r= -0.004) (***Fig.* 2**). On multivariate analysis-requirement of resuscitation, mode of delivery and fetal distress as indication for lower segment cesarean section (LSCS) were found to be significant factors.

**TABLE I** PROFILE OF SUBJECTS INCLUDED IN THE STUDY

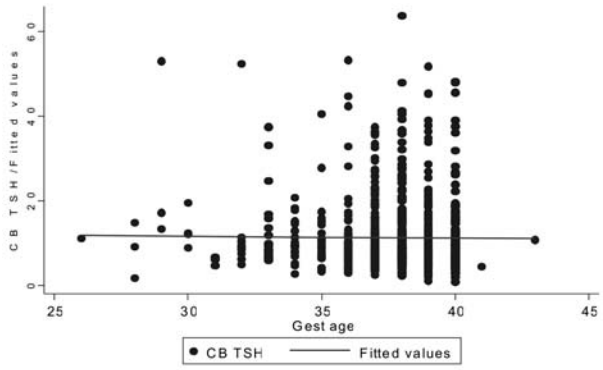
| *Characteristic* | *No (%)* | *No (%)* |
|---|---|---|
| *Birth Order* | | |
| First | 544 | 57.1 |
| Second | 342 | 35.9 |
| Third or Higher | 66 | 6.9 |
| *Mode of Delivery* | | |
| Normal Vaginal Delivery | 438 | 46.0 |
| Assisted Vaginal Delivery | 60 | 6.3 |
| Caesarean Section | 454 | 47.7 |
| *Indication of Caesarean Section* | | |
| Elective | 301 | 31.6 |
| For Fetal Distress | 91 | 9.6 |
| For Non Progress Of Labour | 53 | 5.6 |
| Other | 9 | 0.9 |
| Hypothyroid mother | 48 | 5.0 |
| Euthyroid mother | 904 | 95.0 |
| *Maternal Pregnancy Induced Hypertension* | | |
| PIH | 67 | 7.0 |
| Normotensive | 885 | 93.0 |
| *Weight Appropriateness for Age* | | |
| Small For Gestation | 31 | 3.3 |
| Appropriate For Gestation | 873 | 91.7 |
| Large For Gestation | 48 | 5.0 |
| Male sex | 510 | 53.6 |
| *Resuscitation Required* | | |
| Routine Care | 802 | 84.2 |
| Beyond Initial Steps | 150 | 15.8 |
| *APGAR Scores* | | |
| Less Than 5 | 28 | 2.9 |
| 5 or 6 | 84 | 8.8 |
| 7 or More | 840 | 88.2 |
| *Gestational Age* | | |
| Term (37-41 weeks) | 769 | 80.8 |
| Preterm (<37 weeks) | 182 | 19.1 |
| Preterm (<32 weeks) | 25 | 2.6 |

## DISCUSSION

Though the Screening for congenital hypothyroidism will decrease the burden of mentally retarded children in the society, the method of screening is not uniform [3]. Some countries use T4 while others prefer TSH as the tool since maternal diseases affecting placental dynamics influence

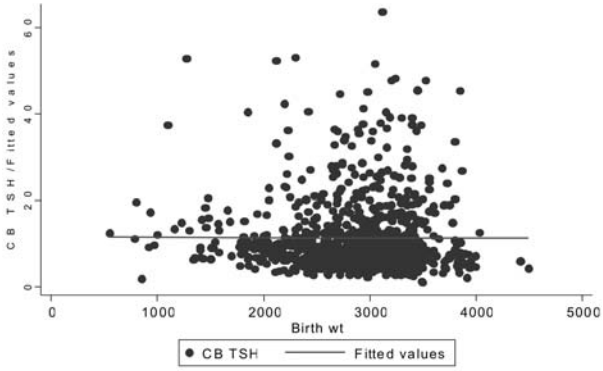
**TABLE II** COMPARISON OF CORD BLOOD TSH VALUES IN ACCORDANCE WITH SUBJECT CHARACTERISTCS

| *Characteristic* | *Number* | *Median (microIU/mL)* | *Interquartile range* | *P value* |
|---|---|---|---|---|
| First order birth | 544 | 9.03 | 6.58 – 15.4 | 0.005 |
| Higher order birth | 408 | 7.47 | 4.83 – 10.56 | |
| Normal & assisted vaginal delivery | 498 | 9.33 | 5.94 – 15.41 | <0.001 |
| Caesarean section | 454 | 7.56 | 5.82 – 9.81 | |
| LSCS for fetal distress and non progress | 153 | 7.69 | 5.3 – 11.05 | <0.001 |
| Elective LSCS | 301 | 7.56 | 5.99 – 9.52 | |
| Hypothyroid mother | 48 | 8.76 | 6.47 -12.06 | 0.220 |
| Euthyroid mother | 904 | 8.05 | 5.47 – 11.72 | |
| PIH In mother | 67 | 9.6 | 7.28 – 12.41 | 0.584 |
| Normotensive mother | 885 | 8.67 | 6.45 – 13.07 | |
| Male baby | 510 | 9.26 | 6.63 – 13.35 | 0.031 |
| Female baby | 442 | 8.22 | 6.21 – 12.48 | |
| Small for gestation | 31 | 8.73 | 6.60 – 12.17 | 0.506 |
| Appropriate for gestation | 873 | 8.8 | 6.51 – 12.87 | |
| Large for gestation | 48 | 7.68 | 5.43 – 14.65 | |
| Resuscitation beyond initial steps | 150 | 13.78 | 8.92 – 21.02 | <0.001 |
| Routine care | 802 | 8.25 | 6.22 – 11.67 | |
| Apgar less than 7 | 112 | 12.42 | 8.18 – 19.23 | <0.001 |
| Apgar 7 or more | 840 | 8.42 | 6.4 – 12.08 | |




Coefficient of correlation = -0.0099

**FIG. 1** *Correlation between gestational age and CB TSH value.*




Coefficient of correlation = -0.0041

**FIG. 2** *Correlation between birth weight and CB TSH value.*

T4 levels [9,10]. Few others use both T4 and TSH. Technically, using both T4 and TSH will be superior but would increase the cost of screening. Most of the countries have accepted TSH either through heel prick or through cord-blood as the screening method for congenital hypothyroidism. Cord blood collection of sample is preferred for its ease of collection of sample, lower rates of follow up losses, more practical for mothers with short hospital stay following delivery and its utility as an indicator of the prevalence of iodine deficiency disorders [11,12].

Researchers have studied different CB TSH cut off levels varying between 20-90 for recall with an objective to keep cost of rescreening low and making it more cost effective. In Indian setup, cord blood TSH value of

**WHAT IS ALREADY KNOWN?**

- Cord blood TSH assessment is a useful screening tool for congenital hypothyroidism but with high false positive rates.

**WHAT DOES THIS STUDY ADD?**

- Perinatal stress factors and mode of delivery significantly impact cord-blood TSH levels and should be accounted for while interpreting the results.

>20μIU/mL is seen as safe cut off for recall [13,14]. We, in the setting of tertiary care referral hospital, found that 11.5% of all samples had values more than 20 μIU/mL which reflected that a high recall rate is associated with CB TSH assessment. The only other comparable study from a near similar geographical area [15] though does not provide the numbers of patients with TSH levels more than 20 microU/mL, but reports the mean CB TSH as 10.6 +/- 6.7 microU/mL and that their high risk patients (>6 % population) had a mean TSH above 20 microU/mL.

Changes in TSH levels in response to T3 and T4 blood levels forms the basis of screening for congenital hypothyroidism through CB TSH estimation. However, other factors may also influence TSH levels. Various authors have correlated an increase in TSH values with factors like birth asphyxia and difficult deliveries [15], perinatal stress events [8], birth weight, male infant sex and instrumental delivery [16], and negatively with cesarean sections as mode of delivery [17]; but the mechanism are poorly understood.

The postnatal surge in TSH levels, common to all newborns, is considered to be mediated through alpha adrenergic stimulation following the cold stress [18]. In a study on neonatal rats, it was demonstrated that perinatal hypoxia increases the secretion of catecholamines [19]. Similarly, a surge in catecholamine secretion was seen in human neonates during parturition; and this was more in asphyxiated newborns and in vaginally delivered newborns compared to those born by elective caesarean section [20]. Others too observed that with perinatal hypoxia there is an increase in endogenous catecholamine [21], which is more pronounced when the scalp PH is less than 7.26 [22]. This alpha adrenergic stimulation in turn might be responsible for the observed increase in CB TSH in our subjects who had low Apgar scores, required active resuscitation after birth, were born through vaginal delivery or non-elective LSCS, and to primiparous mother. However, in our study, no significant difference was found in CB TSH values in male and female neonates; nor any positive correlation found with the birth weight.

Unlike authors who observed a negative correlation of serum TSH with gestational age [23], we did not find it to be significant. At our center, we commonly give antenatal steroids before premature deliveries and Dexamethasone has been shown to blunt the release of catecholamine [24,25], which might have an effect on TSH levels.

Perinatal stress factors and mode of delivery have a significant impact on cord-blood TSH levels and any rise in cord blood TSH should be seen in the light of these factors. The proportion would be higher where high-risk pregnancies are delivered. Larger studies should factor this impact and work out a correction in TSH cut off in accordance to influencing factors if present. Many repeat evaluations of thyroid function can thus be avoided, and would not only save the cost but also would allay the anxiety of parents of neonates undergoing a repeat/ confirmatory test.

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