Review Article

Congenital hypothyroidism

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ABSTRACT

Congenital hypothyroidism (CH) is the one of the most common preventable cause of mental retardation. In the majority of patients, CH is caused by an abnormal development of the thyroid gland (thyroid dysgenesis) that is a sporadic disorder and accounts for 85% of cases and the remaining 15% of cases are caused by dyshormonogenesis. The clinical features of congenital hypothyroidism are so subtle that many newborn infants remain undiagnosed at birth and delayed diagnosis leads to the most severe outcome of CH, mental retardation, emphasizing the importance of neonatal screening. Dried capillary blood is used for screening and it is taken from heel prick optimally between 2 and 5 days of age. Blood spot TSH or thyroxine (T4) or both are being used for CH screening in different programs around the world. Neonates with abnormal thyroid screening tests should be recalled immediately for examination and a venipuncture blood sample should be drawn for confirmatory serum testing. Confirmatory serum should be tested for TSH and free T4, or total T4. Serum TSH and T4 undergo dynamic changes in the first weeks of life; it is important to compare serum results with age-normal reference ranges. Treatment should be started promptly and infant should be rendered euthyroid as early as possible, as there is an inverse relationship between intelligence quotient (IQ) and the age at diagnosis. Levothyroxine (l-thyroxine) is the treatment of choice and American academy of pediatrics and European society of pediatric endocrinology recommend 10-15μgm/kg/day as initial dose. The immediate goal of therapy is to normalize T4 within 2 weeks and TSH within one month. The overall goal of treatment is to ensure growth and neurodevelopmental outcomes as close as possible to their genetic potential.

Key words: Dyshormonogenesis, Levothyroxine, neonatal screening

Introduction

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder in childhood and also is one of the most common preventable causes of mental retardation. After making diagnosis if the treatment is started within in a few weeks of birth, neurodevelopmental outcome is generally normal.[1] The clinical features of congenital hypothyroidism are often subtle and many newborn infants remain undiagnosed at birth.[2] This is due in part to passage of maternal thyroid hormone across the placenta providing a protective effect, especially to the fetal brain and masking the clinical signs.[3] Also, even the most common forms of CH have some moderately functioning residual thyroid tissue[4] making clinical diagnosis difficult. Within few weeks of birth as hypothyroxinemia progresses clinical signs and symptoms of hypothyroidism become more obvious and put neonatal brain at risk of irreversible injury. Because of this danger, it is important to start treatment as soon as possible after birth. For all of the above reasons, screening has become the best way to detect infants with CH in many parts of the world. Pilot screening programs for CH were developed in Quebec, Canada and Pittsburgh, Pennsylvania in 1974 and have now been established in Western Europe, North America, Japan, Australia and parts of Eastern Europe, Asia, South America and Central America.[5,6] As Indian data are lacking, In North America, more than 5 million newborns are screened and approximately 1400 infants with CH are detected annually.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.131748

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Epidemiology

The overall incidence of CH ranges from 1 in 3000 to 1 in 4000 newborn infants.[7,8] The incidence of CH is higher in Hispanic and Asian individuals and lower in black individuals.[8] There is a 2:1 greater incidence in females compared with males and there is an increased risk in infants with Down's syndrome. In India, the prevalence has been reported to be 1 in 2640 in screening 40,000 newborn.[9] In 2007, Harris and Pass reported that the incidence (birth prevalence) of CH detected by newborn screening programs in the United States had nearly doubled over the previous two decades, increasing from 1:3985 (in 1987) to 1:2273 (in 2002).[10] Over the years described above, there has been a 37% increase in Asian births and a 53% increase in Hispanic births in the United States.[11] The exact cause of this increase in incidence is not known but factors that may be implicated include changes in screening methods (lower TSH cutoff), obtaining the screening specimen earlier (closer to the TSH surge after birth) [Table 1].

Etiology

In the majority of patients, CH is caused by an abnormal development of the thyroid gland (thyroid dysgenesis) which is usually a sporadic disorder and accounts for 85% of cases. It presents in three major forms i.e. thyroid ectopy, athyreosis and thyroid hypoplasia. Thyroid ectopy accounts for two thirds of cases of thyroid dysgenesis and is twice more common in females.[12] The exact etiology of thyroid dysgenesis is not known. However; mutations in transcription factor genes that regulate thyroid gland development [thyroid transcription factor 2 (TTF-2), NKX2.1 (also termed TTF-1) or PAX-8] would explain these defects. But, only 2% of cases with thyroid dysgenesis are found to have such genetic mutations.[13] For the remaining one-third of cases, CH results from absence of thyroid (athyrosis) and thyroid hypoplasia. Hereditary inborn errors in the enzymatic cascade of thyroid hormone synthesis, also called dyshormonogenesis, or to defects in peripheral thyroid hormone transport, metabolism, or action are accounted in approximately 15% of cases.[14] Defects in thyroid hormone biosynthesis are familial, generally inherited in an autosomal recessive manner.[15] These include mutations in the genes coding for the sodium-iodide symporter, thyroid peroxidase, hydrogen peroxide generation [thyroid oxidase and dual oxidase maturation factors (THOXand DUOXA)], thyroglobulin (Tg) and iodotyrosine deiodinase. Defects in thyroid hormone transport (mutations in the gene for monocarboxylase transporter 8), metabolism (selenocysteine insertion sequence-binding protein 2), or resistance to thyroid hormone action (mutations in the thyroid hormone receptor) are some rare causes. Of these several defect, mutations in thyroid peroxidase (TPO) gene are the most prevalent causes of inherited defects in CH.[16] Secondary congenital (central) hypothyroidism may be isolated which results from mutation in thyroid stimulating hormone β (TSHβ) subunit gene or TRH receptor gene. More often it is associated with congenital hypopituitarism, which may be due to mutation in transcription factor gene regulating pituitary development i.e. HESX1, LHX4, PIT1 and PROP1.

Transient CH in newborn may be due to maternal thyrotropin receptor-blocking antibodies, exposure to maternal antithyroid medications, iodine deficiency and iodine excess.

Table 1: Etiology of CH*

Primary CH
Thyroid dysgenesis
Aplasia
Hypoplasia
Ectopic gland
Thyroid dyshormonogenesis
Sodium-iodide symporter (trapping) defect
Thyroid peroxidase defect
Hydrogen peroxide generation or maturation defects
Tg defect
Deiododinase defect
Resistance to TSH binding or signaling
TSH receptor defect
G protein defect
Secondary (central) CH
Isolated TSH deficiency
Congenital hypopituitarism (multiple pituitary hormone deficiencies)
Peripheral CH
Thyroid hormone transport defect (monocarboxylase transporter 8)
Thyroid hormone metabolism defect (selenocysteine insertion sequence-binding protein 2)
Thyroid hormone resistance
Transient CH
Maternal or neonatal excess iodine exposure
Maternal or neonatal iodine deficiency
Maternal antithyroid drugs
Maternal TRB-Ab
Heterozygous THOX2 or DUOXA2 mutations
Congenital hepatic hemangiomas

*LaFranchi. Approach to the Diagnosis and Treatment of Neonatal Hypothyroidism. J Clin Endocrinol Metab. 2011 Oct; 96(10):2959-67. doi: 10.1210/jc. 2011-1175.
CH: Congenital hypothyroidism, TSH: Thyroid stimulating hormone

Diagnostic evaluation

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.[17] For the remaining 75% infants, particularly concentrated in developing countries, clinical suspicion of hypothyroid leads to thyroid function evaluation.

Newborn thyroid screening protocols

Newborn thyroid screening tests are carried out before discharge from hospital, optimally between 2 and 5 days

of age. Specimen collected before 48 h of age may lead to false positive result. Screening of very sick newborn or after blood transfusion may lead to false negative result.

In a critically ill infant or preterm neonate, or in case of home delivery, blood sample should be collected by 7 days of age. Capillary blood samples from heel prick are placed on circles of specialize filter paper, dried at room temperature, then sent to a centralized laboratory. Some programs obtain a routine second specimen between 2 and 6 week of age. The additional incidence of CH based on a second screening at 2 weeks of age is approximately 1 in 30 000.[18,19]

Earlier for screening of newborn for CH, most programs undertook an initial T4 test, followed by TSH testing if the T4 value falls under a cut off limit. With increasing accuracy of TSH assays on small blood volumes, many screening programs now have switched to an initial TSH test approach to detect CH.[20] Each program should develop its own T4 and TSH cut off for test result. Both methods allow detection of the majority of infants with CH but each approach has its own advantages and disadvantages. The initial T4 then follow up TSH approach will detect some cases of secondary or central hypothyroidism and infant with "delayed TSH elevation". On other hand initial TSH approach will detect mild or subclinical forms of hypothyroidism. Generally, if the screening T4 value is below the 10th percentile of cut off and/or the TSH is greater than 30mU/liter (15mU/liter whole blood), an infant should be recalled for confirmatory serum testing. In cases with "intermediate results," e.g. low T4 but TSH below cutoff, a program may recommend that a repeat heel prick screening specimen be collected and sent for analysis [Table 2].

Confirmatory serum thyroid testing

Diagnosis and treatment should not be based on screening test results alone. Neonates with abnormal thyroid screening tests should be recalled immediately for examination and a venipuncture blood sample should be drawn for confirmatory serum testing. Confirmatory serum should be tested for TSH and free T4, or total T4 combined with some measure of binding proteins such as a T3 resin uptake. Serum TSH and T4 undergo dynamic changes in the first weeks of life; it is important to compare the serum results with age-related reference values.[21] In the first few days of life, serum TSH can be as high as 39mU/L, because of the TSH surge that is normally seen after birth. Most confirmatory serum tests are obtained within one to two weeks of age, when the upper TSH range has fallen to an approximately 10mU/liter. Although levels of all hormones are higher at 1-4 days of age, by 2-4 weeks of age they have fallen closer to the levels typically seen in infancy.

Table 2: Relative TSH and FT4 Reference Ranges during Gestation and Childhood; LBW, Low Birth Weight*

Age	TSH child/ adult ratio	TSH ranges mIU/L	FT4 child/ adult ratio	FT4 ranges pmol/L (ng/dL)
Midgestation fetus	2.41	0.7-11	0.2	2-4 (0.15-0.34)
LBW cord serum	4.49	1.3-20	0.8	8-17 (0.64-1.4)
Term infants	4.28	1.3-19	1	10-22 (0.8-1.9)
3 days	3.66	1.1-17	2.3	22-49 (1.8-4.1)
10 weeks	2.13	0.6-10	1	9-21 (0.8-1.7)
14 m	1.4	0.4-7.0	0.8	8-17 (0.6-1.4)
5 years	1.2	0.4-6.0	0.9	9-20 (0.8-1.7)
14 years	0.97	0.4-5.0	0.8	8-17 (0.6-1.4)
Adult	1	0.4-4.0	1	9-22 (0.8-1.8)

*Fisher DA, Nelson JC, Carlton Ei and Wilcox RB. Maturation of human hypothalamic-pituitary-thyroid function and control. Thyroid 2000;10:229-34

Test Results

Low T4 and elevated TSH values

A low total T4 or free T4 level in the presence of an elevated serum TSH level confirms the diagnosis of primary hypothyroidism. Replacement therapy with levothyroxine (L-T4) should be initiated as soon as confirmatory tests have been drawn before the results of the confirmatory tests are available. Infant with an elevated serum TSH level and a normal free T4 or total T4 is consistent with the diagnosis of subclinical hypothyroidism.

Normal T4 and elevated TSH values

Infant with an elevated serum TSH level and a normal free T4 or total T4 have either a transient or permanent thyroid abnormality[22] or delayed maturation of the hypothalamic-pituitary axis. There is controversy regarding the need for L-T4 therapy in this setting. As TSH concentration is the most sensitive indicator of hypothalamic-pituitary- thyroid axis. A persistent basal TSH concentration higher than 10mU/L (after the first 2 weeks of age) is considered to be abnormal.[23] Therefore, if the TSH elevation persists, the infant should be treated. If such infants are not treated, measurement of FT4 and TSH should be repeated at 2 and 4 weeks and treatment should be initiated promptly if the FT4 and TSH concentrations have not normalized.

Low T4 and normal TSH values

The low T4 with normal TSH profile may result from hypothalamic immaturity particularly in preterm infants, during illness, in central hypothyroidism or in primary hypothyroidism and delayed TSH elevation. There are no clear-cut guidelines regarding follow-up of such patient, to follow-up with serial filter-paper screening tests until the T4 value becomes normal, or to request a second blood sample for measurement of FT4 and TSH. Most infants

with low T4 and normal TSH have normal FT4 values and the subsequent thyroid function test results are normal. Treatment of these infants (with the exception of those with central hypothyroidism) with L-T4 has not yet been shown to be beneficial.[24]

Diagnostic studies to determine an underlying etiology

Once the diagnosis of CH is confirmed, treatment should never be delayed pending the determination of etiology. Additional studies to determine the underlying cause may be done. But these studies are complimentary as these diagnostic studies do not alter treatment decision [Figure 1].

Thyroid radionuclide uptake and scan

Thyroid radionuclide uptake and scanning are the most accurate imaging tests to define the size and location of any thyroid tissue. Preferred tracer in neonate is Iodine-123 (I-123) or sodium pertechnetate 99m (Tc99m) as I-131 delivers too high a dose of radioactivity to the thyroid and total body. Radionuclide uptake and scan may identify thyroid aplasia (absent uptake), hypoplasia (decreased uptake, small gland in a eutopic location) or an ectopic gland. Absence of uptake can also be seen with TSHb gene mutations, TSH receptor inactivating mutations, iodide trapping defects and with maternal thyrotropin receptor blocking antibodies (TRB-Ab).

A large gland in a eutopic location with increased uptake is compatible with one of the dyshormonogeneses beyond trapping of iodide. a perchlorate discharge test can be performed to confirm this dyshormonogenic CH.

Thyroid ultrasound

Thyroid ultrasound can confirm thyroid aplasia when radionuclide scan showed absent uptake. Detection of thyroid gland in the normal position with absence of radionuclide uptake is suggestive of TSHβ gene mutations, TSH receptor inactivating mutation, iodide trapping defect and maternal TRB-Ab. Large thyroid in ultrasound and absent uptake in radionuclide scan suggestive of dyshormonogenesis. Although Ultrasonography is not as accurate as radionuclide scan in demonstrating ectopic glands but studies have suggested that color Doppler flow can detect up to 90 present of cases of ectopic thyroid.[25]

Serum thyroglobulin (Tg) measurement

Serum Tg level reflects thyroid mass and is generally raised with increased thyroid activity. In a recent study, Beltrão *et al.*, suggested that color Doppler ultrasound and serum thyroglobulin measurement are as valuable combined tools to diagnosis the cause of CH and also allow limitation of more harmful exams in children, like radionuclide scan.[26] In case when thyroglobulin levels are increased and radionuclide scan shows absent uptake, it suggests

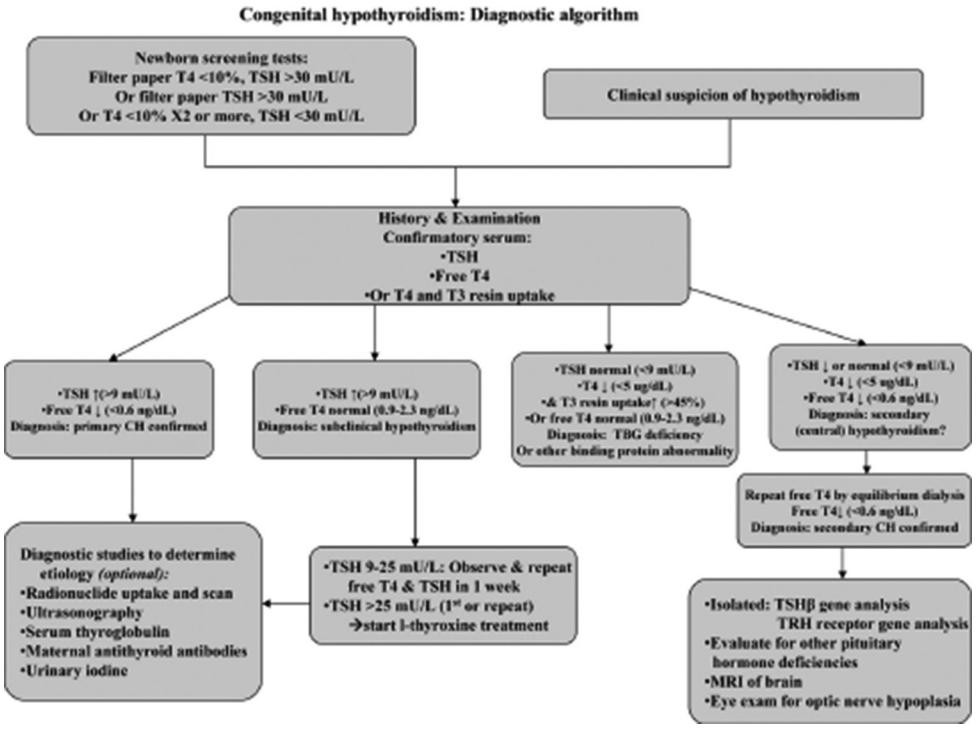

Figure 1: Diagnostic algorithm for congenital hypothyroidism. Note that each screening program sets its own T4 and TSH cutoffs. The results for serum TSH, free T4, T4 and T3 resin uptake are typical for neonates around 2 week of age. It is important for clinicians to compare serum results to age-normal reference ranges for their specific laboratory. *LaFranchi. Approach to the Diagnosis and Treatment of Neonatal Hypothyroidism. J Clin Endocrinol Metab 2011 Oct;96(10):2959-67. doi: 10.1210/jc.2011-1175

that thyroid gland is present and neonate may have a TSH receptor inactivating mutation[27] a trapping defect, or maternal TRB-Ab, rather than aplasia.

Thyroid receptor antibody

Maternal thyroid receptor blocking antibodies (TRB-Ab) can cause triansient CH in newborns. In a small or normal sized eutopic glandabsent radionuclide uptake suggestive of transplacental passage of maternal TRB-Ab causing transient congenital hypothyroidism. It can be confirmed by measurement of serum TRB-Ab in mother and/or infant by a TBII (thyrotropin-binding inhibitor immunoglobulin) test.

Urinary iodine estimation

24 h urinary iodine excretion approximates daily iodine excretion.

The normal range in neonates is approximately 50 to 100mg/24h. Measurement of urinary iodine may confirm iodine deficiency or excess.

Management

As stated above CH is the most common preventable cause of mental retardation. Studies have shown that both the timing and dose of thyroid hormone replacement are important for neurological outcome. Treatment should be started promptly and infant should be rendered euthyroid as early as possible, as there is an inverse relationship between intelligence quotient (IQ) and the age at diagnosis.[28] Even if diagnosed early, neurologic outcome may be ill and this deficit may be due to later onset of treatment, lower starting thyroid hormone dosing and severity of the hypothyroidism, which itself correlates with the underlying etiology.[29]

Formulation

Levothyroxine (l-thyroxine) is the treatment of choice. Although triiodithyronine (T3) is the biologically active but most brain T3 is derived from local monodeiodination of T4 and studies have shown normal serum level of T3 in infant treated with T4 alone,[30] so T3 treatment is not necessary for normal neurological outcome/brain development. Currently, only tablets forms are approved for use in the United States. However, in Europe, l-thyroxine suspension is available and is used to normalize thyroid function. Currently, only tablet forms of levothyroxine is available in India.

Administration

Levothyroxine (l-thyroxine) tablet is crushed and mixed with breast milk, formula or water and resultant suspension is squirted into cheek pad or can put on open nipple for infant to feed. Various substances interfere Levothyroxine (l-thyroxine) absorption through gut, such as calcium and iron preparation, soy protein formula, sucralfate, aluminium hydroxide and cholestyramine should not be given together. Although, recommendation is to take Levothyroxine (l-thyroxine) empty stomach but for infant it may not be possible.

Dosages

The goal of therapy is to normalize T4 within 2 weeks and TSH within one month. In one study infants who took longer than 2 weeks to normalize thyroid function had significantly lower cognitive, attention and achievement scores than those who achievement scores than those who achieved normal thyroid function at 1 or 2 weeks of treatment.[31] As an optimal neurological development depends on both adequacy and timing of treatment, American academy of pediatrics and European society of pediatric endocrinology recommend 10-15 μgm/kg/day as initial dose.[32] Studies show that this dose normalizes serum T4 within 3 days and TSH within 2-4 weeks. Initial LT4 dose and rapid normalization of serum T4 are critical to the optimal neurodevelopmental outcome. In severe CH, it is important to start higher initial dose of the recommended range to achieve these goals. In one study infants who started on higher initial doses 50μgm had full-scale IQ scores 11 points higher than those started on lower initial doses 37.5 μgm.[31]

Target concentrations

Guidelines of American academy of pediatrics[33] and European society for pediatric endocrinology[34] recommend that T4 concentrations should be kept in the upper half of reference range. Target values for T4 are 10-16 μgm/dl; FT4 1.4-2.3ng/dl and TSH <5 μU/dl (optimally 0.5-2.0 μU/dl) for first 3 years of life. Thereafter, T4 should be kept in the upper half of normal range.

One study showed lower IQ in infants with T4 concentration below 10 μgm/dl during first year of life along with TSH above 15 μU/dl compared with those having T4 concentrations more than 10 μgm/dl.[35] Higher doses of Levothyroxine (l-thyroxine) have been associated with better intellectual outcome in children with CH.[36]

However, some studies have shown that higher doses of Levothyroxine may result in behavior problems like increased anxiety, social withdrawal and poor concentration at age of 8 years demonstrating thus potential dangers of overtreatment with levothyroxine in CH children.[37]

Follow up

Infants with CH are at increased risk of developing congenital anomaly (10% in CH compare to 3% in

general population) most commonly cardiac malformation pulmonary stenosis, atrial septal defect and ventricular septal defect. The treating physician must monitor thyroid function tests at intervals frequent enough to ensure timely adjustment of thyroid hormone dosing so as to keep the serum free T4 or total T4 and TSH levels in the target ranges. The American Academy of Pediatrics recommends the following monitoring schedule.[33]

- At two and four weeks after the initiation of l-thyroxine treatment
- Every 1-2 m during the first 6 m of life
- Every 3-4 m between 6 m and three years of age
- Every 6-12 m thereafter until growth is complete
- Four weeks after any change in dose or more frequently if results are abnormal or non-compliance is suspected.

Clinical evaluation can be carried out at less frequent intervals than laboratory evaluation. The overall goal of treatment is to ensure growth and neurodevelopmental outcomes as close as possible to their genetic potential.

Unresolved controversy

The incidence of congenital hypothyroidism appears increasing over the last 20 years. Whether the increase real, or is it the result of lowering of screening test cutoffs, changes in the racial/ethnic population, an increase in preterm births, or something else causing an increase in CH cases is not clear. It is also unclear whether the additional infants now being detected, including those with mild hypothyroidism and those with "delayed TSH rise" will have permanent or transient hypothyroidism. As stated above most common cause of CH is thyroid dysgenesis, but the underlying etiology of thyroid dysgenesis is largely unknown. Only 2 percent cases of thyroid dysgenesis caused by genetic mutation in genes that encode for thyroid transcription factors.

There is also uncertainty concerning permanent vs transient CH during monitoring. We need studies in affected infants detected by abnormalities on a second screening test, to confirm whether or not these infants have transient or permanent hypothyroidism.

Health economics

Public health agencies should seriously consider implementing screening programme for congenital hypothyroidism in India. A study has shown cost-effectiveness of the programme in UK.[38] In 1995 a report from USA declared a 10 fold cost benefit of screening of CH. In France cost benefit ratio of CH screening was found to be 1:12.[39] In developing country like Iran new born screening programme for CH is quite effective and successful.

Conclusion

Congenital hypothyroidism (CH) is one of the most common preventable cause of mental retardation. The best way to detect infants with CH is by screening large populations of newborns. If the diagnosis is made and treatment started within a few weeks of birth, neurodevelopmental outcome generally is normal. The etiology of the most common cause of CH, thyroid dysgenesis, is largely unknown as the increase incidence of CH.

Take home massage

New born screening for congenital hypothyroidism has been included in neonatal screening programmes in the developed world and is considered as a major achievement in preventive medicine. But still more efforts required to create awareness regarding significance of preventive testing to include CH screening in national screening programme in India.

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Cite this article as: Agrawal P, Philip R, Saran S, Gutch M, Razi MS, Agroiya P, *et al.* Congenital hypothyroidism. Indian J Endocr Metab 2015;19:221-7.

Source of Support: Nil, **Conflict of Interest:** None declared.