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Screening For Congenital Hypothyroidism By Umbilical Cord Blood TSH – A Hospital Based Study.

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I. Introduction

Congenital hypothyroidism (CH) is one of the major health problems and the main preventable cause of mental retardation in children. The incidence of congenital hypothyroidism varies across geographic areas and ethnicity. The exact incidence of congenital hypothyroidism in India is unknown. The incidence of CH has shown a wide variation across different states in India. A study done in Hyderabad showed an incidence of 1 in 1700 births.[1] Studies by Desai et al based on a neonatal screening program in Mumbai places the incidence at 1: 2500 –1: 2800.[8] Other studies done in Kerala and Kolkata and have shown a higher incidence of 1:500 to 1:600.[20] CH if diagnosed promptly and treated early, irreversible mental retardation can be prevented. Because signs and symptoms of CH are often scarce at birth, newborns need to be screened at birth for early diagnosis of CH.

Screening programs for detection of CH in neonatal period are widespread in the developed countries for the last three decades [2,3] and are fast gaining momentum in the developing world as well.[4] In most screening programs blood samples are collected within 5-6 days of age, but with large number of babies being discharged early, cord blood samples are being used as well.[4,5]

In our country, it is very difficult to follow up all babies once discharged. Also, an effective social system whereby babies could be reached at home is practically non-existent. Thus cord blood remains a very practical alternative for screening purposes, and thus is the practice in some Asian countries.[4,5] Mixed cord blood samples for TSH values have compared well with filter paper samples taken in the first few days of life.[6,7] The Indian Academy of Pediatrics recommends the use of cord blood samples for screening for CH.[7]However, in Indian literature there are very few reports of TSH values in cord blood[8,9] and hence the current study examines cord TSH as a screening tool for CH.

According to the Nelson Textbook of Pediatrics TSH levels

Premature Infants (28-36 wks) 1st week of life	0.7-27.0 mIU/L
Term Infants Birth to 4 days 2-20 wk	1.0-17.6mIU/L 0.6-5.6mIU/L

II. Objectives

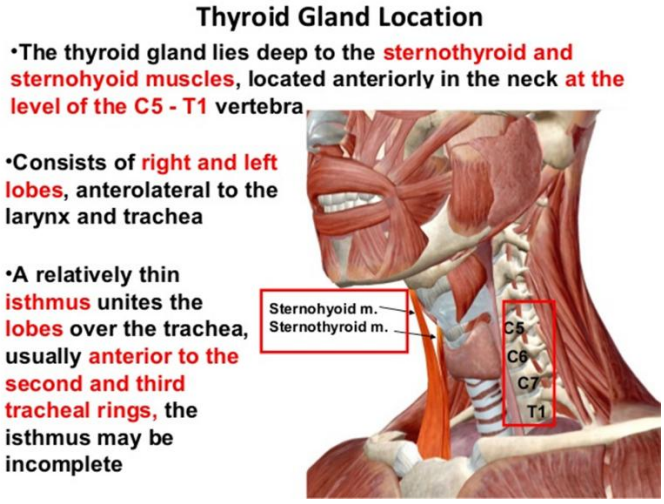
To study the incidence of congenital hypothyroidism among term, and preterm babies born at Kurji Holy Family Hospital, Patna.

To study the effectiveness of Cord Blood TSH as a screening tool to detect cases with hypothyroidism

III. Review Of Literature

Congenital hypothyroidism (CH) is a problem which arises due to the absence of thyroid hormone in the developing newborn. It can also occur due to the inactive thyroid hormone in the circulation of the newborn. Thyroid hormone is critically important for normal brain growth, cellular differentiation, and CNS development early in life.[10] It is one of the important preventable cause for mental retardation.[11] Early diagnosis and prompt treatment can reduce the burden of mental retardation. Early recognition of the disease is difficult as it does not present with signs or symptoms at birth. The absence or inactive thyroid hormone can be due to multiple factors, for which the understanding of the anatomy, physiology and pathology of the thyroid gland becomes essential.

Anatomy of the thyroid gland Figure



Anatomy of the thyroid gland

The thyroid gland is a bilobed organ in the neck which arises from the fourth branchial pouch. Defects in the formation or migration of thyroid tissue can result in thyroid aplasia, dysplasia, or ectopy. During the functional ontogenesis of the thyroid gland an increasing number of transcription factors play fundamental roles in thyroid-cell differentiation, maintenance of the differentiated state, and thyroid-cell proliferation. The early growth and development of the fetal thyroid appears to be generally independent of thyroid-stimulating hormone (TSH). TSH and thyroxine (T4) levels increase from the 12th week of gestation until delivery, whereas triiodothyronine (T3) levels remain relatively low. At birth, a cold-stimulated short-lived TSH surge is observed, followed by a TSH decrease at the day 3 or 4 of life by T4 feedback inhibition. The most prevalent disease, congenital hypothyroidism, is frequently caused by genetic defects of transcription factors involved in the development of the thyroid or pituitary gland.

Physiology of the thyroid gland

The fetal thyroid is capable of producing thyroid hormone by 10-11 weeks gestation. Blood levels of T4 reach term levels by 18-20 weeks gestation. The fetal pituitary-thyroid axis is believed to function independently of the maternal pituitary-thyroid axis.

Pathology of the thyroid gland

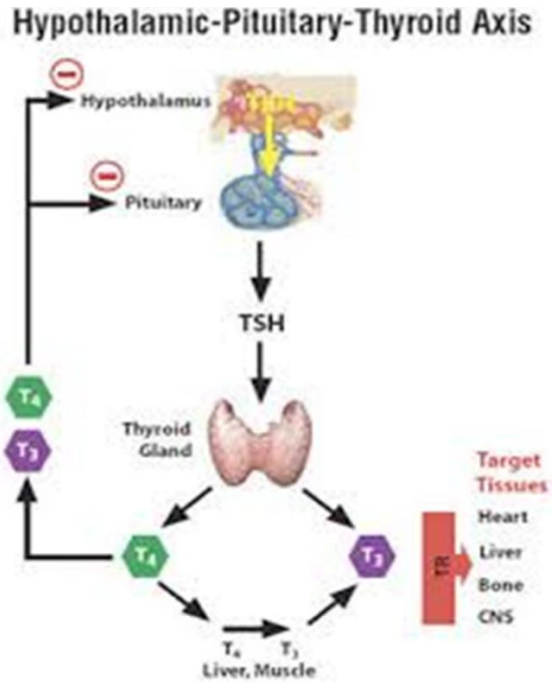


Figure 2:

Regulation of Thyroid gland function Disorders at various steps in thyroid hormone synthesis and action can result in congenital hypothyroidism. Even in children with anatomically normal thyroid glands, congenital hypothyroidism can occur due to inborn errors of thyroid metabolism. Among the thyroid hormones, T3 is the primary mediator of the biologic effects and does so by interacting with a specific nuclear receptor. Abnormalities in thyroid receptors can result in thyroid hormone resistance. In congenital thyroid binding globulin (TBG) deficiency, infants are usually born with low levels of TBG and also have low total T4 levels but are physiologically normal. Familial congenital TBG deficiency can be inherited as an Xlinked recessive or autosomal recessive condition. The contributions of maternal thyroid hormone levels to the fetus are thought to be minimal, but maternal thyroid disease can have a substantial influence on fetal and neonatal thyroid function. Immunoglobulin G (IgG) autoantibodies, as observed in autoimmune thyroiditis, can cross the placenta and inhibit thyroid function. Thioamides used to treat maternal hyperthyroidism can also block fetal thyroid hormone synthesis. Most of these effects are transient. Radioactive iodine administered to a pregnant woman can ablate the fetus's thyroid gland permanently. The importance of thyroid hormone to brain growth and development is demonstrated by comparing treated and untreated children with congenital hypothyroidism. Thyroid hormone is necessary for normal brain growth and myelination and for normal neuronal connections. The most critical period for the effect of thyroid hormone on brain development is the first few months of life[12] In central Africa, where iodine deficiency occurs along with excess dietary cyanate from cassava (Manihot esculenta)[13], as many as 10% of newborns may have both low cord blood T4 concentration and TSH concentrations over 100 mU/L.[14]

Global incidence of congenital hypothyroidism

Globally, the prevalence of CH approaches 1:3000[15] with substantially higher prevalence in iodine deficient areas, sometimes in excess of 1:900.[16] Racial and ethnic differences in the prevalence of CH vary across populations. The prevalence among Japanese is approximately 1:7600, while in Israel it is about three times higher. Variations in prevalence have also been reported within various populations. In the USA, for example, African-Americans appear to have congenital hypothyroidism prevalence about half that of Caucasians, while Hispanics have a rate about 40% higher and Native Americans may have an even higher rate. Studies in the UK[17] and South Africa[18] found that CH appears to be several times more prevalent in children of Asian (including Indian) ancestry; Studies have also found a higher prevalence (approximately 2:1) of CH among females. Recent research has shown that much of this discrepancy may be attributed to differences in thyroid ectopy and are gender related.

Indian incidence of congenital hypothyroidism The incidence of CH has shown a wide variation across different states in India. The exact incidence of congenital hypothyroidism in India is unknown. A recent study in India testing a total of eighteen thousand three hundred newborns, revealed a high prevalence of CH (1 in 1700).[19]

Studies by Desai et al, based on a neonatal screening program in Mumbai places the incidence at 1: 2500 –1: 2800.[8]

A study done at Kolkata, has recorded an incidence of CH as 1 in 600 life births.[20] Incidence of etiological factors for congenital hypothyroidism Incidence of primary hypothyroidism varies from 1 in 1000 to 1 in 3500 live births depending on the iodine sufficiency, laboratory methods, screening practice (changes in test cutoffs), demographic and other unknown factors.[21]

Depending on the iodine sufficiency, the incidence of primary hypothyroidism varies from 1 in 2500 to 1 in 4000 live births. Permanent secondary (thyrotropin deficient) and tertiary (thyrotropin releasing hormone deficient) hypothyroidism is rare, with an incidence of 1:50,000 and 1:100,000 respectively. Prevention of cretinism and optimal neurologic development can be achieved in affected infants by early introduction of hormonal replacement. Screening, based on measurement of hormone levels, aims to pick up hypothyroid children soon after birth because clinical features are not specific during the perinatal period. The cost/benefit ratio determines the method and ultimately the strategies of the screening program. In Europe, Japan, and Australia, a primary thyrotropin determination was introduced as its sensitivity and specificity is greater than T4 measurement. In North America the primary T4 test is followed by backup thyrotropin determination in cases with a low T4 level (usually the lowest 10th –20th percentile).

Canada and some states in the United States have switched to a primary thyrotropin program. In the Netherlands, a primary T4/back up thyrotropin program was supplemented by a thyroxin-binding globulin measurement. Using the three-arm method, the incidence of congenital hypothyroidism increased upto 1:1800 in the Netherlands.[22] A second TSH determination in newborns with borderline TSH results also elevates the incidence mostly with milder forms, in which cases thyroid in situ is present.[23] Although percentages of specific etiologies for CH vary from country to country, ranges are as follows:

Table 1:
Etiology of congenital hypothyroidism
Etiologies Range
Ectopic thyroid 25-50%
Thyroid agenesis 20-50%
Dyshormonogenesis 4-15%
Hypothalamic-pituitary dysfunction 10-15%

An increased incidence of congenital hypothyroidism is observed in twins. [24] Twin births are approximately 12 times as likely to have congenital hypothyroidism as singletons.[25] Usually, only one twin is hypothyroid, but a common in-utero exposure can cause hypothyroidism in both.[26] Congenital hypothyroidism is more common in infants with birth weight less than 2,000 gram or more than 4,500 gram.[27]

Mortality/Morbidity Profound mental retardation is the most serious effect of untreated congenital hypothyroidism. Severe impairment of linear growth and bone maturation also occurs. Affected infants whose treatment is delayed can have neurologic problems such as spasticity and gait abnormalities, dysarthria or mutism, and autistic behavior.

Race

Congenital hypothyroidism is observed in all populations. The prevalence at birth is increased in Hispanics, particularly in Hispanic females, who have a birth prevalence of 1 in 1886 births. [28] Black infants have about one third the prevalence rate of white infants. Gender Most studies of congenital hypothyroidism suggest a female-to-male ratio of a 2:1. A study done in Canada showed that much of the discrepancy is accounted for by infants with thyroid ectopy.[29] The gender ratio for Hispanics is more striking, with a 3:1 female to-male ratio. The ratio is lower among Black infants. An update by the American academy of pediatrics also showed a female preponderance of congenital hypothyroidism.[30]

Age By definition, congenital hypothyroidism is present at, or before birth. Children who develop primary hypothyroidism when aged 2 years or older have poor growth and slow mentation but generally do not exhibit the profound and incompletely reversible neurologic abnormalities observed in untreated congenital hypothyroidism.

History

In regions of iodide deficiency and a known prevalence of endemic cretinism, the diagnosis may be straight forward. Infants with congenital hypothyroidism are usually born at term or after term.

Symptoms and signs of Congenital Hypothyroidism

- Decreased activity
- Large anterior fontanelle
- Poor feeding and weight gain
- Small stature or poor growth
- Jaundice
- Decreased stooling or constipation
- Hypotonia
- Hoarse cry

Often, they are described as "good babies" because they rarely cry and sleep most of the time. Family history should be carefully reviewed for information about similarly affected infants or family members with unexplained mental retardation. Maternal history of a thyroid disorder and mode of treatment, whether before or during pregnancy, can occasionally provide the etiology of the infant's problem.

Physical features

The physical findings of hypothyroidism may or may not be present at birth. A small but significant number (3-7%) of infants with congenital hypothyroidism have other birth defects, mainly atrial and ventricular septal defects.[31] Infants with obvious findings of hypothyroidism (eg, macroglossia, enlarged fontanelle, hypotonia) at the time of diagnosis have intelligence quotients (IQs) 10-20 points lower than infants without such findings.

Newborn screening

- Newborn screening for congenital hypothyroidism involves the following: Identification of infants with congenital hypothyroidism within the first week of life.
- Careful examination for signs of hypothyroidism and confirmation of the diagnosis by repeat testing.

A study done in Australia on congenital hypothyroidism in very low birth weight (VLBW) babies concluded that significant hypothyroidism, transient or permanent, can persist in VLBW babies beyond 2 months of age.[32] They also noted that there is a delayed rise in TSH in some cases, and secondary screening at 1 month of age was recommended in VLBW infants.

Etiology

- Endemic cretinism is caused by iodine deficiency, and is occasionally exacerbated by naturally occurring goitrogens.[33]
- Dysgenesis of the thyroid gland, including agenesis and ectopy (lingual or sublingual thyroid gland) may be a cause.
- Inborn errors of thyroid hormone metabolism include dyshormonogenesis. Most cases are familial and inherited as autosomal recessive conditions.

These may also include the following:

- TSH unresponsiveness (ie, TSH receptor abnormalities)[34]
- Impaired ability to uptake iodide peroxidase, or organification, defect (ie, inability to convert iodide to iodine)
- Pendred syndrome (familial organification defect associated with congenital deafness)
- Thyroglobulin defect (ie, inability to form or degrade thyroglobulin)
- Deiodinase defect and Thyroid hormone resistance (ie, thyroid hormone receptor abnormalities). [34]

In maternal autoimmune disease, transplacental passage of antibodies cause transient or permanent hypothyroidism. [35] Radioactive iodine therapy of pregnant women may cause permanent congenital hypothyroidism. Iodine in contrast agents or skin disinfectants can cause hypothyroidism or hyperthyrotropinemia in premature neonates.[36] Hypothyroidism can also occur in TSH or TRH deficiencies, either as an isolated problem or in conjunction with other pituitary deficiencies (eg, hypopituitarism). If present with these deficiencies, hypothyroidism is usually milder and is not associated with the significant neurologic morbidity observed in primary hypothyroidism.

Diagnostic Considerations

Neonatal hypothyroxinemia

Premature and sick infants have lower levels of thyroid hormone than term infants but usually do not have elevated thyroid-stimulating hormone levels.[37,38]

Reference ranges appropriate to the infant's gestational age should be used to avoid confusing this with hypothyroidism. A meta-analysis suggests that treatment of these neonates with thyroxine is futile.[39]

Transient neonatal hypothyroidism and hyperthyrotropinemia Ingestion of excessive amounts of iodine,[40] or of goitrogens such as lithium,[41] thioamides[42] or amiodarone[43] can cause a temporary hypothyroid state.

Maternal antibodies to the TSH receptor can also cause temporary hypothyroidism. [35] This may require treatment with levothyroxine for a period of days to months. The etiology of transient hypothyroidism is often unclear.[44] Cord blood for screening congenital hypothyroidism: Most programs in the United States chose to use T4 as the primary screen, with TSH as a second-tier screen to confirm a low T4 value, whereas programs outside the United States predominately chose TSH for the primary screening biomarker. This diversity continues today, with 131 newborn screening programs worldwide using TSH only for screening and 75 using the T4/TSH protocol, all using a form of immunoassay. In the United States, 4 programs use TSH only and 35 use the T4/TSH strategy.[45]

Each method will miss certain CH syndromes. The TSH only protocol will miss those infants with central hypothyroidism, that is, of pituitary or hypothalamic origin (estimated at 1 in 50,000 births). The T4/TSH protocol will miss those infants with minimally functioning or ectopic thyroid glands that seem normal at birth, then decline in function.[46]

The preferred protocol would include testing for both biomarkers simultaneously as is done in 5 state programs in the United States, a procedure that was prohibitively expensive and time consuming for large programs until recently. Multi-analyte assays have now been developed that can probe for several biomarkers simultaneously in the same assay well.[47]

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. In our country this practice has serious limitations due to high home delivery rate, early discharge from hospitals and cultural taboos related to newborns. Collection of cord blood may be a feasible alternative and has been used for newborn screening of congenital hypothyroidism in some countries like Malaysia. Proponents of initial screening with TSH point to less analytical variation and fewer false positive results than are found with initial T4 screening.[48] However, most published

reports on TSH testing have relied on testing performed after day 3 of life (the usual protocol in Europe and Japan) and only limited data have been published concerning the utility of TSH screening at earlier ages.[49] While TSH is likely a better diagnostic test than T4, it is subject to a biological surge that occurs shortly after birth, peaks at around between 6 and 12 hours, and diminishes over the next 24–48 hours.[50] The effect of this surge must be considered when choosing the analytical testing procedure. The range of expected TSH results for newborns screened early (within the first 24 hours after birth) is not easily determined because of the biological variability in the timing and level of the surge. The lack of a definite range of expected values within the surge period creates a higher likelihood of false positive screening results when TSH is the initial screening analyte. For this reason, initial T4 screening is often considered as an alternative procedure in screening populations where blood specimens must, of necessity, be collected early (less than 24 hours of age) in a high number of newborns.

In such 21 cases, TSH is often used as a second level test to reduce the number of patients result requiring follow-up testing. Proponents of initial T4 testing also argue that initial screening with T4 allows for detection of secondary hypothyroidism, which is not possible with initial screening for TSH since the TSH levels in secondary hypothyroidism are not usually elevated.

Desai et al [8] , screened 12407 newborns for CH using cord blood TSH measurements. The number of newborns called for retesting was 2.8% and the incidence extrapolated was 1: 2481.[8] In 1994, the same group screened 25,244 neonates at 24-94 hours and measured filter paper T4. The babies recalled were 18.91%; however, this screening missed 3 out of 9 babies despite a high recall. The extrapolated incidence was 1:2804. Considering this high incidence of congenital hypothyroidism, availability of low cost therapy and a robust screening test like TSH, it is highly desirable to start a screening program nationwide to prevent the most preventable cause of mental subnormality. Both ELISA and time resolved fluroimmunoassay can be used in the screening phase and confirmatory tests can use either radioimmunoassay or chemiluminescence.

Fuse et al [52] concluded that the TSH value in cord blood was less influenced by perinatal factors, including the sampling method. They also suggested that mixed cord blood might be a feasible and useful alternative specimen for a TSH screening program in countries where neonatal blood is not available.

Walfish et al [6], conducted a study to test the different types of screening methods to evaluate congenital hypothyroidism. They used dried capillary blood thyroxine (T4), Serum T4 and cord blood TSH assays. They concluded that cord blood TSH assay as an initial screening test had a higher specificity and sensitivity for the diagnosis of primary hypothyroidism. In most screening programs blood samples are collected at 5-6 days age, but with large number of babies being discharged early, cord blood samples are being used as well.[4,5] In our country, it is very difficult to call back babies once discharged. Also, an effective social system whereby babies could be reached at home is practically nonexistent. Thus cord blood remains a very practical alternative for screening purposes in some Asian countries.[5] Mixed cord blood samples for TSH values have compared well with filter paper samples taken in the first few days of life.[51] The Indian Academy of Pediatrics recommends the use of cord blood samples for screening for CH.

Drawbacks of using primary cord TSH:

A primary TSH strategy will miss the rare secondary and tertiary hypothyroidism, thyroxin binding globulin deficiency, and hyperthyroxinemia, while a primary T4/backup-TSH program will miss compensated hypothyroidism. Apart from those infants missed, depending on the exact strategy employed, infants with atypical congenital hypothyroidism (delayed thyrotropin rise) will be missed because their TSH and T4 levels are normal on initial screening. TSH cutoff Cord blood thyroxine (T4) levels of 50 mU/mL were used as cut offs. Their data showed that the incidence of CH was about a hundred-fold more in seriously iodine deficient endemic districts. [19] Wu et al[4] in their large cohort of 11,000 neonates had a recall rate of 2.27% which is in concordance with other large studies. Normal cord TSH values show a wide range of 1-38.9 mIU/L[53] , and we have used a cutoff of 20 mIU/L. Manglik et al deduced that by opting for higher cutoff of 25, 30 or 40 for recall purposes, the recall rates could be brought down to 1.08%, 0.91% or 0.42% respectively.A 5-year prospective study from Thailand[54] used a cut-off value of 30 to begin with and had a recall rate of 1.1% in a large sample size of 35,390 neonates. They subsequently modified their recall policy and raised the cutoff value to 40 leading to a fall in recall rate to 0.43%. However, considering our annual birth rate of about 25 million, a recall rate of close to 2% may envisage calling back almost 500,000 newborns for full thyroid profile. Higher cutoff values of cord TSH for recall purposes and thus a lower recall rate will vastly improve the economic and practical logistics in any widely organized public health program particularly so in our country.

Prognosis

If T4 replacement is adequate, somatic development in children with congenital hypothyroidism is similar to that in normal children. That is, height and weight are normal. Also, retardation of bone maturation is also reversible in children with congenital hypothyroidism, if T4 replacement is adequate. Early (onset of replacement before 2 weeks of age) and high dosage (initial dose of 10–15 mg/kg/d) treatment appears

necessary.[55] Damage of psycho-neuro-intellectual development (eg, cognitive deficit, sensorineural hearing loss) do not seem to occur (or only rarely) in children treated early and with sufficient dosages.[56] However, the noncompliance beyond the first 3 years of life can affect mental development. Thyrotropin should not be the only determinant of T4 dose because certain infants—mostly those who were affected by severe in utero hypothyroidism—have some (shorter or longer) transient hypothalamic-pituitary resistance to thyroid hormones. Women with hypothyroidism should be advised to have thyroid hormones measured before and during pregnancy also for the protection of the fetus; mostly they need a higher dose of T4 replacement. Genetic counseling may helpful in detecting genetic thyroid dysgenesis. The risk of a new congenital hypothyroidism in a family is probably about 2%. The final outcome of CH screening is truly encouraging. We agree with MacGillivray's opinion: ―The most gratifying discovery that has come from the newborn thyroid screening programs is the attainment of normal intelligence in congenital hypothyroid infants because of early diagnosis and treatment.[57]

IV. Materials And Methods

A. STUDY AREA: A Hospital based prospective cohort study will be undertaken in the department of pediatrics,KURJI HOLY FAMILY HOSPITAL,Patna,Bihar which is a tertiary care referral hospital for children.Neonates delivered here and fullfilling our inclusion criteria will be studied.The study is planned over a period of one year.

B. STUDY POPULATION: Study group will comprise of live term/ preterm neonates delivered in this hospital by vaginal/L.S.C.S.

C.SAMPLE SIZE: A cohort of neonates delivered in this hospital will constitute the sample size of this prospective cohort study. my sample size will be 2500.

D.STUDY DESIGN: A hospital based prospective cohort study in Department of Pediatrics,Kurji Holy Family Hospital,Patna Bihar,a tertiary care referral hospital.

E. STUDY DURATION:
From 1 December 2017 to 30 November 2018.

F. INCLUSION CRITERIA:
Term
Preterm babies (32-36wks).

G.EXCLUSION CRITERIA:
Mothers on thyroid medications.
Birth Aspyxia
Babies with neurodeveolpmental malformations.

H. METHODOLOGY:

After getting approval from the institution's ethical committee and on the basis of inclusion criteria,this study will include 2500 newborns as sample size.The written informed consent will be obtained from parents/legal representatives of children after fully explaining the study procedure to their satisfaction.A standard case record form will be maintained for each subject.
Newborns will be examined at birth according to the performa given in protocol.

With strict aseptic precautions 3ml cord blood is collected in plain vial(red capped) by the investigator at birth and will be sent to biochemistry lab for assessment of TSH levels. Cord blood TSH will be measured using "ARCHITECT PLUS".

PRINCIPLE- The ARCHITECT TSH assay is a two-step immunoassay to determine the presence of Thyroid Stimulating Hormone (TSH) in human serum and plasma using the Chemiluminescent Microparticle Immunoassay (CMIA) technology with flexible assay protocols, referred to as Chemiflex. In the first step, sample anti-β TSH antibody coated paramagnetic microparticles and TSH Assay Diluent are combined. TSH present in the sample binds to the anti-TSH antibody coated microparticles. After washing, anti-α TSH acridinium labeled conjugate is added in the second step. Pre-Trigger and Trigger Solutions are then added to the reaction mixture; the resulting chemiluminescent reaction is measured as relative light units (RLUs). A direct relationship exists between the amount of TSH in the sample and the RLUS detected by the ARCHITECT PLUS" system.

As per the Nelson Textbook of Pediatrics we know that-

The normal range of blood TSH in pretern infants 0.7-27.0 mIU/L in term infants 1.0-17.6 mIU/L. All babies wherein the cord TSH was found to be over 20mIU/L were intimated within 24hrs of the test. A second venous blood sample from these babies for serum T4 and TSH estimation was collected between 2- 4 day of life. 4.

A prospective study of all consecutively Neonates delivered Kurji Holy Family Hospital, Patna, Bihar between 1 December 2017 to 30 November 2018 was conducted. Umbilical cord mixed blood samples were collected in a sterile container, drawn from placental side of the umbilical cord incised while severing it at the time of birth of the baby. The type of medications given to the mother till birth of the baby was recorded. At birth, the babies weight, gender, time to first cry, congenital abnormalities, were noted. TSH was estimated within 24 hours by electrochemiluminescence immunoassay 'ECLIA' on elecsys 2010 analyser. All babies wherein the cord TSH was found to be over 20mIU/L were intimated within 24hrs of the test.

V. Statstical Analysis:

All the data was entered into Microsoft Excel 2007 spreadsheet and analysed using SPSS software version 13.0. The various clinical parameters like gestational age and birth weight were correlated with the cord blood TSH levels using the Contingency coefficient analysis (Cross tabs procedure). Chi square test was used to test the nominal significance at the p value < 0.05 level, for high significance at the p value was < 0.01 and for not significant at the p value > 0.05. Descriptive statistics of the various clinical and laboratory parameters and measures of central tendency using the mean and median with standard deviation have been performed

VI. Results

A total of 2500 newborn were delivered in Kurji Holy Family Hospital from 1 December 2017 to 30 November 2018. Four hundred and eight newborns were excluded from the study because of lack of availability of data pertaining to TSH levels due to various reasons such as cord blood hemolysis, emergency deliveries and birth asphyxia.

The results obtained are as follows:
Total No. of Neonates and their Cord blood TSH levels included in the study

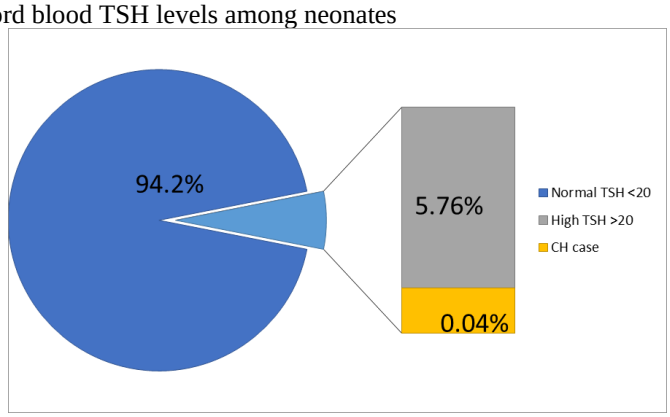
Cord Blood TSH levels

	Normal TSH	High TSH	CH Case
No. of Neonates	2500	144	1
Percentage	94.2	5.76	.04

Table representing of cord blood TSH levels among neonates A cut off of 20 mIU/L was used to consider cord blood TSH levels as low or high. Majority of the neonates (94.2%) had cord blood TSH levels of < 20 mIU/L and 5.76% of neonates had high cord blood TSH levels (> 20 mIU/L). However, when the TSH levels were repeated after 7days among those with high cord blood TSH levels, the TSH levels dropped down to normal levels except in 1 (0.04%) neonate, where the TSH levels was still high.

A significant higher number of babies had normal cord blood TSH values, which was expected because of the low prevalence of congenital hypothyroidism.

Graph representing of cord blood TSH levels among neonates



Gestational Age

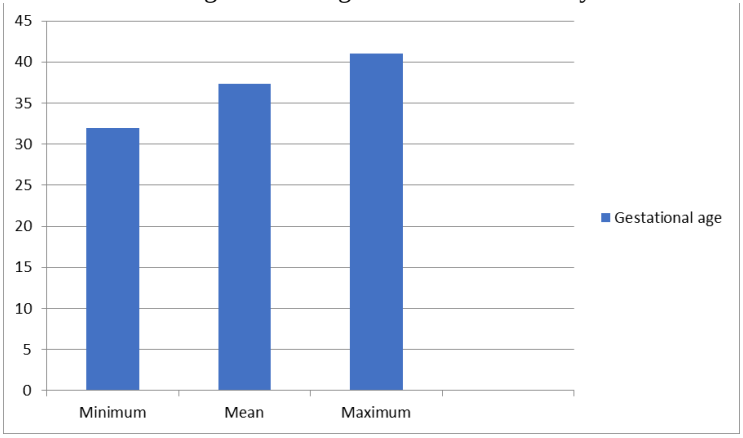
Table: showing minimum and maximum gestational age included in the study

	Minimum	Maximum	Mean	Median	Std. deviation
Gestational Age	32.00	41.00	37.5800	37.0000	.9670

The minimum gestational age included in the sample size was 32 wks and the maximum gestational age was 41 wks. The mean gestational age was 37.58 wks.

Table showing minimum and maximum gestational age included in the study

Chart showing minimum and maximum gestational age included in the study



The minimum cord TSH that was recorded in the data collected was 0.56 and the maximum was 436.64. The mean cord TSH level was 14.8809

Table: Cord Blood TSH level recorded in the study

Table: Cord Blood TSH level recorded in the study	Minimum	Maximum	Mean	Median	Std. Deviation
	0.56	436.64	14.8809	9.0700	31.4149

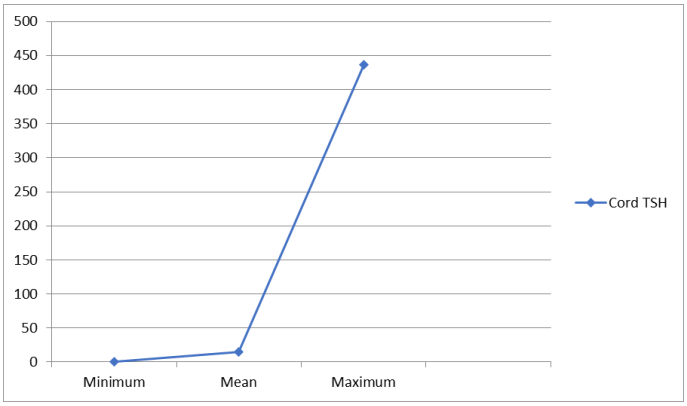


Table: Cord Blood TSH level according to gender

GENDER	CORD TSH		No. of patients N =2500	
	Normal (<20) % age	High (>20) % age	% age	
Male	1200 50.9	75 52.1	1275 1225	51 49
Female	1156 49.1	69 47.9		

X^2 =0.072

df =1 p = 0.77 R=NS

p>0.05

The total number of male taken in the study was1275 (51%) and the total number of female taken in the study was 1225(49%). Out of this 1200 male newborns and 1156 female newborns had normal cord blood TSH level.

High cord blood TSH level was recorded in 75 (52.1%) male newborns and 69 (47.9%) female newborns. A slight male predominance was noticed. However the p valve was >0.05 , not significant.

Table: Cord Blood TSH level according to gender

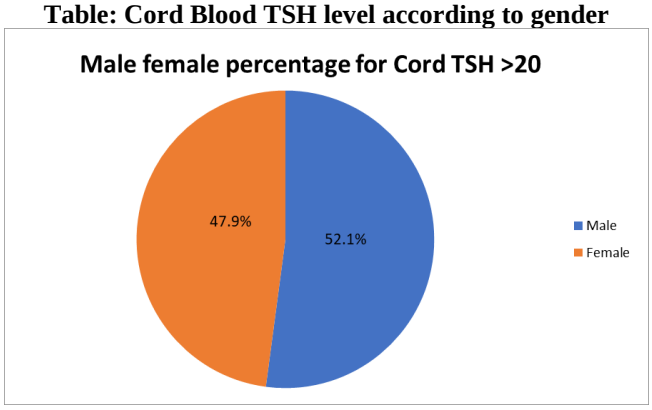


Table: Cord Blood TSH level according to Gestational Age

Gestational Age	CORD TSH				No. of patients N=2500	
	Normal (<20)	%	High (>20)	%		%
>37(Term)	1081	45.9	66	45.8	1147	45.9
34-37(Late Preterm)	1270	53.9	78	54.2		
<34(Preterm)	5	0.2	0	0	1348	53.9
					5	0.2

X^2 =0.0001

df=1 p=0.991 R=NS

p>0.05

Cord Blood TSH level was high in 45.8% of Term babies and 54.2% of preterm babies.

The p value was >0.05 which is non significant. No significant difference in cord blood TSH was noted between term (>37weeks), late preterm's(34-37 weeks) and preterms(< 34weeks).

Graph: Cord Blood TSH level according to Gestational Age

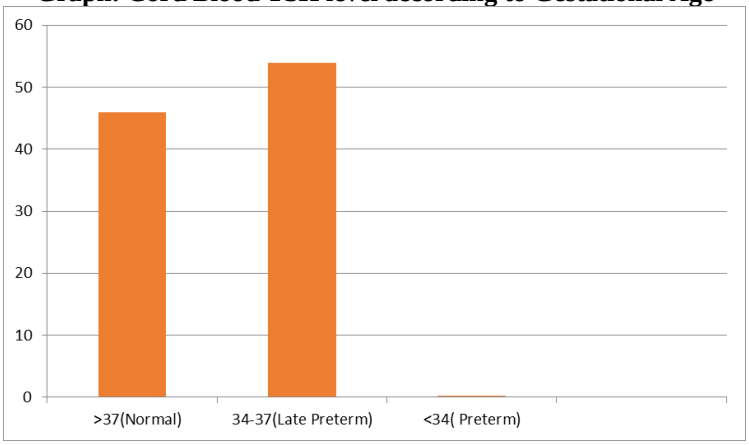


Table: Cord Blood TSH level according to birth weight

Birth Weight	CORD TSH				No. of patients N=2500	
	Normal (<20)	%	High (>20)	%		%
LBW	91	3.9	12`	8.3	103	4.1
Normal	2260	95.9	131	91	2391	45.6
VLBW	5	0.2	1	0.7	6	0.3

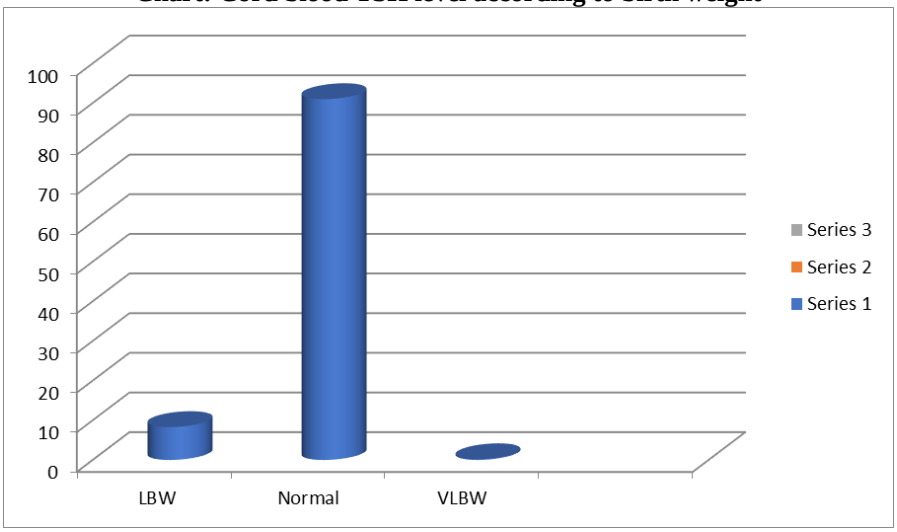
X^2= 6.87

df =1 p=0.009 R=SS

p>0.05

A significantly low correlation was seen between cord blood TSH and birth weight. It was significant at 1 % level.

Chart: Cord blood TSH level according to birth weight



Statistics: Comparision of Mean Cord TSH level according to Gestational Age

Gestational Age	Frequency	%	Mean	Std. Deviation	Minimum	Maximum
1)>37 (Normal)	1147	45.9	14.8903	32.3556	.56	436.64
2)34-37(Late Preterm)	1348	53.9	14.8988	30.6587	.56	
3)<34(Preterm)	5	0.2	7.8820	6.0488	1.99	328.58
						18.01

Pair	t- value	p- value	R
1,2	0.01	>0.05	NS
2,3	0.51	>0.05	NS
3,1	0.48	>0.05	NS

Statistics: Comparison of Mean Cord TSH level according to Gender

GENDER	Frequency	%	Mean	Std. Deviation	Minimum	Maximum
Male	1275	51	1225	32.2147	.56	436.64
Female	1225	49	5510	30.5698	.56	341.02

t- value = 1.82 p-value>0.05 R=NS

Statistics: Comparsion of Mean Cord TSH level according to gestational age and gender

Gestational Age	Gender	N	Mean	Std. Deviation	Minimum	Maximum
>37(Normal)	Male	583	15.7094	35.6601	.56	436.64
	Female	564	14.0435	28.5480	.56	341.02
34-37(Late preterm)	Male	689	14.7866	29.0750	.56	312.92
	Female	659	15.0162	32.2533	.57	328.58
<34(Preterm)	Male	3	10.2300	6.8472	5.12	18.01
	Female	2	4.3600	3.3517	1.99	6.73

Gestational Age	t- value	p- value	R
>37	0.87	>0.05	NS
34-37	0.14	>0.05	NS
<34	1.09	>0.05	NS

Statistics: Comparison of Mean Cord TSH level according to birth weight

BWT		N	Mean	Std. Deviation	Minimum	Maximum
1)	LBW	103	18.1445	40.4574	1.09	278.78
2)	Normal	2391	14.7092	30.9415	.56	436.64
3)	VLBW	6	27.2733	42.6053	2.67	113.36

Pair	t- value	p- value	R

1,2	1.08	>0.05	NS
2,3	0.99	>0.05	NS

STATISTICS: Comparision of Mean Cord TSH level according to Gestational age and birth weight

Gestational Age	BWT	N	Mean	Std. Deviation	Minimum	Maximum
1) >37(Normal)	LBW	2	10.1950	7.4600	4.92	15.47
	Normal	1145	14.8985	32.3825	.56	436.64
2) 34-37(Late preterm)	LBW	101	18.3019	40.8374	1.09	278.78
	Normal	1241	14.5620	29.6219	.56	328.58
	VLBW	6	27.2733	42.6053	2.67	113.36
3) <34(Preterm)	Normal	5	7.8820	6.0488	1.99	18.01

>37

	t-value	p- value	R
	0.21	0.05	NS

34-37

Pair	t- value	p- value	R
1,2	1.18	>0.05	NS
2,3	1.04	>0.05	NS
3,1	0.52	>0.05	NS

VII. Discussion

Cord blood TSH for screening for congenital hypothyroidism

Thyroid hormones are necessary for normal development of the human fetal brain n and the maturation of other organs. Insufficient production of thyroid hormones during the fetal and neonatal period may result in serious complications and the central nervous system is affected most. It plays an important role for myelination and for normal neuronal connections.[58] Cord blood TSH screening for CH is a simple and accessible procedure. Previous studies have shown a transient TSH surge in the first 24–48 hours of life.[59] However, the measurement of cord serum TSH for CH screening is well established.[60]

Walfish et al. suggested that cord TSH had a better specificity and sensitivity as compared with cord or filter paper T4 at 3–5 days of age.[6]

Fuse et al. showed that cord serum is a good sampling technique for screening CH.[52]

Mahachoklertwattana et al. showed that, if TSH is measured for screening CH, samples should be obtained from the umbilical cord of infants.[59]

In India, Singapore, Japan and Ethiopia, cord serum TSH levels have been used for neonatal screening for CH because of the difficulty of calling neonates back[4,5,20].

Newer TSH assay techniques, such as the enzyme-linked immunoassays, chemiluminescent assays and fluoroimmunoassays offer the advantages of using nonradioactive labels and greater sensitivity with the potential for better separation between normal and abnormal TSH concentrations. Thus, many screening programs are considering switching to a primary TSH approach. A majority of European and Japanese programs favor screening by means of primary TSH measurements, supplemented by T4 determinations for those infants with elevated TSH values.[58,61]

The neonatal serum FT4 levels rapidly increase after delivery to the maximum level at 1 day of age. Thereafter, they decline to a steady state level within 2–4 weeks. After a transient TSH surge in the first 24–48 hrs of life, neonatal serum TSH levels decline and the level at 1–3 days of age is similar to that of the cord serum.[52,62] It changes little after 3 days of age. Therefore, for those infants with initial cord blood TSH > 20mIU/L a repeat blood sample should be obtained after >48 hours. However, the trend towards early discharge of infants and mothers presents problems with this approach. This would result in an unacceptably high recall rate for this group of infants unless the TSH cutoff was adjusted for age. Experience using newer assays in a primary TSH screening approach, in a population of infants discharged early, is necessary to determine the effects on recall rates and the possibility of any false-negative test results.

Congenital hypothyroidism incidence

Incidence rates vary by race or ethnicity. Among Asian Indians, 1:1,200; Hispanic, 1:1,600; Asian (Chinese and Vietnamese), 1:2,380; non-Hispanic White, 1:3,533; and non-Hispanic Black, 1:11,000.[63] Incidence was higher in preterm, low birth weight babies: more than 2500 grams, 1:1843; 1500–2500g, 1:851; and less than 1500 grams, 1:396. Harris and Pass[58] reported a 23% increase in babies born weighing less than 1500 grams.[64] In this study 1 in 2053 infants was found to have congenital hypothyroidism.

Recall rates based on cord blood TSH cut off

In the United States, the recall rate after primary TSH screening is approximately 0.05%.[65]

In the study conducted by Azizi et al in Tehran and Damavand using cord blood samples for screening of CH, a recall rate of 1.06% was obtained with a TSH cutoff level of more than 20mIU/L,[66] whereas in Esfahan, the recall rate was approximately 2.2% after primary screening for serum TSH levels using the same Cutoff limit of 20mIU/L.[67]

These varying recall rates for different TSH cutoff levels may be because of several factors, such as the use of T4 or TSH level or both for screening, differences in sample-collection methods and analysis procedures in different laboratories, and differences in recall criteria, which are related to the cultural, regional, and social factors of a country.[4]

The recall rates in other countries, after primary TSH level assessment in neonates aged 3–5 days, may vary from 0.2% to 3.3%. The recall rates with TSH cutoff of more than 20mIU/L were 0.16% in the Philippines, 0.35% in Austria, 0.3% in Greece, 0.28–0.29% in Hungary, 2.3% in Turkey, and 3.3% in Estonia. In contrast, studies conducted in Italy, the recall rate measured on the basis of T4 levels was 2.5%, while that measured on the basis of both T4 and TSH levels was 0.11%.[68]

In this study, using only primary cord blood TSH for screening congenital hypothyroidism we had a recall rate of 6.23%. If the cutoff is raised to 40 mIU/L we would have a recall rate of 0.6%. Therefore, the laboratory screening methods and TSH cutoff level need to be revised to ensure more specific and sensitive CH screening.

Recent studies have shown a high prevalence of CH and high patient recall rate after primary screening, which was in line with the results of previous studies in Iran. Although environmental and genetic variations in addition to the low cutoff TSH level may be responsible for the high recall rate, a nationwide study is necessary to clarify the reasons for the high incidence of CH.

Future studies should also be able to clarify why small changes in TSH cutoff levels during screening lead to substantial changes in the number of neonates with undetected CH. The downside to lowering TSH cutoffs is an 7 increase in recall of infants with false positive tests. Each screening program needs to work out its own test cutoff, weighing increased detection of mild cases vs. harm from recall of normal infants. In our opinion, until there is good evidence of no intellectual impairment, we can come down on the side of detection and treatment of these milder cases.[63] The study of a birth cohort in Southern Spain revealed an impaired mental development at 4 years of age in children with higher neonatal TSH levels compared with children with lower neonatal TSH levels within the normal reference range. These findings indicate that a more thorough screening for neonatal thyroid deficiency is required to prevent long-term developmental effects. Further research is warranted into the influence on neurodevelopment of marginally altered TSH concentrations in newborns.[69]

Congenital hypothyroidism

CH was diagnosed if cord blood TSH > 20mIU/L and repeat serum TSH was above and fT4 was below the age appropriate cutoff. In this study, cord blood TSH level was investigated for 2500 infants. The missed cord blood was attributed to emergency deliveries, cord blood lysis, birth asphyxia. Of the 2500 infants, 144 infants had cord blood TSH > 20mIU/L. Repeat TSH levels were done on all infants on Day 7 of life. Of them only 1 infant was confirmed to have congenital hypothyroidism and were started on treatment.

Incidence and prevalence

CH prevalence has been found to differ among races and regions, with a higher prevalence among Asian neonates than among neonates of other regions.[17,70] The incidence of CH in live births varies from 1:3000 to 1:4000 in different parts of the world[71] and the incidence and prevalence of the disease is influenced by multiple environmental, genetic and autoimmune factors.[72] The one year incidence of hypothyroidism was estimated to be 1 in 895 live births,[72] whereas the corresponding rates in Tehran and Damavand were about 1 in 950.[66] In Isfahan a state in Iran, a study of 93381 neonates showed that the prevalence of CH was l in 349 live births.[73] The worldwide prevalence of CH is reported to be 1 in 3000–4000 live births.[74] The highest incidence of 1in 370 live births was noted in Isfahan state of Iran.[5]

Review of incidence of congenital hypothyroidism among Indian literature shows a high incidence of 1 in 600 in a study done at Kolkata.[20] Another study done in Mumbai showed an incidence of 1 in 2481[8] which is line with this study of 1 in 2053.

VIII. Conclusion

The present study adds emphasis on the need for continuing screening for the most important preventable cause of mental retardation. The infant diagnosed to have congenital hypothyroidism had no risk factors for the disease. Furthermore, both the infant, as with other children with congenital hypothyroidism had no signs or symptoms suggestive of the disease. It was the implementation of the screening program which helped to identify them and start treatment within the first 2 weeks of life. In India and other developing nations primary cord blood TSH followed by serum TSH and fT4 if cord blood TSH is above cutoff levels, seems to be the best cost effective and sensitive screening tool. This study showed a high recall rate of 6.23% when compared to other studies. The reason for the high recall rate was possibly a low cord blood cutoff levels. Screening for congenital hypothyroidism was taken up for the first time in our hospital. Hence a safe cutoff of level in order to prevent false negative cases was implemented.

One of the Indian study done in Kolkata also used the similar cutoff of 20 mIU/L and a high incidence of 1 in 600 prompting us to use the same cutoff for screening in our hospital. However from this study, it is evident that both the truly positive cases had a Cord TSH which was >200mIU/L.

The latest guidelines from the United States have also raised the Primary TSH cutoff to 100mIU/L if screened on the first day. It was also noted in this study that if we had raised the cutoff from 20-40mIU/L we would have a recall rate of 0.46% which is line with the global recall rates. Hence going forward it will be prudent to raise the cord blood TSH cutoff to 40mIU/L which will reduce the recall rate and increase the sensitivity and specificity of the program.

IX. Summary

1.In this study the incidence of congenital hypothyroisim was noted to be 1 in 2500 live births.
2. The infant with congenital hypothyroidism were delivered at term with no risk factors such as low birth weight, maternal age or gestational age.
3. Primary cord blood TSH as a screening tool is ideal for the setup in developing countries where the discharges take place early.
4. No significant difference in cord blood TSH levels between infants born preterm and term.
5. Low cord blood TSH cutoff levels were probably one of the reasons for a high recall rate of 6.2%.
6. Raising the cord blood TSH cutoff from 20 to 40 mIU/L reduced the recall rate by 90 percent.

X. Recommendations

1. Primary cord blood TSH as a screening tool is ideal for the setup in developing countries where the discharges take place early.
2. No significant difference in cord blood TSH levels between infants born preterm and term.
3.Early detection of congenital hypothyroidism and early initiation treatment shall prevent mental retardation.
4. The study reinforces the importance of cord blood TSH values as an important screening tool for early detection of CH because of its simplicity and accessibility and avoid consent for blood sampling for TSH levels.

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