Review Article

# The Consensus on the Diagnosis and Management of Congenital 2 Hypothyroidism in Term Neonates

**Abstract**

Congenital hypothyroidism (CH) is one of the most treatable endocrine disorders in infants and children that can influence the function of many organs in the body. On-time diagnosis and treatment can prevent the adverse effects of thyroid hormone deficiency on the child's neurodevelopment. There are many challenges in screening, post-screening, diagnosis, and managing this disorder. Therefore, this article aimed to mention updated information on this issue. Although there are different approaches for the treatment of hypothyroidism, the authors decided to create a national approach based on the conditions of our country.

**Keywords:** *Congenital hypothyroidism, infant, newborn*

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## Introduction

Congenital hypothyroidism (CH) is one of the most common treatable disorders. If not treated appropriately, it could have many adverse effects on the child's neurodevelopment.[1,2] Most neonates born with CH may be missed due to normal appearance and no detectable physical signs.[3] Despite the on-time diagnosis and proper treatment, deterioration in neurodevelopmental outcomes might occur due to missed diagnosis and interpretation of laboratory tests.[4]

## Screening of CH in Term Neonates

Despite the limited observations, screening newborns for congenital hypothyroidism seems logical because it is a cost-effective strategy that provides maximum health improvement, especially in countries with limited resources.[5] There are different screening strategies for CH worldwide.[3] Based on the diversity of screening programs in other countries, only thyroid stimulating hormone (TSH) or T4 plus TSH should be measured.[3,6,7]

The prevalence of primary congenital hypothyroidism and central hypothyroidism is 1 in 3000–4000 and 1 in 11000–100000 live births, respectively.[8] In Iran, the prevalence of primary congenital hypothyroidism is estimated to be 1 in 1100–1400 live births.[9-11]

Although T4 is a sensitive screening test, it has a high frequency of false-positive mainly in low birth weight and premature infants.

Therefore, due to the low incidence of central hypothyroidism, screening newborns with only TSH is the most sensitive screening test.[3] It is noteworthy that clinicians screen patients with free T4 (FT4) plus or followed by TSH in case of financial approval. By this protocol, central hypothyroidism and thyroid-binding globulin (TBG) disorders could not be missed.[3,12]

In countries with economic difficulties, clinicians recommend screening of T4 and TSH in all neonates with the following conditions:

- A familial history of central CH
- Signs or symptoms of hypopituitarism such as micropenis with undescended testes, hypoglycemia, prolonged jaundice, or unexplained failure to thrive.
- Dysmorphic and mid-facial abnormality and cleft lip and palate.

## Post-Screening Conditions

### Who are the appropriate candidates for the second screening test?

The exact characteristics of the second screening for hypothyroidism in infants have been updated over time.[13-15]

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Generally, a second screening is performed on the following neonates:

Preterm neonates, birth weight <2500 g, low and very low birth weight neonates, birth weight >4000 g, history of hospitalization due to non-thyroidal illness, history of blood transfusion, TSH of 5-9.9 in first screening test, insufficient sampling, history of taking corticosteroid and dopamine, iodine exposure in mother and neonate, same-sex twins, multiple births, gestational age >40 weeks, history of thyroid disease and diabetes in mothers, administration of steroid, amiodarone, and dopamine to the mothers, congenital heart disease in the neonate, DOWN syndrome, other malformations and syndromes, and hemangioma. It is better to have a monthly hypothyroidism screening in patients with hemangioma for a year. It is better to have a hypothyroidism screening at least for the first month and every 6 to 12 months until three years of age in patients with Down syndrome due to an extra chromosome 21[16-18] that causes thyroid damage.

## Second Screening Time

The second screening must be performed at 2, 6, and 10 weeks after birth. Recently, it has been recommended that in case of normal results at four to six weeks of age in preterm infants born at >33 weeks of gestation, no further screening is required. For infants born <33 weeks of pregnancy, it may be prudent to perform other screening tests until they reach term-corrected (37 weeks) gestation.[19] Although second screening at 2, 6, and 10 weeks is recommended in many countries, further investigation is needed to assess the necessity of the 10$^{th}$-week of screening.[20]

## Normal Range of FT4 and TSH

The authors had previously published a guideline for premature neonates[21] to avoid clinicians' confusion due to differences in the normal range of FT4 based on different gestational ages. Fortunately, the guideline indicated a specific range of FT4 (between 0.8 and 2.6 ng/dl) in premature neonates. However, there is still confusion regarding hypothyroidism in term infants despite a certain age. Therefore, the same reference range of FT4 (0.8 and 2.6) of premature neonates is accepted in this guideline.[22]

## Guideline of Treatment

The treatment guideline is similar in preterm and term neonates, except when TSH is between 6- 10 mIU/L, and FT4 is low. In this case, FT4 and TSH should be repeated two weeks later in preterm and term neonates. In addition, in term neonates, the pituitary axis, especially the adrenal axis, should be checked and treatment started. Treatment based on various types of TSH is summarized in Table 1 and Figure 1.

## Evaluation of Central Hypothyroidism

As Figure 2 shows, low-dose (LD) ACTH is usually given to diagnose central hypothyroidism. Clinicians have to measure cortisol, inject one microgram of ACTH intravenously, and measure cortisol again 30 and 60 min later.

It should be noted that cortisol is naturally low in infants. Still, increased cortisol to above 18 μg/dL is valuable because the interpretation of the LD ACTH test is challenging in neonates. Investigators believe that in central hypothyroidism, first clinicians should blindly give low-dose hydrocortisone for at least 48 hrs, then start levothyroxine and finally taper the drug dose over time. Others believe in performing a low dose ACTH test for the patient to check the adrenal axis.

To evaluate congenital hypothyroidism, clinicians should do a low dose of ACTH test if they had an abnormal test (cortisol level less than 18 μg/dL in stimulation with one microgram of ACTH). Hydrocortisone is recommended

**Table 1: Guideline of treatment in term and premature neonates**

| | |
|---|---|
| TSH >20 mIU/L with any level of FT4 | Treatment should be started in premature and term neonates. |
| >10 TSH <20 mIU/L with low FT4 | Treatment should be started in premature and term neonates. |
| >10 TSH <20 mIU/L and normal FT4 | TSH should be rechecked after two weeks in premature and term neonates. If TSH was still above 10 mIU/L, treatment should be started. In premature infants, if TSH was less than 10 mIU/L, it should be rechecked 6 and 10 weeks later. |
| 6< TSH <10 mIU/L and low FT4 | The FT4 and TSH should be rechecked in premature neonates after two weeks. If it still had the same result, treatment should be started with suspicion of central hypothyroidism. Clinicians should evaluate the pituitary axis, especially the adrenal axis, but whenever TSH was above 10 mIU/L, treatment should be started with suspicion of primary hypothyroidism. If free T4 was low in 3-6 weeks and there was normal TSH without any reason, treatment should be restarted in term neonates. |
| Normal FT4 and TSH in premature neonates | TSH and FT4 should be rechecked at 6 and 10 weeks. |
| 6< TSH <10 mIU/L and normal FT4 | Premature and term patients should be referred to pediatric endocrinologists, and treatment should be started based on the clinical symptoms and ultrasound by an endocrinologist. In the lack of access to a pediatric endocrinologist, free t4 and TSH should be measured until reaching the normal range. The increasing trend of TSH needs treatment as well. |
| TSH <6 mIU/L with normal T4 or free T4 | Follow-up should be done in premature and term neonates. |
| Persistent TSH >10 mIU/L at six weeks of age | Treatment |

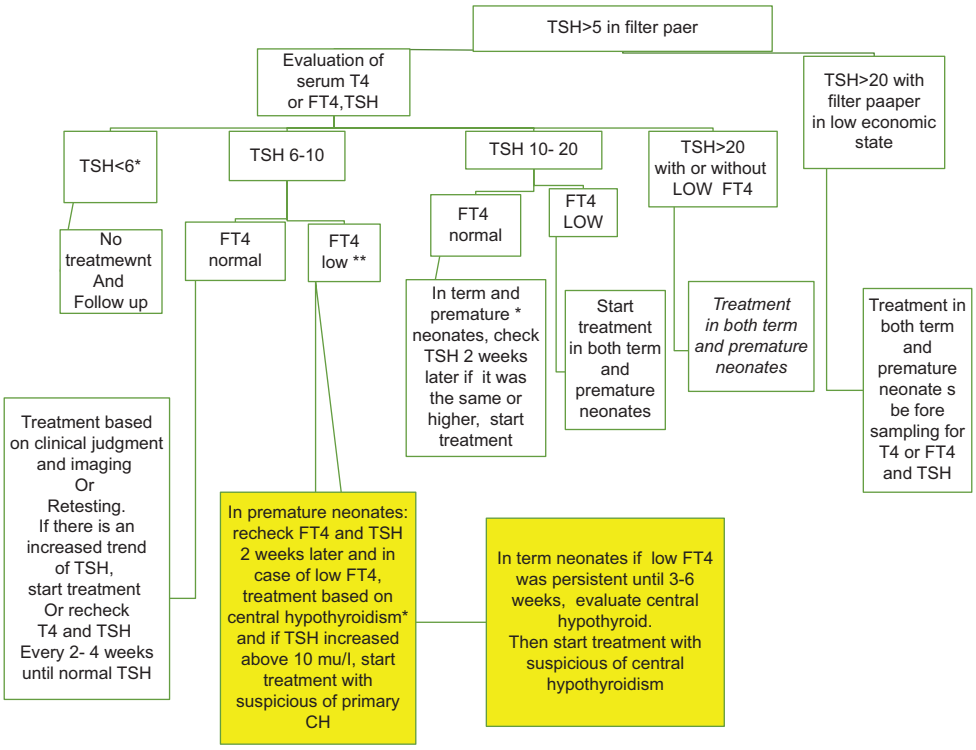


**Figure 1: Guideline of treatment in term and premature neonates. *In premature neonates, tests should be rechecked at 2, 6, and 10 weeks despite normal laboratory tests. **The only difference between term and premature neonates**

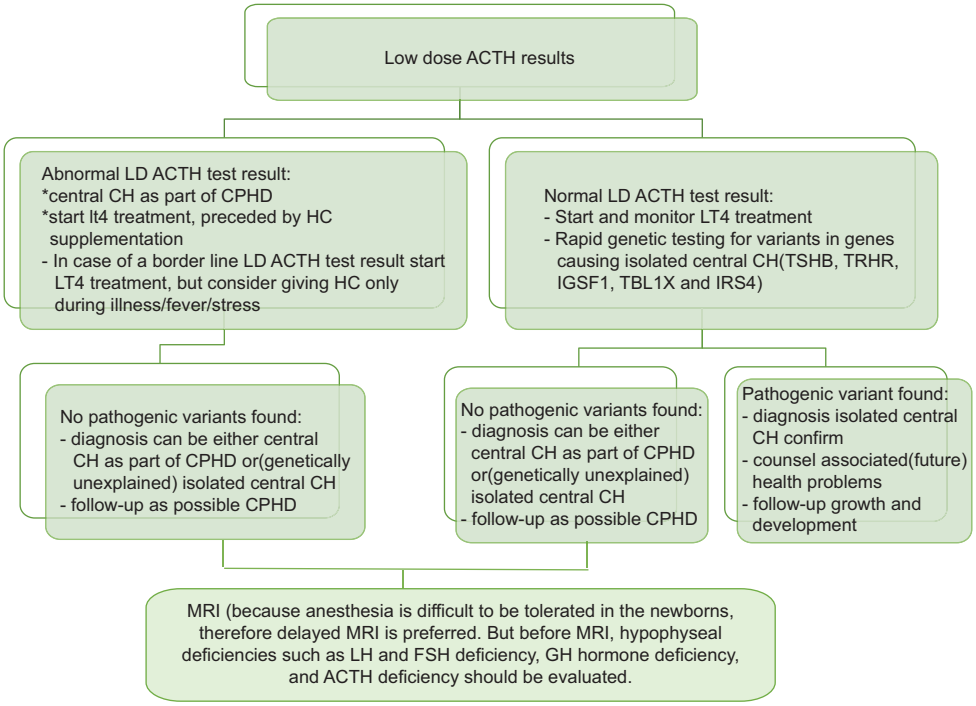


**Figure 2: Evaluation of central hypothyroidism by low dose ACTH results. CH: Congenital hypothyroidism. HC: Hydrocortisone**

before starting treatment with levothyroxine. However, sometimes in moderate deficiency, only hydrocortisone is recommended under stress.

In case of combined pituitary deficiency (CPD), LH and FSH, GH, and ACTH should be assessed in these infants, and magnetic resonance imaging (MRI) for abnormal low dose ACTH test is recommended.

In patients with normal low-dose ACTH tests, first clinicians should evaluate isolated TSH deficiency with the genetic study. Although MRI is recommended in these

**Table 2: Dose of levothyroxine in primary and central hypothyroidism based on FT4**

| FT4 (ng/d L) | Dose of levothyroxine in primary hypothyroidism | Dose of levothyroxine in central hypothyroidism |
|---|---|---|
| <0.4 ng/dl | 10-15 µg/kg | 10-15 µg/kg |
| 0.4-0.8 ng/dl | 10 µg/kg | 5-10 µg/kg |
| >0,8 ng/dl | 5-10 µg/kg | No treatment |

1 ng/dL=0.07770008 pmol/L

cases, it should be delayed because the infants cannot tolerate MRI under anesthesia.[23]

## Dose of Levothyroxine

For congenital hypothyroidism, it is better to start treatment based on FT4 because general therapy of 10–15 µg/Kg sometimes causes hyperthyroidism.[17,24,25] Treatment based on FT4 is summarized in Table 2.

## Permanent and Transient Hypothyroidism

At the age of three years, in patients who have no evidence of thyroid dysgenesis on ultrasound or thyroid scan and do not have any increase in TSH during treatment, we can discontinue levothyroxine for one month and retest of T4 or FT4 and TSH.

The patient would have transient hypothyroidism if the TSH was below 5 mIU/L with normal FT4 two or three times. After discontinuing levothyroxine, if TSH reaches above 20 mIU/L with one testing or above 10mIU/L after two testings, the patient would have permanent hypothyroidism, and we have to restart treatment.

If, after stopping treatment, TSH was between 5 and 9.9 mIU/L, the patient has permanent hyperthyrotropinemia and does not need treatment and needs follow-up.

Some physicians believe that treatment may be temporarily started as off-treatment in suspected cases. If the patient has euthyroidism taking levothyroxine at a dose of fewer than 3 µg/Kg, we can discontinue its treatment at six months of age and reevaluate it.[17,18]

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### Conflicts of interest

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