Optimizing Cord Blood Thyroid Stimulating Hormone Cutoff for Screening of Congenital Hypothyroidism—Experience from Screening 164,000 Newborns in a Tertiary Hospital in India

Praveen G. Paul, Grace Rebekah1, Sophy Korula, Manish Kumar2, Joseph D. Bondu3, Raghupathy Palany4, Anna Simon, Sarah Mathai
Division of Paediatric Endocrinology, Department of Paediatrics, Christian Medical College Hospital, 1Department of Biostatistics, Christian Medical College, Departments of 2Neonatology and 3Clinical Biochemistry, Christian Medical College Hospital, Vellore, Tamil Nadu, 4Department of Paediatric Endocrinology, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India

Abstract

Background and Objectives: In our institution, we have an ongoing newborn thyroid screening (NBS) program since July 2001. In the initial 9 months, we used cord blood thyroid-stimulating hormone (TSH) (CBTSH) cutoff of 20 mIU/L and thereafter the cutoff was increased to 25 mIU/L. Our objective was to evaluate whether a CBTSH cutoff of 25 mIU/L is sensitive and cost-effective in NBS of congenital hypothyroidism (CH). Materials and Methods: All in-born babies are screened and those with CBTSH ≥25 mIU/L are recalled for confirmatory TSH/T4/FT4 tests. CH is confirmed with elevated TSH and low T4/FT4. Those with CBTSH 20–24.99 mIU/L were recalled for confirmatory tests in initial period of our NBS and prospectively between January and August 2017. Statistical analysis was done to derive positive predictive value and sensitivity to diagnose CH for each CBTSH between 20 and 30 mIU/L. Results: A total of 164,163 neonates were screened from July 2001 to August 2017. Of the 2352 babies with CBTSH ≥25–30 mIU/L, 1763 returned for retesting and 5 confirmed as CH (4 gland-in-situ and 1 absent uptake on nuclear scan). Of the 14,742 screened during the study period, 195 of the 293 babies with CBTSH 20–24.99 mIU/L returned for retesting and none diagnosed as CH. A CBTSH of 25 mIU/L has 99.2% sensitivity and 97.5% specificity. A lower screen TSH cutoff 20 mIU/L would result in recall of additional 300 babies/year with no definite improvement in sensitivity. Conclusions: Our data justify the continuation of using screen TSH cutoff of 25 mIU/L while using cord blood for NBS in our population. With a diverse and large population, it is important that we use feasible regional screen cutoffs for optimal use of our resources.

Keywords: Congenital hypothyroidism, cord blood, newborn screening, TSH

Introduction

Congenital hypothyroidism (CH) is one of the most common causes of preventable mental retardation in children. With maternal euthyroid status during pregnancy and optimum early L-thyroxine supplementation after birth, even children with severe CH have excellent neurodevelopmental outcomes. As the clinical features of CH evolve after several weeks, it is imperative that all newborns are screened for CH at birth. Most of the newborn screening programs (NBS) use thyroid-stimulating hormone (TSH) for CH screening.

Worldwide, the prevalence of CH varies with a lower prevalence reported from western countries (1 in 3000–4000) and a much higher prevalence from Asia (1 in 1200–2000). Even within India there is region-wise variation in prevalence of CH with Chandigarh reporting 1 in 3400, Hyderabad 1 in 1700, Lucknow 1 in 1221, and Chennai 1.6/1000. An important factor that affects CH prevalence is the screen TSH cutoff used. The consensus guidelines for newborn thyroid screening (NBS) published by the Indian Society for Pediatric and Adolescent Endocrinology justify the continuation of using screen TSH cutoff of 25 mIU/L while using cord blood for NBS in our population. With a diverse and large population, it is important that we use feasible regional screen cutoffs for optimal use of our resources.
Endocrinology (ISPAE) recommends a screen TSH cutoff of 20 mIU/L.\cite{3}

The focus of NBS is to diagnose and treat CH as early as possible to optimize the neurodevelopmental outcome. While a higher screen cutoff reduces the overall recall rate, a lower cutoff increases sensitivity as well as recall rates. In resource-limited countries such as India, one of the major considerations is to identify maximum number of children with CH while minimizing recall.

In our institution, there is an ongoing NBS for CH using cord blood TSH (CBTSH) operational since July 2001. In the initial nine months, the CBTSH cutoff for recall was established as 20 mIU/L (serum units) based on the current literature of that time. It was then observed that ~10% values obtained were in the range of 19–23 mIU/L, although, on re-evaluation, all the infants with these reports were found to be biochemically euthyroid. As the recall rate was proving to be high with unnecessary cost implications, it was decided to raise the TSH cutoff to 25 mIU/L from April 2002. This study was undertaken to evaluate and ascertain whether a cutoff of 25 mIU/L is appropriate when using cord blood to screen for CH.

Materials and Methods

All inborn live babies born ≥26 weeks of gestational age were screened using CBTSH. Serum TSH and free thyroxine (FT4) were analyzed by fourth generation (since 2010 and 2009, respectively) and serum thyroxine (T4) by third generation (since 2015) chemiluminescence assays. TSH, T4, and FT4 were performed by chemiluminescence method in the ADVIA Centaur XP immunoassay system, Siemens Healthineers, Germany. Babies with CBTSH ≥25 mIU/L serum units were recalled for confirmatory testing (TSH, T4, FT4) after 72 h of life or at the earliest possible date within 2 weeks of life. Those with confirmed CH (elevated S.TSH and low FT4 level) underwent Tc-99m pertechnetate thyroid scan on the same day and l-thyroxine replacement was commenced. If confirmatory test was inconclusive, thyroid function tests were repeated every one to two weeks until CH is confirmed or ruled out. In recent years, athyreosis is confirmed by ultrasonography done at a later date.

The cohort in this study includes babies with CBTSH between 20 and 30 mIU/L [Figure 1]. They were divided into two groups:

- **Group 1:** Babies with CBTSH 20–24.9 mIU/L which includes both retrospective and prospective cohorts.
  - Retrospective cohort: Data of babies born between July 2001 and March 2002 were obtained from systematically maintained patient records and analyzed.
  - Prospective cohort: Babies born between January 2017 and August 2017 who were recalled for review as part of the study.

- **Group 2:** Babies with CBTSH 25–30 mIU/L observed in our NBS program from July 2001 to August 2017.

Figure 1: Algorithmic representation of CBTSH groups and study periods when babies were recruited into the study

For CBTSH values between 20 and 30 mIU/L, the number and percentages were presented with histogram to examine the data distribution. The cutoff points of indices of CBTSH for predicting a diagnosis of CH were obtained by receiver-operating characteristic (ROC) curve analysis. For each cutoff point, sensitivity, specificity, positive, and negative predictive values were obtained. Using verification bias, point estimates and confidence intervals were calculated. The software used for analysis was IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. The corrected recall rate was calculated based on the number of babies who actually returned for retesting. This study proposal was approved by the Institutional Review Board of Christian Medical College Vellore (IRB minute no.: 10304). Written informed consent was obtained for all participants in the prospective cohort and waiver of consent was obtained for participants included in the retrospective cohort.

While comparing our results with other studies, all TSH values are mentioned as approximate serum units (whole blood units × 2.2) for uniformity and easy reading. Unless mentioned as cord blood, all screen TSH values in other studies are dried blood spots (DBS) collected at different times after birth.

Results

**Group 1 (CBTSH 20–24.99 mIU/L)**

For babies with CBTSH of 20–24.99 mIU/L, repeat thyroid profile after 72 h of birth was available only for babies recruited during the study period. A total of 14,742 babies were screened during the 17 months of the study period. Two hundred and ninety-three babies with CBTSH between 20 and 24.99 mIU/L were recalled and 195 came for repeat testing [Table 1]. The mean repeat TSH at >72 h was 3.760 ± 2.783 and 4.140 ± 3.382 mIU/L in the prospective and retrospective cohorts, respectively. The mean age at which repeat TFT was done was 8.5 ± 9.9 days. In the prospective cohort, 13% of babies were low birth weight (birth weight <2500 g) and 9% were preterm (<37 weeks). Nearly two-thirds (69%) were born by spontaneous vaginal delivery while 8% and 23% were born by cesarean section and instrumental delivery, respectively. None were confirmed to have CH. Among those who did not
respond for retesting (98/293 babies), families of 73 babies were telephonically contacted after 3 years. Seventy-one children were reported to have normal development and two children had expired, none were diagnosed as CH thus far.

**Group 2 (CBTSH 25–30 mIU/L)**

A total of 164,163 babies were screened which represented 99.1% of all live deliveries in our hospital. A total of 2532 babies with CBTSH between 25 and 30 mIU/L were recalled and 1763 returned for confirmatory testing [Table 2]. Five babies were confirmed to have CH, four had gland-in-situ, and one had absent tracer uptake on nuclear scan [Table 3]. Four of these children were successfully trialed off levothyroxine therapy at 3 years of age.

The sensitivity, specificity, positive, and negative predictive values to diagnose CH for each CBTSH value between 20 and 30 mIU/L are shown in Table 4. The sensitivity and specificity for CBTSH level 25 mIU/L were 99.2% and 97.5%, respectively, and for CBTSH 30 mIU/L was 95.1% and 98.6%, respectively. The corrected recall rates with CBTSH of 25 and 30 mIU/L were 2.57% and 1.5%, respectively.

**Discussion**

In this study, of the ~15,000 babies screened, none with CBTSH 20–24.99 mIU/L was diagnosed with CH. More importantly, from the larger cohort of 164,163 babies, none with CBTSH 20–24.99 mIU/L returned later with a diagnosis of CH. While there is a possibility of missed cases, as the vast majority of our cohort is local population, it is less likely that a later diagnosis of CH may have been made elsewhere.

It is difficult to compare our data with other NBS programs within and outside India for three reasons: (1) very few NBSs use cord blood, (2) there are limited data evaluating screen TSH levels 20–24.99 mIU/L, (3) there is wide variation in age of sampling from 24 to >96 h after birth. Despite these limitations, it was reassuring to note similar results from other screening programs. In a large cohort of 161,244 infants from Ohio NBS which uses screen TSH cutoff 20 mIU/L, none with screen TSH ≤28 mIU/L had CH. Similar data have been reported from India. In a cohort of 19,800 babies in Bangalore, using a TSH cutoff ~24 mIU/L sampled at 36–48 h of birth, the lowest false positivity was for TSH of ~30 mIU/L. This study reported a high CH prevalence of 1:1042 in their mixed North and South Indian population. Interestingly there were no missed CH cases reported over a period of 7 years. Similar to our study, the above study is a single hospital-based study with ~100% coverage and thyroid scintiscan at diagnosis. Recently, in a large cohort of 174,000 babies in New Delhi, only <3% (3/105) babies confirmed with CH had screen TSH >20–40 mIU/L. Unfortunately data for babies with TSH level 20–25 mIU/L were not available.

There were good sensitivity and specificity for screen TSH cutoff of 25 mIU/L in our study. The difficulty in calculating indices for TSH levels 20–24.9 mIU/L was the issue of verification bias inherent with screening tests. The gold standard to diagnose CH is a combination of elevated TSH and low T4/free T4 level in the confirmatory test. However, in our NBS only, those with CBTSH >25 mIU/L as per the existing practice and 195 babies with CBTSH 20–24.9 mIU/L during the study period had a confirmatory sample done. As

### Table 1: Mean CB TSH, repeat S.TSH, T4, and FT4 among those with CBTSH between 20 and 24.99 mIU/L (results expressed as mean±SD)

| Patient no. | CBTSH (mIU/L) | GA (weeks) | BW (g) | TFT at initiation of thyroxine TSH (mIU/L) | FT4 (ng/dL) | Nuclear scan | Duration of LT4 treatment (years) | Age of last follow-up (years) |
|-------------|--------------|-----------|--------|----------------------------------------|-------------|--------------|-------------------------------|-----------------------------|
| 1           | 25.67        | 38        | 3140   | 37.88                                  | 0.66        | Gland-in-situ | 3                            | 6                           |
| 2           | 25.93        | 37        | 1840   | 214                                    | 0.79        | Gland-in-situ | Lost to follow-up after 15 months of treatment |                             |
| 3*          | 25.99        | 39        | 3620   | 21.79                                  | 1.58        | No uptake    | 3                            | 4                           |
| 4           | 27.69        | 36        | 2220   | 29.2                                   | 0.56        | Gland-in-situ | 3                            | 4                           |
| 5           | 25.28        | 37        | 3000   | 157                                    | 0.50        | Gland-in-situ | 3                            | 3.5                         |

*All except patient 3 were diagnosed after 2010 using fourth-generation TSH assay
there was only one baby in the entire NBS who was screen negative (CBTSH 11.8 mIU/L) and later presented with CH, we have included one as false negative on the assumption that all those who were screen negative and did not undergo the gold-standard test were disease free. This verification bias may have affected the reported sensitivity and specificity. As it is not possible to do the “gold standard test” for all babies, such assumptions are acceptable and have been reported by other researchers as well. Large sample size, single-center experience, and longitudinal data for 16 years may minimize the verification bias to a large extent.

Lower screen threshold has the advantage of identifying babies with mild or even subclinical CH. In Italy, reducing screen TSH from ~24 to 20 mIU/L resulted in an increase in CH prevalence from 1:1816 to 1:1154 and recall rate from 0.7 to 1.07%. Among the additional cases, there was a high proportion of babies with low birth weight and gland-in-situ. In the Canadian NBS, among babies with mild TSH elevation (~34–60 mIU/L) and confirmed CH, only 47% had low FT4. In the New Delhi cohort, only 20% babies with screen TSH ~40–59.9 mIU/L had low FT4. Most CH with mild TSH elevation are often, though not always, functional disorders with gland-in-situ. Long-term data on the permanence of milder forms of CH and their neurodevelopmental outcome are scarce. Despite 86% permanence of mild CH in the Quebec NBS, the authors have questioned the need for l-thyroxine supplements in these children. While some advocate treatment of even mild CH pending developmental outcome data, others do not recommend this practice. In our institution, only those with elevated TSH and low FT4/T4 at recall were confirmed as CH.

Most NBS programs have a two–three-tier referral system. While those with marked TSH elevation are referred immediately, those with lower/borderline TSH are retested using the same/fresh DBS or venous sample. In the New Delhi cohort, fresh DBS was collected for the screen positives on the second/third day and only those with persistent TSH ≥20 mIU/L were recalled. While this practice ensures that false positivity is minimized, repeat sampling would either mean revisit to hospital or health-care worker making home visits. Although those with mild-screen TSH elevation represent only around 1–1.5% of the total cohort, the logistics involved with retesting and collecting fresh DBS is enormous in India. Using a CBTSH cutoff 20 mIU/L, the calculated projected recall rate in our NBS is 4.9% [Table 5]. With ~15,000 annual deliveries in our institution, this would mean a recall of additional 300 babies/year.

Using cord blood for newborn screening for CH is a practical option in countries where most deliveries are hospital based and mothers are discharged within 24–48 h. With several issues such as inadequate facilities for community-level follow-up, limited access to several geographical locations, as well as unrealistic expectations for parents to do heel-prick sampling at home, mass NBS based on DBS after discharge from hospital has significant practical limitations in countries such as India. It remains a disadvantage that cord blood cannot be used for simultaneous screening of inborn errors of metabolism.

Good correlation between TSH levels in CB and samples collected >48 h has been reported and ISPAE guidelines recommend similar cutoff for both samples. Several factors are known to impact CBTSH level. Higher CBTSH levels have been reported in the offspring of mothers with even borderline iodine deficiency. The maternal iodine status of our cohort is not known. Other known factors which impact CBTSH are mode of delivery, perinatal risk factors, birth asphyxia, and high-risk pregnancy with higher CBTSH reported in those with instrumental deliveries and fetal distress as compared to those born by elective LSCS. It is possible that CBTSH reflects the TSH surge associated with the “stress” of even normal birth. This could explain the higher recall rate inherent with NBS using CBTSH. Although factors such as gestational age, birth weight, and mode of delivery did not have significant correlation with CBTSH in our prospective cohort, it was interesting to note that 31% of babies in this group were not born by normal vaginal delivery (23% instrumental delivery, 8% LSCS). Our data suggest the possibility of proposing a higher TSH cutoff while using cord blood compared to samples collected >48–72 h of age.

This study includes data from a subgroup of the largest cohort of NBS for CH done in a single hospital in India with a long follow-up period of 16 years. The entire cohort is of inborn babies, and their sample collection, biochemical studies, recall, and CH confirmation including thyroid scintiscan were done in one hospital using uniform protocol. Decision to treat as well as follow-up was uniform under the pediatric endocrinology

### Table 4: Sensitivity, specificity, PPV, and NPV of babies with CBTSH between 20 and 30 mIU/L

| Total babies screened | CBTSH (mIU/L) | Screen positives who were resampled n (corrected recall rates) | True positives | Positive predictive value | Negative predictive value | Sensitivity | Specificity |
|-----------------------|--------------|---------------------------------------------------------------|---------------|--------------------------|--------------------------|------------|------------|
| n=14,742              | 20-25        | 195                                                           | 123           | 2.9%                     | 100%                     | 99.2%      | 97.5%      |
|                       | 25-30        |                                                               |               |                          |                          |            |            |
|                       | >30          |                                                               |               |                          |                          |            |            |
| n=164,163             | 20-25        | 195                                                           | 119           | 3.1%                     | 100%                     | 95.9%      | 97.8%      |
|                       | 25-30        |                                                               |               |                          |                          |            |            |
|                       | >30          |                                                               |               |                          |                          |            |            |

Using cord blood for newborn screening for CH is a practical option in countries where most deliveries are hospital based and mothers are discharged within 24–48 h. With several issues such as inadequate facilities for community-level follow-up, limited access to several geographical locations, as well as unrealistic expectations for parents to do heel-prick sampling at home, mass NBS based on DBS after discharge from hospital has significant practical limitations in countries such as India. It remains a disadvantage that cord blood cannot be used for simultaneous screening of inborn errors of metabolism.

Good correlation between TSH levels in CB and samples collected >48 h has been reported and ISPAE guidelines recommend similar cutoff for both samples. Several factors are known to impact CBTSH level. Higher CBTSH levels have been reported in the offspring of mothers with even borderline iodine deficiency. The maternal iodine status of our cohort is not known. Other known factors which impact CBTSH are mode of delivery, perinatal risk factors, birth asphyxia, and high-risk pregnancy with higher CBTSH reported in those with instrumental deliveries and fetal distress as compared to those born by elective LSCS. It is possible that CBTSH reflects the TSH surge associated with the “stress” of even normal birth. This could explain the higher recall rate inherent with NBS using CBTSH. Although factors such as gestational age, birth weight, and mode of delivery did not have significant correlation with CBTSH in our prospective cohort, it was interesting to note that 31% of babies in this group were not born by normal vaginal delivery (23% instrumental delivery, 8% LSCS). Our data suggest the possibility of proposing a higher TSH cutoff while using cord blood compared to samples collected >48–72 h of age.

This study includes data from a subgroup of the largest cohort of NBS for CH done in a single hospital in India with a long follow-up period of 16 years. The entire cohort is of inborn babies, and their sample collection, biochemical studies, recall, and CH confirmation including thyroid scintiscan were done in one hospital using uniform protocol. Decision to treat as well as follow-up was uniform under the pediatric endocrinology.
Projected recall rate

| CBTH | n screened | n returned | Recall rate |
|------|------------|------------|-------------|
| >20 (July 2001-July 2010) | 77,829 | 3856* | 4.9%* |
| >25 | 164,163 | 4224 | 2.57% |
| >30 | 164,163 | 2465 | 1.5% |

*Calculated based on (80%) of the total 4820 babies with CBTH >20 mIU/L who are likely to return for retesting. 'Projected recall rate

The small sample size in the CBTH 20–24.9 mIU/L group is a limitation. In addition, a large proportion of the babies recalled during the study period did not return for retesting; however, at least 75% of them were not diagnosed with CH till 3 years of age and were reported to have normal development.

Conclusions

Our data justify the continuation of using a TSH cutoff of 25 mIU/L when using cord blood for screening. A lower threshold of 20 mIU/L would result in recall of additional 300 babies/year with no definite improvement in sensitivity. Countries with high prevalence of CH and limited resources should probably focus on identifying maximum number of children born with CH. In addition, with a diverse population, it is important that we use feasible regional screen cutoffs for optimal use of resources. NBS cannot replace careful clinical examination. If clinical suspicion is high, biochemical tests have to be done irrespective of screen results.

Acknowledgments

We would like to acknowledge Prof. A.K. Jana and Prof. Selvakumar R, the former Head of the Departments of Neonatology and Biochemistry, respectively, for supporting the commencement of newborn thyroid screening program at Christian Medical College, Vellore along with Prof. P. Raghupathy. We would also like to acknowledge our pediatric endocrine nurses Mrs. Marthal, Mrs. Ida, and Mrs. Gnanasoundari who help with the NBS on a day-to-day basis.

Financial support and sponsorship

This study was supported by a grant from the Fluid Research fund of Christian Medical College, Vellore, India (Ref: IRB min no: 1304 [OBSERVE] dated 12.10.2016).

Conflicts of interest

There are no conflicts of interest.

References

1. Rose SR, Brown RS. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006;117:2290-2303.
2. Grüters A, Krude H. Detection and treatment of congenital hypothyroidism. Nat Rev Endocrinol 2011;8:104-13.
3. Ford G, LaFranchi SH. Screening for congenital hypothyroidism: A worldwide view of strategies. Best Pract Res Clin Endocrinol Metab 2014;28:175-87.
4. Chen C-Y, Lee K-T, Lee CT-C, Lai W-T, Huang Y-B. Epidemiology and clinical characteristics of congenital hypothyroidism in an Asian population: A nationwide population-based study. J Epidemiol 2013;23(2):85-94.
5. Afroz B, Humayun KN, Qadir M. Newborn screening in Pakistan - Lessons from a hospital-based congenital hypothyroidism screening programme. Ann Acad Med Singap 2008;37(12 Suppl):114-3.
6. Kaur G, Srivastav J, Jain S, Chawla D, Chavan BS, Atwal R, et al. Preliminary report on neonatal screening for congenital hypothyroidism, congenital adrenal hyperplasia and glucose-6-phosphate dehydrogenase deficiency: A Chandigarh experience. Indian J Pediatr 2010;77:969-73.
7. Devi ARR, Naushad SM. Newborn screening in India. Indian J Pediatr 2004;71:157-60.
8. Desai MP, Sharma R, Riaz I, Sudhanshu S, Parikh R, Bhatia V. Newborn screening guidelines for congenital hypothyroidism in India: Recommendations of the Indian society for pediatric and adolescent endocrinology (ISPAE)-Part I: Screening and confirmation of diagnosis. Indian J Pediatr 2018;85:440-7.
9. Saleh DS, Lawrence S, Geraghty MT, Gallego PH, McAssey K, Wherrett DK, et al. Prediction of congenital hypothyroidism based on initial screening thyroid-stimulating-hormone. BMC Pediatr 2016;16:24.
10. Lott JA, Sardovia-Iyer M, Speakman KS, Lee KK. Age-dependent cutoff values in screening newborns for hypothyroidism. Clin Biochem 2004;37:791-7.
11. Kishore KR, Ranieri E, Fletcher J. Newborn screening for congenital hypothyroidism in India- Is OVERDUE. J Neonatal Biol 2014;3:129.
12. Verma P, Kapoor S, Kalaiavani M, Vats P, Yadav S, Jain V, et al. An optimal capillary screen cut-off of thyroid stimulating hormone for diagnosing congenital hypothyroidism: Data from a pilot newborn screening program in Delhi. Indian Pediatr 2019;56:281-6.
13. Bates AS, Margolis PA, Evans AT. Verification bias in pediatric studies evaluating diagnostic tests. J Pediatr 1993;122:585-90.
14. Korada SM, Pearce M, Ward Platt MP, Avis E, Turner S, Wastell H, et al. Difficulties in selecting an appropriate neonatal Thyroid stimulating hormone (TSH) screening threshold. Arch Dis Child 2010;95:169-73.
15. Corbetta C, Weber G, Cortinovis F, Cailebiro D, Passoni A, Vignone MC, et al. A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of Congenital hypothyroidism (CH). Clin Endocrinol (Oxf) 2009;71:739-45.
16. Deladoëy J, Ruel J, Giguère Y, Van Vliet G. Is the incidence of congenital hypothyroidism really increasing? A 20-year retrospective study and clinical characteristics of congenital hypothyroidism in an Asian population: A nationwide population-based study. J Epidemiol 2011;28:175-87.
17. LaFranchi SH. Increasing Incidence of congenital hypothyroidism: Some answers, more questions. J Clin Endocrinol Metab 2011;96:2395-7.
18. Cheetham T. Congenital hypothyroidism: Managing the hinterland between fact and theory. Arch Dis Child 2011;96:205.
19. Kruide H, Blankenstein O. Treating patients not numbers: The benefit and burden of lowering TSH newborn screening cut-offs. Arch Dis Child 2011;96:121-2.
20. Gopalakrishnan V, Joshi K, Phadke S, Dabhadhao P, Agarwal M, Das V, et al. Newborn screening for congenital hypothyroidism, galactosemia and biotinidase deficiency in Uttar Pradesh, India. Indian Pediatr 2014;51:701-5.
21. Peters C, Brooke I, Heales S, Ifeduru A, Langham S, Hindmarsh P, et al. Defining the newborn blood spot screening reference interval for TSH: Impact of ethnicity. J Clin Endocrinol Metab 2016;101:3445-9.
22. Albert BB, Cutfield WS, Webster D, Carll J, Derraik JGB, Jefferies C, et al. Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993-2010. J Clin Endocrinol Metab 2012;97:3155-60.

23. Seth A, Rashmi M, Bhakhri BK, Sekri T. Neonatal thyroid screening: Relationship between cord blood thyroid stimulating hormone levels and thyroid stimulating hormone in heel prick sample on 4th to 7th day-of-life. Indian J Endocrinol Metab 2014;18:125-6.

24. Kung AWC, Lao TT, Chau MT, Tam SCF, Low LCK. Goitrogenesis during pregnancy and neonatal hypothyroxinaemia in a borderline iodine sufficient area. Clin Endocrinol (Oxf) 2000;53:725-31.