

## The emerging role of a newborn screening program for congenital hypothyroidism: a prospective study

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**Aim:** The current study aims to evaluate the incidence & screening of neonates for congenital hypothyroidism for timely diagnosis and integral psychomotor development. **Material & Methods:** A prospective study was carried out in the Department of Pediatrics, Chirayu Medical College & Hospital Bhopal, India from a period from January 2015 to December 2018. All newborns with the gestational age of 34 weeks or more delivered in the hospital during the study period were screened for hypothyroidism and analyzed. **Result:** A total of 1363 babies were enrolled out of which 1272 were an eligible candidate for the study period. Numbers of term deliveries were 1109 and preterm deliveries were 163, with 665 (52.28%) males and 607 (47.72%) female babies. Of the total eligible neonates, 1109 were term babies and 163 were preterm babies with more than 34 weeks. Neonatal thyroid-stimulating hormone was estimated in all 1272 neonates out of which 2 cases were positive for CH, 12 cases had initially high values between 10-19  $\mu$ IU/L but later on, repeat testing after two weeks were found to be within normal limits and rest all 1258 cases were normal. **Conclusion:** Timely diagnosis and treatment of CH are important in order to prevent its consequences. NBS is the need of the hour for early diagnosis of CH, which is simple, fast as well as cost-effective.

**Keywords:** Congenital Hypothyroidism, Neonate, Thyroid hormone

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## Introduction

Congenital hypothyroidism (CH) is defined as thyroid hormone deficiency present at birth. Thyroid hormone plays a vital role in the normal development of the central nervous system. Congenital Hypothyroidism is one of the most common causes of the preventable and treatable cause of mental retardation and intellectual disability. In various neonatal screening programs, it has an incidence of 1: 4000 live births [1]. It was first performed by Dassault in Quebec, Canada in 1972 and they detected 7 cases of CH among 47000 newborns during 3 years [2]. The thyroid gland develops from a midline thickening of the pharyngeal floor and paired caudal extensions of the fourth pharyngobranchial pouches.

Thyroid hormone is very essential for brain development during 1-2 years of life. The need for neonatal screening for CH is essential as the majority of sign and symptoms does not exhibit until 3 month of age due to residual thyroid function or transplacental passage of maternal thyroid hormone [3]. If being delayed or neglected, it may cause mental retardation. The clinical manifestations are often subtle or not present at birth.

Common symptoms include decreased activity and increased sleep, feeding difficulty, constipation, and prolonged jaundice while myxedematous facies, large fontanelles, macroglossia, a distended abdomen with umbilical hernia and hypotonia are common signs. To assess the various causes of congenital hypothyroidism one should ascertain the site of defect, whether it is in the thyroid gland, thyroid regulatory system, due to deficient thyroid hormone receptor activity or due to inborn errors of the thyroid hormone synthesis.

Most congenital hypothyroidism is caused by defects in the thyroid gland itself (primary hypothyroidism). Causes of primary congenital hypothyroidism can be broadly classified as the failure of the thyroid gland to develop normally (*dysgenesis*) or failure of a structurally normal thyroid gland to produce normal quantities of thyroid hormone (*dysmorphogenesis*). Thyroid dysgenesis which encompasses the spectrum of thyroid agenesis, hypoplasia, and ectopy—is the most common cause of congenital hypothyroidism, and its incidence (about 1:4000 infants) has not changed significantly over the last several decades.

The thyroid-stimulating hormone receptor (*TSHR*) and the transcription factors *PAX8*, *NKX2-1*, and *FOXE1* are all expressed in the developing thyroid, and disruption of any of these genes can lead to failure of normal thyroid gland formation [4].

Congenital hypothyroidism may be permanent (thyroid aplasia, hypoplasia, ectopia or dysmorphogenesis) or transient (due to maternal blocking antibodies, iodine excess or deficiency, or some types of dysmorphogenesis [5]). Central hypothyroidism is caused by dysfunction of hypothalamic or pituitary control of the thyroid axis that leads to inadequate production and/or bioactivity of TSH. Congenital hypothyroidism of central origin is rare. Permanent CH required lifelong treatment and monitoring whereas, transient CH shows normal thyroid hormone production after the first few months. TSH screening is more sensitive for diagnosis, while T4 is more specific. This study is an attempt to find out the incidence of CH in our hospital, which is a tertiary level medical college in central India, where we are doing regular neonatal screening for CH.

## Materials & Methods

**Setting:** Department of Pediatrics, Chirayu Medical College & Hospital, Bhopal, Madhya Pradesh, India.

**Duration:** A period from January 2015 to December 2018.

**Type of study:** A Prospective Study.

**Sampling method:** All live newborn gestational age > 34 weeks delivered in Chirayu Medical College and outborn delivered with an age of fewer than five days.

**Sample size:** A total of 1363 babies were enrolled, but 1272 were an eligible candidate for the study period

**Inclusion criteria:** All newborns with a gestational age of 34 weeks or more delivered in the hospital during the study period were included in the study.

**Exclusion criteria:** Preterm neonates with gestational age less than 34 weeks, blood transfusion prior to sampling, refusal of informed consent and outborn babies with age more than 5 days were excluded from the study.

**Data collection and procedure:** Before sampling well written informed consent was taken from either of the parents.

The blood sample was taken in a sterile container under aseptic precautions, between 3-5 days of life to minimize the false positive high TSH values due to the physiological neonatal surge that elevates TSH level and causes T4, T3 changes in 1-2 days. In cases with a healthy newborn baby, sampling was done between 3-5 days.

Detailed antenatal history, parity, medical history, thyroid status, and community were recorded on a predesigned proforma. Details of the baby were recorded on a separate proforma. TSH was estimated within 24 h by chemiluminescence Immunoassay (kit supplied by Roche E411). Newborn with TSH value more than 20µ IU/L were labeled as a case of congenital Hypothyroidism and whose values were between 10-20 µIU/L were followed up with repeat TSH level after weeks.

**Data analysis:** All the data were analyzed by descriptive statistics and expressed in terms of percentage and tabulated form. The analysis was done on Microsoft Excel 2013.

**Ethical permission:** The study was approved by the institutional ethics committee. A well written informed consent was taken from all of the participants after explaining the details, benefits, and risks to them.

**Interpretation of screening test:** Venous TSH >20 mIU/L (serum units) is taken as the cut-off for postnatal screen samples after 48-72 hours of age is to be taken as positive newborn TSH between 10-20 mIU/L were taken for a second TSH sample at 7 to 10 days of age.

## Results

A total of 1363 babies were enrolled, but 1272 were an eligible candidate for the study period. Those, not eligible candidates received a blood transfusion, death within 3 days, left against medical advice (LAMA) or shifted to other hospitals and non-consenting of parents for the study. Out of the delivered babies, 820 were born by lower section caesarian section and 452 were vaginally delivered and there were 36 mothers who were hypothyroid and were on medication.

Numbers of term deliveries were 1109 and preterm deliveries were 163, with 665 (52.28%) males and 607 (47.72%) female babies. Of the total eligible neonates, 1109 were term babies and 163 were preterm babies with more than 34 weeks (Table 1).

Neonatal thyroid-stimulating hormone was estimated in all 1272 neonates out of which 2 cases were positive for CH, 12 cases had initially high values between 10-19 µIU/L which were later on repeat testing after two weeks were found to be in normal limits and rest all 1258 cases were normal (Table 2). From the 2 positive cases of CH, one baby was of Down’s syndrome on 12.5 mcg of Eltroxin and one baby was positive of elderly primi mother on 25 mcg of medication and on regular follow up since last 5 months.

**Table-1: Demographic profile from the study.**

Variable	Number	Percentage
Mother’s age (Years)		
≥18-25	673	52.9
26-30	459	36.08
>30	140	11.02
Sex		
Male	665	52.28
Female	607	47.72
Gestational age (Weeks)		
34-<37 weeks (Preterm)	163	12.81
≥37 weeks (Term)	1109	87.19
Birth weight (Kg)		
<2.5 kg	365	28.7
≥2.5 kg and above	907	71.3
Mode of delivery		
LSCS	820	64.47
Normal	452	35.53
Maternal history of hypothyroidism	84	6.6

**Table-2: TSH value among Neonates.**

Variable	TSH value at 48-72hrs	TSH value after 14days
TSH < 10mIU/L	1258	Normal
TSH 10-20mIU/L	12	Normal
TSH >20mIU/L	02	Higher

## Discussion

Hypothyroidism results from a deficient production of thyroid hormone either from a defect in the gland itself as a result of reduced thyroid-stimulating hormone. The disorder may be congenital or acquired. CH is commonly due to non-genetic cause, deficient thyroid embryogenesis leading to thyroid gland agenesis or dysgenesis while few cases are due to genetic reason or inborn error of metabolism while impaired thyroxin (T4) synthesis. Many mutations are also implicated in CH, namely that if in transcription factor PAX-8 and TTF-2 and in genetic coding for sodium iodide symporter, thyroid peroxidase and thyroglobulin are also responsible

For causing CH [6,7]. Deficiency of maternal iodine is another common contributing factor resulting in CH consequently leading to abnormal fetal depression. Transfer of excess of iodine to the fetus through placenta or secretion of iodine in breast milk may also result in CH among neonates [8,9].

As consanguinity is common in our country, CH although autosomal recessive in inheritance is expressed more commonly than in other developed countries.

Screening for CH by monitoring thyroid level at birth remains one of the most cost-effective tools in preventing mental retardation in these children. This neonatal screening is the norm in developed countries but unfortunately, such a nationwide program is non-existent in our country. There are two main screening ways for CH: primary T4 testing (with backup TSH) or primary thyroid-stimulating hormone (TSH) testing. In some states of USA, T4 estimation is done for screening while some US states screen T4 and TSH simultaneously [10], which may not be cost-effective for developing countries like India. The primary TSH screen is more sensitive and specific for the diagnosis of primary CH compared to the T4 screen [11].

In India, the first Newborn Screening program for CH was at BJ Wadia Hospital Mumbai in 1982 using cord blood TSH and subsequently in 1984 using postnatal dried blood spot [12,13]. A study conducted in 2001 reported that only 5%-10% of children have been diagnosed with CH under a screening program in India [14]. Therefore, India warrants an effective, robust, and cost-effective screening program. A study conducted by ICMR which screened for inborn metabolic disorders in neonates from the years 2007 to 2012 from Delhi, Mumbai, Chennai, Hyderabad, and Kolkata reported an incidence for CH of 1:1130 newborns. [15]

The most influential drawback of the present study is the small sample size. Large population-based studies are required to gauge and calculate the incidence of CH in our country. Therefore, India warrants a simple, effective, fast, and cost-effective screening program with adequate infrastructure, space, and resources as a part of Newborn screening.

In India, an attempt has been made to screen neonates for thyroid abnormalities at various centers, but a national program does not exist at present.

The method of screening is also not uniform. Various cut-offs for TSH levels have been used in different studies [16,17,18], but it has been accepted to take cut-off of >20  $\mu$ IU/mL for recall.

Due to the subtle manifestation of CH in the newborn period, it is often missed which results in delayed diagnosis, mental retardation and growth failure hence it is very important to implement a neonatal screening program.

Whilst taking into consideration the mode/type of deliveries the newborns delivered by elective Caesarean Section had significantly lower mean levels of cord blood TSH as compared to those delivered by vaginal delivery or emergency lower segment cesarean section. This difference can be explained on the basis of a surge in catecholamine secretion during the process of parturition and this can be more in asphyxiated newborns and in vaginally delivered newborns compared to those born by elective cesarean section [19,20]. In contrast, two studies have shown no difference in neonatal TSH levels according to the mode of delivery [21,22].

Babies who received active intervention in the form of resuscitation and LSCS for fetal distress were expected to have raised TSH levels as a response to the stress that they had endured due to the procedures. Thus raised TSH in these neonates has to be interpreted in that context.

The incidence of consanguinity is very common in India and varies from 1 % in the northern region to 30% in Karnataka [23]. Thus, the incidence of expression of autosomal recessive CH is raised in these geographic regions.

In our country implementation of the universal screening program is difficult due to the high number of non-institutional/home deliveries and early discharge of patients. A study conducted among the urban Delhi population in 2014 reported 53% home births [24]. But now the health statistics of our country have improved due to an increased number of institutional deliveries and the mortality rate has declined but now we have to think beyond this implement newborn screening (NBS) to prevent neuro disability.

Being diverse in all aspects, it is very difficult to launch a universal program of NBS. So, the government should prepare such a program that should be effective, rapid, cost-effective and improve coverage from the grass-root level.

In the present study, the overall incidence is 1:636 while some studies showed 1 in 248 and 1 in 1700 [25,26]. This may be due to less sample size and geographic variation. The prevalence of CH was 1.57 per thousand live birth. The male to female ratio in the present study was 1:1 while 1.2:1 was in Japan [27] in Bosnia [28] and 1.8:1 in Saudi Arabia [29]. However, some studies did not find any significant differences in mean TSH level according to sex [30,31] Out of the two babies who were diagnosed CH both were male. The first one had Down's syndrome with cyanotic congenital heart disease (CHD) and second, it was of an elderly primi mother. At present both are under treatment with control.

Studies have reported that TSH levels increase with increasing gestational age however higher TSH levels in preterm than in terms have been reported. There is no statistical significance between low birth weight and normal weight babies with respect to their TSH values in the present study, but some studies have reported that low birth weight is related to high TSH [30].

**Limitations:** Geographic ethnic differences are responsible for this wide variation in incidence and a cohort size of 1272 samples is too less to access incidence. To have more conclusive evidence for the current findings, the studies to be conducted in the future should be designed in order to evaluate more babies/population as well as include other maternal and perinatal parameters in the analysis.

## Conclusion

Timely diagnosis and treatment of CH are important in order to prevent psychomotor development disability & improve school progress. NBS is the need of the hour for early diagnosis of CH, which is simple, fast as well as cost-effective. Although universal newborn screening is implemented in developed countries; our country has still not implemented this universally. The policy should be formed so that this can be implemented at the grass-root level from ASHA workers to PHCs level to government/ private medical colleges.

## What does the study add to the existing knowledge?

New-born screening for CH if made compulsory in all centers has the potential to prevent intellectual impairment in India.

**Recommendations:** Increase societal awareness of CH and its identification by newborn screening. Health care providers should inform all pregnant mothers during the antenatal visit about CH, newborn screening and its cost-effective benefit. Newborn screening should be mandatory and ultimately made free by legislation, just the way it is for birth registration and immunization.

## Author's contributions

**Dr. Saurabh Kumar, Dr. Minhajuddin Ahmed, and Dr. Nitesh Upadhyay** reviewed the literature, drafted the manuscript, obtained extensive inputs from the editorial team, and finalized the manuscript incorporating these inputs.

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