



**ORIGINAL RESEARCH PAPER**

**Paediatrics**

**SCREENING FOR CONGENITAL HYPOTHYROIDISM: A REVIEW**

**KEY WORDS:**

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The term 'newborn screening' (NBS) is used to describe various types of tests that are done during the first few days of a newborn's life. Screening separates those who might have the disorder from those who probably do not have the disorder. In contrast, diagnostic testing is performed to establish the presence of a condition. NBS that is properly timed and performed has the potential for preventing catastrophic health outcomes, including death [1].

Congenital hypothyroidism, a common congenital endocrine disorder with an overall incidence ranging from 1 in 3000 to 1 in 4000 newborn infants[2,3] has estimated incidence of 1:2500-2800 live births in India[4,5].

Primary congenital hypothyroidism, the most common form of congenital hypothyroidism, occurs as a result of developmental defects of the thyroid gland, known as thyroid agenesis or dysgenesis, or is due to disruptions in thyroid hormone biosynthesis, also known as thyroid dyshormonogenesis. Secondary or central congenital hypothyroidism is caused by deficiencies in TSH due to pituitary insufficiency or structural abnormalities of the pituitary gland or hypothalamus. Less commonly, the hypothyroidism is transient which can be caused by transplacental passage of maternal medication, maternal blocking antibodies, or iodine deficiency. In rare cases, CH may result from a pituitary or hypothalamic abnormality.[6]

Despite the critical importance of TH on multiple organ systems, especially the brain, most infants with CH appear normal at birth[2,7]. Neonatal screening programs for CH are thus of immense help in detecting such hypothyroid cases at an early stage, thus initiating early treatment and prevention of mental retardation. NBS for congenital hypothyroidism and for some other metabolic disorders is done in most of the developed countries but not routinely done in developing countries including India.

In countries where newborn screening programs take place, all infants with CH are diagnosed after detection by newborn screening tests. However, of the worldwide birth population of 127 million, only 25% of babies are invited for screening for CH. For the remaining 75% infants, particularly concentrated in developing countries, clinical suspicion of hypothyroid leads to thyroid function evaluation. With no NBS screening programme existing in India there is no national representative data on CH available at present however small data from different states is available.[1,4,8-10] A study conducted by Kapil U et al [11] in Kangra, Himachal Pradesh the prevalence of neonatal hypothyroidism was found to be 4.4%.

**Signs and Symptoms**

Despite the critical importance of TH on multiple organ systems, especially the brain, most infants with CH appear normal at birth. The hypothyroid foetus appears to be protected atleast in part by placental transfer of maternal TH. This was best illustrated by demonstrating that cord blood T4 concentration at birth in infants who were unable to synthesize T4 was about one third to one half that of normal infants.[7,12] These results indicate that a steep maternal-

foetal gradient of T4 overcomes the placental barrier, permitting maternal T4 to enter the foetal circulation.[7,13] Also there is increased intra-cerebral conversion of T4 to T3, resulting in increased availability of T3 in brain despite the low serum concentrations.[12,14,15]

Common symptoms, when present, are very subtle and include decreased activity and increased sleep, feeding difficulty, constipation and prolonged jaundice. On examination, signs like myxedematous facies, large fontanels, macroglossia, a distended abdomen with umbilical hernia, and hypotonia may be present.[6,12]

**Rationale of Screening for CH**

It has been observed that most babies with CH appear normal at birth and show minimal evidence of thyroid deficiency[7,12,16]. Clinical diagnosis is made in only 10% children in the first month of life and 30% in the first 3 months. Hence there is a high risk of delayed diagnosis based on clinical examination alone[17].

It is seen that early diagnosis with newborn screening and hence early initiation of therapy improves the intellectual outcome and growth of the baby. Favourable cognitive outcome is possible in even the most severely affected infants with CH when postnatal therapy is initiated early in optimum doses and maternal thyroid function is normal.[1]

Moreover newborn screening programs for CH were found to be cost effective as reported by Pollitt RJ et al.[18] Hence it is very important to screen every newborn for CH within a few days of birth.

The ideal screening test should have high sensitivity and specificity so as not to miss any case of CH. There are two main screening strategies for CH: primary T4 testing (with backup TSH) or primary TSH testing.

Primary T4 testing helps to identify patients with primary and secondary (central) CH. However, it misses neonates with compensated forms of CH (normal T4 with high TSH, which is commonly seen in ectopic thyroid, the most frequent cause of CH). Moreover, there is a high rate of false positive results, whether done from cord blood or postnatal day 3-5 sample. These include infants with thyroid-binding globulin (TGB) deficiency and preterm and sick neonates. Hence, low T4 values must be followed by backup TSH on the same DBS. TSH is measured in the samples with the lowest percentiles of T4 (from 3 to 20%, the range varying between different programs) [19-22]. Neonates are recalled for confirmatory venous sampling if TSH is greater than the cut-off. Primary T4 screening is followed in some states in US and in Israel[23] as it is more sensitive and specific for the diagnosis of primary CH compared to T4 screen. [24] Primary TSH screening may miss infants with delayed rise of TSH most often seen in preterm babies due to immaturity of the hypothalamic-pituitary-thyroid (HPT) axis.[25] Overall, primary TSH-based CH screening is more practical and cost-effective. It is followed in most parts of the world. Many states in the USA have shifted from T4 to TSH testing and most newly developed CH screening programmes in different parts of the world have adopted the primary TSH strategy. [23,25,26]

**TSH Cut-Offs to be used for the Screening Test**

Very few babies with abnormal screen TSH value will finally have true CH. Confirmatory test must be done for all babies whose screen TSH is above a chosen cut-off. To identify true positive CH various cut-offs have been used in different studies across the world. A TSH cut-off of >20 mIU/L for recall has been shown to be associated with reasonable specificity and recall rate[27]. Mildly elevated screen TSH (between 20 and 40 mIU/L) dictates recall early in the second week of life for a repeat screening TSH (most of the mildly high TSH reports due to unresolved neonatal TSH surge or other reasons would have normalized in a few days). However a clear-cut high screen TSH >40 mIU/L necessitates immediate recall (after 72 h of age) for a confirmatory venous sample.[2,28]

**Decision Making for Borderline Thyroid Function Reports**

For elevated venous TSH and normal FT4 levels, the baby may be retested after 2 weeks and if TSH remains persistently >10 mIU/L even with normal range of T4/FT4, levothyroxine treatment may be started to avoid insult to the developing brain. One may also encounter low T4/FT4 with normal TSH levels. Thyroid imaging may also help to get a definitive diagnosis. Re-evaluation is recommended after 3 y of age, by which age the phase of rapid brain development has been achieved.[29,30]

Screening in the first days of life seems to be the most important step in the approach to CH and replacement of related deficient hormones, thus preventing consequences that cannot be remedied. Hence, it is the time to begin with NBS, especially for this high risk group of neonates.

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