

# Incidence of Congenital Hypothyroidism in Western Rajasthan Using Cord Blood Thyroid-stimulating Hormone Levels as a Screening Tool: A Cross-sectional Hospital-based Study

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## Abstract

**Background:** Congenital hypothyroidism (CH) is considered the most common preventable cause of intellectual impairment, with a worldwide annual incidence of 1:4000 live births. In the absence of screening program actual incidence in India is not exactly known, but in previous studies it varies from 1:500 to 1:3400. We wished to find out the incidence of CH in Western Rajasthan using cord blood TSH as a screening tool and venous TSH within 14 days of life as a confirmatory test. **Methods:** This cross sectional descriptive study was conducted over a period of six months in teaching hospitals attached to Medical College. Cord blood TSH value of 20 mIU/L or >20 mIU/L was taken as cut off for screening and all screen positive neonates were re-tested for serum TSH by taking venous samples within 14 days of life. Repeat TSH levels of 20mIU/L or more tested by Enzyme Linked Fluorescent Assay were considered confirmatory. **Results:** Total 9558 cord blood samples were analyzed for TSH levels, out of which 533 came out to be screen positive (recall rate 5.57%). Out of these 58 could not be confirmed, so were excluded from the further analysis. Effective sample size and screen positive cases dropped to 9500 and 475 respectively, and out of these 13 were confirmed as CH (incidence - 1.37 per thousand live births). **Conclusions:** Considering the previous studies, incidence of CH is much higher in Western Rajasthan than the anticipated. Overall in India CH seems to be more prevalent than the other parts of the world, necessitating the need of national screening program.

**Keywords:** Congenital hypothyroidism, cord blood TSH, incidence

## INTRODUCTION

Congenital hypothyroidism (CH) is considered as the most common preventable causes of intellectual impairment. It has a worldwide annual incidence of 1:4000 live births.<sup>[1,2]</sup> In India, its incidence varies across the states. It is as high as 1:500 in Kochi (Southern India) and 1:1000 in Manipur (Eastern India) to as low as 1:3400 in Chandigarh (North India).<sup>[3-5]</sup>

Specific features of CH are mostly absent at birth which requires universal screening for early diagnosis and timely intervention.<sup>[6]</sup> Screening protocols have been well established in most of the developed countries in the last three decades. National screening program has been found to be cost-effective because of its profound clinical benefit.<sup>[7]</sup> Due to the limitation of resources, developing countries are still shying away from launching a national screening program.<sup>[8-10]</sup>

There are three types of screening methods; primary thyroid-stimulating hormone (TSH) with backup T4 measurements, primary T4 with backup TSH measurements, and combined primary TSH and T4 measurements. Each one has its own merits and demerits. In most of the Europe and United States, primary TSH approach is followed. This test is optimally employed within 2–4 days of life to avoid false positive tests resulting from initial TSH surge.<sup>[10,11]</sup>

This delayed approach (after 48 h of life) will miss a lot of cases in developing countries such as India. Here, most

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of the normal vaginally delivered mothers are discharged within 48 h of childbirth and some of them never come for follow-up. Moreover, a lot of parents would not allow taking blood sample of their seemingly healthy baby. Recently, cord blood TSH level has shown a good correlation with the heel prick TSH levels obtained between 4<sup>th</sup> and 7<sup>th</sup> day of life.<sup>[12]</sup>

This study was planned to find out the incidence of CH in Western Rajasthan, using cord blood TSH level as a screening test. It was followed by venous TSH within 14 days of life as a confirmatory test.

## MATERIALS AND METHODS

This cross-sectional observational study was conducted over a period of 6 months after the approval from Institutional Ethics Committee. All newborns delivered in the hospitals attached to our institute were included in the study.

Neonates with major congenital malformations and whose mother's receiving antithyroid drugs were excluded from the study. Informed written consent was obtained from the parents regarding collection of cord blood before delivery. Umbilical cord was clamped using three clamp techniques: one close to the baby and two near placental end after cessation of pulsations. A 10 ml of blood was collected in a sterile plain vial from the cord between abdominal end and placental end by removing the clamp of placental end. Blood was transported to the laboratory within 24 h of collection for analysis of TSH level. Weight, gestational age, mode of delivery, and sex of all the included babies were noted at the time of birth.

TSH level was measured using enzyme-linked fluorescent assay method. The machine used for TSH analysis was VIDAS manufactured by bioMerieux. This assay combines one-step enzyme immunoassay sandwich method with a final fluorescent detection. The solid-phase receptacle (SPR) serves as the solid phase as well as the pipetting device for the assay. Reagents for the assay are ready-to-use and predispensed in the sealed reagent strips. All of the assay steps are performed automatically by the instrument. The antigen binds to antibodies coated on the SPR and to the conjugate forming a "sandwich." Unbound components are eliminated during the washing. During the final detection step, fluorescence of substrate is analyzed. The intensity of the fluorescence is proportional to the concentration of antigen present in the sample. Results were calculated automatically by the instrument in relation to the calibration curve stored in memory (4-parameter logistic model) and were expressed in mIU/L.

Cord blood TSH value of 20mIU/L or more was taken as cutoff for screening. All screen positive neonates were retested for serum TSH by taking venous samples within 14 days of life. Repeat TSH level  $\geq$  20 mIU/L was considered confirmatory for CH. Levothyroxine was started at a dose of 10–15 mcg/kg/day in these newborns.

Keeping the maximum prevalence of 0.2% (as reported in Kochi), 95% confidence interval, and 0.01 precision errors,

the sample size was calculated to be 6147. The data obtained were analyzed using Microsoft Excel 2010 with the help of SPSS (version 20.0). Continuous data were summarized as mean  $\pm$  standard deviation and categorical data as proportion. These data were finally analyzed using Student's *t*-test and Fisher's exact test, respectively.

## RESULTS

During this period, a total of 11355 samples were subjected to cord TSH levels. Out of them, 1797 samples got hemolyzed. After excluding them, the study cohort comprised 9558 neonates. Out of which, 4983 (52.10%) were males and 4575 (47.90%) were females. Four thousand eight hundred and ninety newborns (51.15%) were term followed by 3362 preterms (35.174%) and 1306 postterms (13.66%). Among the preterm group, 30.56% were late preterms. Most of the neonates (93.25%) weighed between 2 and 4 kg (48.05% in 2–3 kg and 45.21% in 3–4 kg group). The 4.94% and 1.77% neonates were <2 kg and more than 4kg, respectively. Percentage of lower segment caesarean section delivered babies was slightly higher than that of vaginally delivered (56.73% vs. 43.265%). Mean TSH level of the study cohort was  $7.8 \pm 5.235$  mIU/L.

Out of total 533 screen positive newborns, 58 lost to follow-up or expired. Out of 475 newborns retested, 13 had confirmed hypothyroidism. The incidence of hypothyroidism was calculated as 1.37 per 1000 live births (13/9500) with a recall rate of 5.57% (533/9558). Birth weight and gestational age were higher in screen positive group in comparison to screen negative,  $P < 0.0001$  [Table 1]. No correlation was noted between very high cord TSH levels and true hypothyroidism. None of the babies with cord TSH levels >40 mIU/L had serum

**Table 1: Comparison between screen positive and negative population**

	Normal population (Normal cord TSH)	Screen positive (High cord TSH)	P
Sample size (n)	9025	533	
Birth weight (kg)	2.90 $\pm$ 0.53	3.25 $\pm$ 0.70	<0.0001
Gestational age (weeks)	38.13 $\pm$ 2.56	39.25 $\pm$ 2.91	<0.0001
Cord TSH level ( $\mu$ IU/L)	7.64 $\pm$ 3.44	36.26 $\pm$ 12.26	<0.0001

**Table 2: Relation between true hypothyroidism and cord TSH levels**

	Cord TSH 20-40 ( $\mu$ IU/L)	Cord TSH >40 ( $\mu$ IU/L)
Venous TSH < 20 ( $\mu$ IU/L)	443	19
Venous TSH > 20 ( $\mu$ IU/L)	13	0
		P fisher 1

TSH level >20 mIU/L on retesting. It implies the effect of perinatal stress on cord blood TSH levels [Table 2].

## DISCUSSION

The present study area belongs to a desert state located in Western Rajasthan, India. Here, the incidence of CH was found to be 1.37 per 1000 live births, with a recall rate of 5.57%. Male:female ratio of confirmed cases was 1.6:1. None of the babies with cord TSH levels >50 mIU/L had true hypothyroidism.

The major strength of our study was large and adequate sample size. There were certain limitations such as no follow-up of the patients with confirmed CH; hence, a difference between transient or permanent CH could not be made. Furthermore, the etiological differentiation of the confirmed cases was not made. Finally, we used primary TSH approach which can miss the newborns with primary hypothyroidism. However, this entity in itself is very rare (1:60,000).<sup>[10]</sup> Not only this but previously also cord TSH has been found to be better than the cord T4.<sup>[13]</sup>

There is no universally accepted cutoff of cord TSH level for screening. In Thailand, initially 30 mIU/L was used which was later modified to 40 mIU/L to decrease the recall rate from 1.1% to 0.67%.<sup>[14]</sup> If we used these cutoffs, our recall rate would decrease to 2.8% and 0.9%, respectively. However then, we would have missed 69.23% (9/13) and 100% (13/13) true cases, respectively. The lower threshold of 20 mIU/L may also miss the true hypothyroid case rarely. Balancing the false positivity and risk of missing true cases, 20 mIU/L is considered the optimum cutoff for mass screening.<sup>[1]</sup>

Keeping cord TSH cutoff 20 mIU/L, our recall rate was much higher than reported by Manglik *et al.* (1.833% in Kolkata). However, their sample size was quite small (1200) and they had included only term neonates.<sup>[15]</sup> In Iran, Ordoorkhani *et al.* took a larger sample of 20,107 neonates and found a recall rate of 1.3%. However, they used a different method (two-site immunoradiometric assay on air dried cord blood spot) for TSH measurement.<sup>[16]</sup> On the other hand, Sangeeta *et al.* and Gupta *et al.* reported a very high recall rate (9.4% and 11.45%, respectively). However again, their sample size was small (500 and 952, respectively) and inclusion criteria were different (term neonates only and hypothyroid mother also, respectively).<sup>[9,17]</sup>

In most of the Indian studies, the incidence of CH varies between 1 and 2 per 1000 live births. Kaur *et al.* in Chandigarh reported exceptionally very low incidence of 0.29 per thousand live births. However, instead of TSH alone, they used T3, T4, and TSH to confirm CH.<sup>[5]</sup>

These Indian figures on the incidence of CH are much higher than the international data (1:3000–4000). In Iran also, the incidence of CH was found to be high (1:914). The reason cited for this high incidence was parental consanguinity and iodine excess.<sup>[16]</sup> Other factors can also influence the incidence of CH

like laboratory method employed, cutoff used for screening, demographic, geographic, ethnic, and racial factors.<sup>[1]</sup>

## Cost-benefit analysis

For cost-benefit analysis, we contacted a local laboratory. They were ready to do TSH levels at rate Rs. 40 per sample at mass level. If we calculate the hypothetical investment of our study, it comes out to be Rs. 4 Lakh for testing around 10,000 TSH samples. We prevented a total of 13 cases of intellectual impairment with each case costing <Rs. 40,000 (4 Lakh/13 cases). This cost is nothing when compared to the lifelong morbidity and burden on family, society, and country. If we extrapolate the present incidence of CH on whole of Indian population considering 34 births/min in India, we are missing 50 cases of CH daily in the absence of a screening program.

## CONCLUSION

The incidence of CH is much higher in India than reported in the world. Delayed diagnosis is increasing the prevalence of intellectual impairment. Cost-benefit analysis supports the feasibility of universal newborn screening program at national level.

## Take home message

Newborn screening for CH if made compulsory in all centers has the potential to prevent approximately fifty cases of intellectual impairment daily in India.

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## Conflicts of interest

There are no conflicts of interest.

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