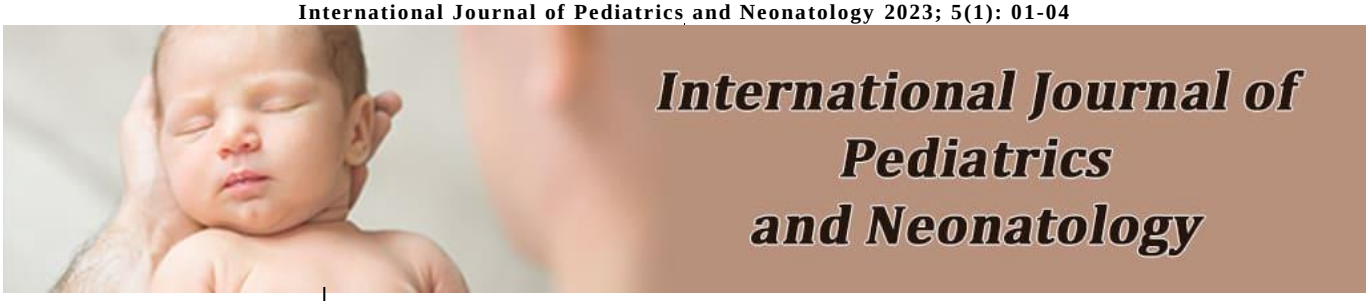

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Effect of perinatal factors on neonatal thyroid stimulating hormone

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Abstract
Background: Congenital Hypothyroidism (CH) is a common cause of mental retardation. Its incidence varies in different parts of the world from 1:4000 to 1:2000.
Objective: To study effect of perinatal factors on heel prick blood TSH levels and to find incidence of congenital hypothyroidism.
Study Design: Prospective Observational birth cohort study.
Method: Heel prick blood samples of total 3151babies, 1673 (53.1%) males and 1478 (46.9%) females was taken on special graded filter paper within 48 hours of life and screened by fluoroimmunometric assay. Babies with TSH value more than 9µU/ml were recalled at 5 to 7 days of life for repeat sample of T3, T4, TSH. Babies with low T4 less than 7 µgm/dl and TSH more than 20 µU/ml were labelled as congenital hypothyroidism. The effect of perinatal factors was analyzed statistically.
Result: In our study, thyroid screening in two third of neonates was done at 12 to 24 hours of age. Median (IQR) TSH of 3151 neonates was 3(1.4-5.5) µU/ml. TSH level was significantly low in neonates with sampling at age of >24 hours. Recall rate in our study was 7.6% (238 cases) and 2 neonates were diagnosed as congenital hypothyroidism. Neonates with assisted deliveries showed a higher median (IQR) TSH level 5.3(3-9.1µU/ml) as compared to normal vaginal deliveries and lower segment caesarean section. This was statistically significant (p<0.001). Neonates with perinatal asphyxia had higher median (IQR) TSH values 8.2(1.7-12.5) µU/ml and this was statistically significant.
Conclusions: Incidence of congenital hypothyroidism in our study was 1:1575. TSH levels were high in neonates with assisted delivery and perinatal asphyxia. TSH level was low in neonates delivered by caesarean section. There was no effect of birth weight, sex and gestational age on neonatal TSH level.

Keywords: Congenital hypothyroidism (CH), thyroid stimulating hormone (TSH)

Introduction
Congenital Hypothyroidism (CH) is one of the most common preventable causes of mental retardation [1]. CH in newborn period is almost always overlooked and delayed diagnosis leads to dangerous consequences like neurologic, motor and growth deficits [2]. The worldwide incidence of CH is 1:4000 with male to female ratio 1:2 [3]. The estimated incidence in India varies from 1:500 to 2300 as per different studies. 1:2925 live births in (Mumbai), [4] 1:600 (from Kolkata), [5] and 1:1700 (from Hyderabad) [6] and 1:3400 (Chandigarh) [7].
After birth term baby experience a surge in thyroid stimulating hormone (TSH) as a physiological response to cold environment, which stabilizes at 24-48 hours of life. This surge peaks at 30 minutes and declines over next few days. The increased TSH results in concomitant sharp rise in T_4 and T_3 levels peaking at 36-48 hours of life and then declines to adult value at 4-5 weeks. Preterm infant demonstrates a similar but blunted response to hypothalamic-pituitary axis (HPA) and results in an overall lowering of total T_4, free T_4 and T_3. This attenuation increases with decreasing gestational age and in extremely preterm [9]. In the developed world universal newborn screening is practiced in all newborns to screen inborn errors of metabolism (IEM) [2].
Perinatal asphyxia provokes multiple alterations in body due to failure in gas exchange system. Some studies showed that neonatal TSH is elevated in case of stressful perinatal conditions as perinatal asphyxia, forceps delivery, caesarean section and prematurity, while other studies do not favour any influence of perinatal factors on neonatal TSH levels [14, 15].

Hence, we planned a prospective study to analyze the effect of perinatal factors on neonatal TSH as well as to estimate the incidence of CH.

Material and Methods

This prospective observational study was conducted on all newborn babies delivered at Government Multi Speciality Hospital, Sector 16, Chandigarh.

January 2009 to June 2009 (six months).

All newborns with congenital malformations and sick newborns admitted in nursery with death in first 24 hours of age were excluded from the study.

Blood sample by heel prick method was taken on graded filter paper after informed consent of one of the parents. TSH < 9 µU/ml blood was labeled as normal, TSH 9-18 µU/ml as borderline and TSH >18 µU/ml as high. Perkin Elmer Delfia Neonatal kits were used for sampling and tests were done by time resolved fluoroimmunoassay. Babies with borderline and high TSH values were recalled at 5-7 days of life for a repeat sample for T_3, T_4 and TSH testing by Elisa. Babies with low T_4< 7 µgm/dl and high TSH more than 20 µU/ml were labeled as congenital hypothyroidism. Details about the newborn were recorded on the proforma.

Birth Asphyxia- was defined as APGAR score at 1 minute of 0-6 as per National Neonatology Forum.

Birth weight was recorded up to nearest of 5 grams.

Low Birth Weight (LBW) was defined as babies with birth weight< 2500 grams (up to and including 2499 grams).

Very Low Birth Weight (VLBW) was defined as babies with birth weight less than 1500 grams (up to and including 1499 grams.)

Statististical Analysis

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). For all quantitative variables, central tendencies and their standard deviations were calculated. Data was checked for skewness by Kolmogorov Smirnov test of normality. For normally distributed data means were compared using student's t-test for two groups. When samples were very small or for skewed data, Mann Whitney test was applied. For more than two groups One Way ANOVA or Kruskal Wallis test was applied depending on type of distribution. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared using Chi square or Fisher's exact test whichever was applicable. All statistical tests were two-sided and performed at a significance level of $\alpha = 0.05$.

Results

A total of 3774 babies were born during the study period of which 3153 (83.5%) underwent TSH estimation. Male to female ratio was 1.13:1.

Mean birth weight of neonates was 2870±460 gms with a range of 1040 to 4290 gms, 647(20.5%) neonates were low birth weight (LBW) and 20(0.6%) neonates were very low birth weight (VLBW).

Gestational age was in a range of 28 to 40 weeks, 59 (2%) neonates being preterm (<37wks) and 3092 (98%) neonates were born at term. There were 2464 (78.2%) neonates delivered normally per vaginally, 665 (21.1%) by LSCS and 22(0.7%) by assisted (forceps and ventouse) delivery. Twenty-two (0.7%) neonates had perinatal asphyxia.

Mean age of neonates at time of first TSH sampling was 22±8.3 hours with a range of 8 to 48 hours. Two hundred seven (6.6%) had their first sampling between 6 to 12 hours of age, 2108 (66.9%) babies had their sampling between 12 to 24 hours of age and 836 (26.5%) of babies had their sampling at > 24 hours of age. In about two thirds (66.9%) of neonates, thyroid screening was done at 12-24 hours of age.

Median (IQR) TSH level was 3(1.4-5.5) µU/ml. Median (IQR) value in male and female babies was 3.1 (1.4-5.5) and 2.9 (1.3-5.3) µU/ml respectively and the difference in their values was not significant (*P*=0.031). 2913 (92.4%) neonates had normal TSH, 220 (7%) neonates with borderline TSH and 18 (0.6%) neonates with positive TSH values.

Out of 220 number of neonates with borderline TSH values (9-18 µU/ml), complete thyroid profile could be done in 167 (75.9%) of neonates and none of them was hypothyroid. Out of 18 neonates with high TSH, thyroid profile could be done in 13 (72.2%) of neonates and 2 neonates were found to be having CH. Incidence of CH was 1:1575. Profile of both patients is depicted in Table 2. Both patients were started on L-Thyroxine and followed up for one year. Developmental milestones were normal at regular follow-ups.

Median TSH (IQR) in normal weight, LBW and VLBW groups was 3 (1.5-5.5), 3.1 (1.4-5.4) and 3.2 (2-4.6) µU/ml respectively. Median (IQR) TSH level in term and preterm neonates was 3 (1.4-5.5) and 3.6 (1.2-6.5) µU/ml respectively. There was no significant difference of TSH levels in relation to birth weight and gestation.

Median (IQR) TSH values in normal delivery, LSCS and assisted group was 3.4 (1.7-5.9), 1.8 (0.95-3.7) and 5.3 (3-9.1) µU/ml respectively. Neonates delivered by vacuum/forceps had significantly higher TSH levels than by normal delivery and LSCS (*P*=0.001). Mean age of sampling of LSCS neonates (26 hrs) was significantly higher (*P*=0.002) than normal delivery (20 hrs) and assisted delivery (18 hrs). Median (IQR) TSH in non-asphyxia and perinatal asphyxia groups was 8.2 (1.7-12.5) and 3 (1.4-5.4) µU/ml respectively. Neonates with perinatal asphyxia had significantly higher TSH values (*P*=0.002).

Table 1: TSH in relation to Birth weight

TSH in relation to Birth weight					
Birth weight Groups	TSH Median (IQR) µU/ml	Number of neonates with TSH value			*P* value
		<9	9-18	>18	
≥2500gms (n=2484)	3(1.5-5.5)	2289 (92.2%)	180 (7.2%)	15 (0.6%)	0.9
<2500gms (n=647)	3.1(1.4-5.4)	604 (93.3%)	40 (6.2%)	3 (0.5%)	
<1500gms (n=20)	3.2(2-4.6)	20 (100%)			
TSH in relation to Gestational Age					
Group (According to gestational age)	TSH Median (IQR) µU/ml	Number of neonates with TSH value			*P* value
		<9	9-18	>18	

Term neonates (n=3092)	3(1.4-5.5)	2860 (92.5%)	217 (7%)	15 (0.5%)	0.136
Preterm (n=59) neonates	3.6(1.2-6.5)	53 (90%)	3 (5%)	3 (5%)	

TSH in relation to Mode of delivery					
Group according to mode of delivery	TSH Median (IQR) µU/ml	Number of neonates with TSH value			*P* value
		<9	9-18	>18	
Normal delivery(n=2464)	3.4 (1.7-5.9)	2249 (91.3%)	202 (8.2%)	13 (0.5%)	0.001
LSCS (n=665)	1.83 (0.95-3.7)	647 (97.3%)	16 (2.4%)	2 (0.3%)	
Assisted (n=22)	5.3 (3-9.1)	17 (77.3%)	2 (9%)	3 (13.6%)	
TSH in relation to Perinatal Asphyxia					
Group according to APGAR score	TSH Median (IQR) µU/ml	Number of neonates with TSH value			*P* value
		<9	9-18	>18	
Perinatal Asphyxia (n=21)	8.2 (1.7-12.5)	11 (52.4%)	8 (38%)	2 (9.6%)	0.002
No Asphyxia (n=3130)	3 (1.4-5.4)	2902 (92.7%)	212 (6.8%)	16 (0.5%)	

Table 2: Profile of neonates with CH

Parameters	Case 1	Case2
Sex	Male	Female
Birth Weight (gms)	3500	2900
Mode of Delivery	NVD	NVD
APGAR score (1 min.)	9	9
Hypothyroidism in mother	Nil	Nil
Parity of mothers	G2P1A1	G1P1A0
Maternal age (yrs)	23	21
Age of 1st sampling (hours)	15	26
1st TSH report	330 µU/ml	30.5 µU/ml
Clinical features	PF open	PF open, lethargy, NNJ
Age at second sampling	30days	18days
T3 ng/ml	0.25	1.07
T4 ug/dl	1.17	3.65
TSH µU/ml	700	100

PF-posterior fontanelle, NNJ-neonatal jaundice, NVD-normal vaginal delivery
TSH-Thyroid Stimulating Hormone.

Discussion

Three IEM are common in Northern India as Glucose 6 Phosphate Dehydrogenase deficiency, congenital hypothyroidism and congenital adrenal hyperplasia. Cord blood is useful in screening of G6 PD deficiency and CH. Heel prick is minimally invasive and has an easy access and simultaneous tests can also be done at a time [8].

The time at which the sample is taken may vary between centers, with majority taking blood from heel prick after 24 hours of age to minimize false positive high TSH due to physiological neonatal TSH surge that elevates TSH levels and causes dynamic T_4, T_3 changes in the first 1 to 2 days after birth. Early discharge of post-partum mothers has increased the rate of false positive TSH elevations. Blood collection after 72 hours and within 7 days of life on a filter paper is the standard method of screening newborns for hypothyroidism and metabolic disorders. Collection of cord blood may be feasible alternative. American Academy of Pediatrics suggests samples to be taken optimally from 48 hours to 4 days of age. Samples taken between 24 to 48 hours may lead to false positive TSH elevation [2]. In our study age of sampling was lower than other studies because of early discharge of apparently normal neonates. In a study held at Govt. Medical College Hospital Sector 32 Chandigarh, heel prick blood samples were collected on Whatman 903 filter paper between 24 to 48 hours.

Median (IQR) TSH in our study was 3(1.4-5.5) µU/ml, others reported mean TSH varying from 6.13 to 10.6 µU/ml. [5, 20, 21]. Recall rate in our study was 7.6% with a cut off value of TSH of 9µU/ml. Various studies quoted recall rates ranging from 0.32 to 4.8% with variable cut off level of TSH of 9 to 25 µU/ml. [5, 7, 17, 19, 20]. We used a cut off value of 9 µU/ ml, use of cut off value higher than this would have led to lower recall rates.

Incidence of CH in India varies from 1:600 to 1:3400 [6, 8, 19]. Incidence of CH (1:1575) in our study could have been higher, had all neonates with borderline and positive TSH levels been sampled subsequently for complete thyroid profile.

There was a significant correlation between mode of delivery and TSH level in our study. Assisted deliveries showed a higher TSH levels as compared to normal deliveries and caesarean section. Neonates delivered by caesarean section had significantly lower TSH level than normal deliveries. Other studies also observed significantly higher TSH in forceps deliveries as compare to normal delivery and LSCS.

Our study showed that neonatal TSH is elevated in other stressful condition as perinatal asphyxia and not elevated in prematurity and low birth weight babies. There were few limitations of our study as this was done over a six months period only and 16.5% could not be screened due to early discharge. Recall rate in our study was high as 7.6% because screening in 73.5% neonates was done at less than 24 hours of age. Out of neonates with abnormal TSH values at time of screening, 75% could be recalled for second sampling. Number of preterm and asphyxiated neonates was quite small. A larger study is required to analyze effect of perinatal factors on neonatal TSH level.

Conclusions

Incidence of congenital hypothyroidism in our study was 1:1575.

TSH levels were high in neonates with assisted delivery and perinatal asphyxia.

TSH level was low in neonates delivered by caesarean section.

There was no effect of birth weight, sex and gestational age on neonatal TSH level.

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