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Original Research Article

Perinatal variables influencing cord blood thyroid stimulating hormone

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ABSTRACT

Background: Newborn screening using cord blood Thyroid Stimulating Hormone (TSH) is an effective and an easy way to screen babies for congenital hypothyroidism. Congenital hypothyroidism is a common preventable and treatable cause of mental retardation. Early diagnosis with the help of newborn screening aids in timely management and decreased morbidity. Various maternal and neonatal variables can affect cord blood TSH level thereby affecting the accurate diagnosis of congenital hypothyroidism. This study aims at studying the perinatal variables affecting cord blood TSH.
Methods: In a retrospective cross-sectional study conducted in a tertiary care hospital, the hospital case records of 1465 newborn and their mother were studied for variables including cord blood TSH, maternal age, mode of delivery, parity, gender of baby, gestational age and growth of baby. The effect of these perinatal variables on cord blood TSH was analysed statistically. P value below 0.05 was considered as statistically significant. The statistical analysis was done used the SPSS software version 18.0.
Results: The median cord blood TSH was 8 microIU/ml (IQR= 6-12) with 8.1% newborns having values more than 20 microIU/ml. Cord blood TSH was significantly raised in male babies ($p < 0.01$) and in neonates born by assisted vaginal delivery ($p < 0.01$). Significant increase in cord blood TSH ($p < 0.02$) was observed in neonates born to primiparous mothers. Maternal age, gestational age of the newborn and growth of the newborn did not have significant effect on cord blood TSH values.
Conclusions: The mode of delivery, parity and gender of the baby were found to be significant variables affecting cord blood TSH values. Hence, cord blood TSH values should be interpreted in the light of these perinatal variables.

Keywords: Congenital hypothyroidism, Cord blood thyroid stimulating hormone, Newborn screening, Perinatal variables

INTRODUCTION

Congenital hypothyroidism (CH) is a major preventable and treatable cause of mental retardation with an incidence ranging from 1:1700 to 1:2800.[1,2]

Most newborns with congenital hypothyroidism appear normal at birth, making clinical diagnosis difficult. Newborn screening aids in early diagnosis and timely treatment to prevent disability. Most of the developed countries have a well-structured newborn screening program for congenital hypothyroidism but it is still lacking in India.[3]

Newborn screening method measures Thyroid Stimulating Hormone (TSH) either in cord blood sample or a heel prick sample on day 3 or 4 of life.

Cord blood TSH has high sensitivity with a high false positive rate.[4] It also has the advantages of being easy to

collect, non-invasive, faster availability of results before maternal discharge and further intervention if indicated.

Various maternal and perinatal variables are known to affect cord blood TSH levels.[5-11]

This study was conducted to find the influence of the various maternal and perinatal variables on cord blood TSH levels as it is used as a means of screening for congenital hypothyroidism.

METHODS

This retrospective cross-sectional study was conducted in the neonatal unit of a tertiary care hospital in South India from January 2011 to June 2013. Necessary data was collected from the hospital case records of one thousand nine hundred and eighty-five newborns and their mothers.

The perinatal variables analysed for their influence on cord blood TSH levels included maternal variables like age, parity, mode of delivery, antenatal complications and neonatal variables like gestational age, gender and growth. Neonates with antenatally detected central nervous system malformations, major congenital life-threatening malformations and whose mothers were on anti-thyroid medications were excluded.

Blood samples were drawn for blood group and TSH assay as per the hospital protocol at the time of delivery. Blood was collected from the maternal end of the cord immediately after cutting the cord and transported to laboratory within one hour for processing.

The samples were analyzed using electro chemiluminescence assay on Cobas e 411 analyzer with functional sensitivity of 0.014 microIU/ml. Out of the 1985 newborns whose records were studied, case records of 520 newborns did not have the cord blood TSH level mentioned in the record for various reasons, and they were excluded from the study.

Serum TSH along with free Thyroxine (FT4) was repeated after 72 hours of life for all neonates who had cord blood TSH values more than 20microIU/ml. Congenital Hypothyroidism was diagnosed if the value of TSH was >10microIU/ml and FT4 was <0.7ng/ml after 72 hours of life.

Statistical analysis

The data was entered in Microsoft Excel and analysed in SPSS version 18 software. Relationships between variables were evaluated by correlation, linear regression and multiple regression analyses.

Differences between groups were analysed by ANOVA and independent t-test. Differences were regarded as significant at values of $p < 0.05$.

RESULTS

A record-based retrospective study was conducted to find out the effect of maternal and neonatal variables upon neonatal cord blood TSH level.

In the study, total of 1985 case sheets of newborns were studied of which only 1465 cases were found eligible having the cord blood TSH levels and hence included in the study. Thus, the study population comprised of 1465 subjects (Table 1).

Table 1: Profile of subjects included in the study.

Characteristic		Frequency	%
Maternal parity	Primiparous	701	47.8
	Multiparous	764	52.2
Mode of delivery	Normal vaginal delivery	893	61.0
	Assisted delivery	115	7.8
	Caesarean section	457	31.2
Sex of the baby	Female	687	46.9
	Male	778	53.1
Maternal age (years)	17-24	885	60.4
	25-35	550	37.5
	>35	30	2.0
Gestational age	Preterm (<37 weeks)	167	11.4
	Term (37-41 weeks)	1106	75.5
	Post term (>41 weeks)	192	13.1
Growth	Appropriate for gestation	1229	83.9
	Large for gestation	133	9.1
	Small for gestation	103	7.0

Of the 1465 neonates, 61% were delivered by normal vaginal delivery and about 84% were appropriate for gestational age (AGA).

The cord blood TSH values ranged between 0.7- 79.24 microIU/mL with median at 8 microIU/ml (IQR = 6-12). Out of 1465, 119 (8.1%) neonates had cord blood TSH above 20 microIU/ml.

At 72 hours of life, a repeat TSH and free T4 were done and out of these 119 babies, 2 (0.13%) were found to have low FT4 satisfying the criteria for Congenital Hypothyroidism. Among the neonatal variables, only the gender of the child was found to be significantly associated (p value = 0.002) with cord blood TSH higher among male neonates. Cord blood TSH level was significantly raised among neonates born through assisted delivery (p value= 0.0001) as compared to spontaneous

delivery. Also, cord blood TSH level was significantly raised among neonates born to primigravidae mothers as compared to multiparous mothers (p value = 0.019). On multivariate linear regression, mode of delivery, parity and gender were found to be significant variables (Table 2,3).

Table 2: Comparison of cord blood TSH with subject characteristics.

Characteristics		Median	IQR	p-value
Maternal parity	Primiparous	8.30	5.80-12.55	0.019*
	Multiparous	7.80	5.40-11.20	
Mode of Delivery	Normal vaginal delivery	8.00	5.60-11.80	0.0001*
	Assisted delivery	11.10	7.60-18.50	
	Caesarean section	7.60	5.40-10.35	
Sex of the baby	Female	7.60	5.4-11.10	0.002*
	Male	8.30	5.90-12.2	
Maternal age	17-24	7.90	5.60-12.05	0.984
	25-35	8.20	5.80-11.20	
	35-45	7.65	5.57-12.63	
Gestational age	Preterm	7.80	6.00-11.70	0.283
	Term	7.90	5.60-11.50	
	Post term	8.70	5.40-13.90	
Growth	Appropriate for gestation	7.90	5.60-11.75	0.601
	Large for gestation	8.30	5.75-12.90	
	Small for gestation	7.80	5.90-11.00	

*p <0.05 is significant

Table 3: Multivariate linear regression.

Parameters	Unstandardized coefficients (B)	t test	p value
(Constant)	9.758	7.169	0.000
Growth	-0.537	-1.191	0.234
Sex	0.854	2.224	0.026
Parity	-0.562	-2.709	0.007
Mode of delivery	0.719	4.868	0.000

R-square: 15.9%

DISCUSSION

New-born screening for congenital hypothyroidism is a must for timely diagnosis and treatment of a preventable condition whose consequences will be detrimental if left unidentified. Screening is done by assessing TSH levels and can be done either by heel prick or cord blood sample. In country like India, use of cord blood TSH as a screening tool is a better option due to its simplicity and accessibility.

Cord blood TSH is non-invasive, easy to collect and has the distinct advantage in terms of results being available faster before discharge leading to lower rates of loss to follow-up. It also helps to confirm the diagnosis of congenital hypothyroidism by repeating TSH and FT4 at 72 hours of life and to initiate early treatment before discharge.

Fuse et al had shown that mixed cord blood is a good sampling technique for screening for congenital hypothyroidism.[11] Walfish concluded that cord blood TSH had a better specificity and sensitivity as compared to cord or filter paper T4 at 3-5 days of age.[12]

To make screening cost effective, researchers have studied different cord blood TSH cut-off values for recall and rescreening.[2,13,14] In India, we can safely use >20mIU/ml as a cut-off for recall for rescreening.[15] In our study, 119 (8.1%) neonates had cord blood TSH above 20microIU/ml reflecting a higher recall rate. This was comparable to the study done by Gupta et al where 11.5% of the study population had cord blood TSH value of >20microIU/ml and hence, a higher recall rate.[5]

Authors found median cord blood TSH was 8microIU/ml (IQR = 6-12) which was similar to the results obtained by Gupta et al who found median cord blood TSH level of 8.75 microIU/ml (IQR = 6.475-12.82) in their population.[5] Other studies have used mean cord blood TSH values and their results were also comparable to our findings.[6,7,9,10]

On rescreening, we found 2 out of 119 babies had low FT4 fulfilling the criteria for congenital hypothyroidism. The incidence of congenital hypothyroidism in our study was 1 in 730 which is comparable to the results by Manglik et al who found incidence of congenital hypothyroidism of 1 in 600.[15]

A much lower incidence of 1:1700 and 1:2800 was found in studies done by Devi AR et al and Desai MP et al, respectively.[1,2] Other Indian studies have found even

higher incidence of 1 in 248, 3 in 1000 and 3 in 430.[2,6,7] This variation could probably be explained by the geographical and ethnic differences. A larger cohort should be studied to find out the incidence.

The main objective of our study was to study the effects of various perinatal variables upon the cord blood TSH level. The values of cord blood TSH can be affected by various maternal and perinatal variables.[5-11]

In our study, we found that cord blood TSH was significantly higher in neonates born through assisted vaginal delivery than in those born through caesarean section, which was similar to various studies by Gupta et al, Lakshminarayana et al, Lee SY, Aarmanian et al and Rashmi et al.[5,6,8-10]

In our study, we found significant increase in cord blood TSH levels among neonates of primiparous mothers. Similar findings have been published in other studies as well.[5,6,8] We found that cord blood TSH were significantly elevated in male newborns in line with studies done by Chan LY and Herbstman J; whereas Gupta et al, Lakshminarayana et al and Fuse et al observed no significance of gender on cord blood TSH levels.[5,6,11,16,17] We did not find any significant correlation of cord blood TSH with maternal age in our study. Lakshminarayana et al and Lee SY et al also did not find any significant association between maternal age and cord blood TSH level.[6,8]

In our study, no significant effect was seen on cord blood TSH level by gestational age which was similar to findings by Gupta et al, Lee SY et al and Armanian AM et al.[5,8,9] Few studies have found varying effect of gestational age on cord blood TSH. Positive correlation was observed in a study conducted by Raj et al[7] whereas Rashmi et al observed a negative correlation with gestational age.[10]

Unlike Rashmi et al who observed a negative correlation of cord blood TSH with growth, we did not find any significant correlation between intrauterine growth of newborn and cord blood TSH level.[10]

On multivariate linear regression, authors found mode of delivery, parity and gender to be variables significantly affecting cord blood TSH level. Intrauterine growth was not found to be a significant variable. Other studies have analysed variables like mode of delivery, requirement of resuscitation, APGAR score, gestational age and birth weight.[5,6,8-10] The only variable common in all these studies which had significant effect on cord blood TSH was mode of delivery. All the studies had observed a higher cord blood TSH with vaginal delivery, primarily assisted vaginal delivery.

From our study, we found that perinatal factors like gender of the neonate, mode of delivery and parity have significant effect on cord blood TSH. Any rise in cord blood TSH should be interpreted after taking these factors into account. In institutions with high risk deliveries, cord blood TSH if interpreted in the light of these factors may help in reducing the rescreening number thereby saving cost and time.

A well-structured screening programme for congenital hypothyroidism is a universal need for all developing countries. Institutional deliveries will identify babies with congenital hypothyroidism early so that rescreening can be done before discharge and early and appropriate therapy instituted.

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