Review Article

Guideline for the Treatment of Hypothyroidism in Prematurity

Abstract

Congenital hypothyroidism is one of the most common endocrine disorders in infants and children. Thyroid hormone effects the function of most organs of the body. In premature neonates, thyroid abnormalities are very common but transient. There is a significant difference between the appropriate time for screening in premature and term neonates and there are different viewpoints in treating hypothyroidism in prematurity. According to the probable exceptions in this issue, there is no definite guideline. Therefore, regarding this confusion, this guideline aimed to help clinicians for rapid on-time decision making.

Keywords: *Hypothyroidism, infant, premature birth*

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Introduction

Congenital hypothyroidism is one of the most common endocrine disorders in infants and children. Thyroid hormone effects the function of most organs of the body.[1] It has diverse risk factors and treatment in different societies, however its treatment in prematurity have significant considerations.[2-4] Although, low levels of thyroid hormones and delay in treatment in preterm infants can be associated with neurodevelopmental impairments.[1] No untreated disease can have this much impact on growth and development. With regards to the importance of early diagnosis and treatment in preventing complications, recently in many countries, newborns are examined for congenital hypothyroidism at birth to diagnose the disease. The embryo's thyroid gland is developed in the 12 weeks of gestation, and thyroid function is completed in 4 weeks after childbirth.[5-7]

In premature neonates, thyroid abnormalities are very common but transient.[1] The frequency of congenital hypothyroidism is high in preterm and low-birth-weight (LBW) newborns compared to normal ones due to insufficient development of the hypothalamic-pituitary axis (1/400 vs 1/4000).[8-9]

Causes of hypothyroxinemia in prematurity hypothyroxinemia, which is defined as the decreased level of T4 in premature neonates is physiologic and should not be considered as a disease.[10-12]

The causes of hypothyroxinemia are as below:

- Low thyroid binding globulin (TBG) during the first 2 weeks of life
- Decreased T4 binding affinity to TBG
- Limited thyroid gland reserve
- Obtunded neonatal thyroid stimulating hormone (TSH) surge
- Minimal T4 to T3 conversion
- Immaturity of the hypothalamic-pituitary-thyroid
- medications including dopamine, dexamethasone, aminophylline, etc.
- Respiratory distress syndrome
- Sepsis
- Necrotizing entrocolitis
- Nonthyroidal illness
- Iodine deficiency
- Transfer withdrawal of maternal-placental T4
- Perinatal asphyxia
- Limited thyroglobulin iodine stores.

Treatment and screening of hypothyroidism are challenging. Though some studies suggested repeated screening in VLBW newborns, others recommended other strategies such as lowering the TSH screening cutoff.[13-17]

The challenges for screening occur because of physiologic hypothyroxinemia and delayed hyper thyrothyotropinemia. Treatment of hypothyroidism depends

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on the nonthyroidal illness process, which worsens the interpretation of the disease. On the other hand, the normal value of T4 and the variant duration for reaching normal thyroid hormones (T4, TSH, FREE T4) is commonly based on gestational age. For instance, <30 weeks of gestation needs 1 month, >30 weeks of gestation needs 1to 2 weeks, early low birth weight infants need 4 to 12 weeks, and very low birth weight and low birth weight need 1 to 2 weeks to be normal.

In preterm newborns, the amount of umbilical cord T4 is less than term neonates. Gestational age and birth weight usually determine the level of T4. Decreased level of TBG causes a significant reduction of T4 in preterm infants at birth, an abrupt rise in thyrotropin (TSH), T4, and T3 occurs in term neonates as well as preterm newborns, however, this increase is lower in preterm neonates compared to term ones. Furthermore, a decrease in the levels of T3 and T4 during the first week of life can be reported in preterm neonates. It can be as a result of nutritional problems and reduced production of liver TBG, immaturity of the hypothalamus-hypothyroid axis, an increase in the use of T4 in the tissues, and complications of prematurity, such as respiratory distress syndrome, and nonthyroid disease.[10,18]

In the first 2 weeks of birth, in premature babies, the TSH level is low, and then it increases until the 5th week of birth. Up to the 14th week, the level of TSH can become normal. In addition, in 10–14 days after birth, the lowest level of T4 is commonly reported, the normal level would be identified within 2–8 weeks, and the highest at 12 weeks of birth. Also, a normal level of free T4 is commonly reported within 1 to 2 weeks after birth.[19,20] On the other hand, premature neonates may face sick euthyroid syndrome after birth, which occurs under stress. In this setting, the body tries to decrease the *basal-metabolic-rate* and uses energy to combat the disease. T3 regulates the *basal-metabolic-rate* in the body. Accordingly, in this process, at the beginning, conversion of T4 to reverse T3 will be increased, but if it does not succeed, the levels of T4 and eventually TSH will be decreased in premature neonates. But during the recovery period, TSH will be increased. Therefore, the occurrence of this process in premature neonates, and the treatment by levothyroxine will worsen the patient's condition.

However, for survival in neonates aged <28 weeks of gestation at birth, *basal-metabolic-rate is needed* and the mentioned treatment with levothyroxine could be acceptable (there is no consensus on the onset of treatment in these children).[21-24]

There is a significant difference between the appropriate time for screening in premature and term neonates.

As, there is a delayed increase in TSH in premature infants, thyroid screening (TSH) is recommended for 1 to 2 weeks until the 38 weeks of gestation. In most countries, this screening is conducted at the age of 2, 6, and 10 weeks, therefore, the normal TSH level in newborns with hypothyroidism cannot rule out the hypothyroidism.[9,10,16-18]

The most sensitive test for diagnosis of hypothyroidism is TSH and the level of TSH above 10 miu/L has a diagnostic value.[7,10,24,25] Regarding the transient hypothyroxinemia, sick euthyroid illness, and different levels of thyroid hormones, the diverse duration for being normal, and the complications of untreated status in preterm neonates, authors aimed to provide this guideline for the treatment of congenital hypothyroidism.

Normal levels of free T4 and T4 in premature neonates was summarized in Table 1. To mitigate the confusion, the free T4 normal values was considered as 0.8 to 2.6 ng/dL. If the level of T4 is below 2 standard deviation of the mean, it can be considered abnormal.[9] Also, the normal value of free T4 in preterm infants based on gestational age in the first week after birth is 0.8–2.6 ng/dL. Owing to the low level of T4 in the first weeks after birth in premature neonates, the table is used to interpret the normal level of this hormone. If the level of T4, is below 2 standard deviation, the level of the hormone would be considered low.

Treatment

Regarding the levels of T4 and free T4 in gestational age, free T4 lower than 0.8 and TSH upper than 10 should be considered as the first and second positive points, respectively. The strategy of treatment is summarized in Table 2 and Figure 1. The treatment initiates for patients with TSH >20 with and the existence of two positive points.

If the patient had one positive point, laboratory findings should be rechecked 2 weeks later, and if one positive point was reported in a recheck, the treatment should be initiated.

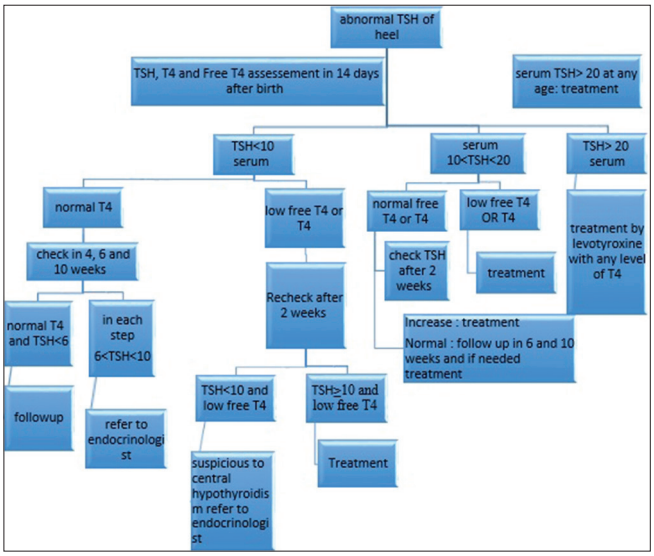

Figure 1: The flowchart for treating abnormal TSH of heel

Table 1: Levels of Thyroid hormones in different gestational ages

Gestation (week)	Age of specimen	Free T4 (ng/dL) ± sd	T4 (µg/dL) ± sd	TSH (mu/L) ± sd
23-27	cord	1.28±0.4	5.4±2	6.8±2.9
	7	1.47±0.6	4±1.8	3.5±2.6
	14	1.45±0.5	4.7±2.6	3.9±2.7
	28	1.5±0.4	6.1±2.3	3.8±4.7
28-30	cord	1.45±0.4	6.3±2	7±3.7
	7	1.82±0.7	6.3±2.1	3.6±2.5
	14	1.65±0.4	6.6±2.3	4.9±11.2
	28	1.71±0.4	7.5±2.3	3.6±2.5
30-34	cord	1.49±0.3	7.6±2.3	7.9±5.2
	7	2.14±0.6	9.4±3.4	3.6±4.8
	14	1.98±0.4	9.1±3.6	3.8±9.3
	28	1.88±0.5	8.9±3	3.5±3.4
>37	cord	1.41±0.3	9.2±1.8	6.7±4.8
	7	2.7±0.6	12.7±2.9	2.6±1.8
	14	2.03±0.3	10.7±1.4	2.5±2
	28	1.65±0.3	9.7±2.2	1.8±0.9

Table 2: The indication of treatment in prematurity

TSH >20 with any level of T4 should be treated
>10 TSH <20، LOW free T4 start treatment
>10 TSH <20، T4 or free T4 N recheck after 2 weeks
If the results repeated start treatment
If it was normal, we follow up at 6 and 10 weeks
TSH <10، LOW T4 or free T4 recheck after 2 weeks
If free T4 was low and TSH >10 start treatment as primary hypothyroidism
TSH <10، LOW T4 or free T4 recheck after 2 weeks
If the results repeated start treatment as central hypothyroidism
TSH <10، with normal T4 OR free T4 recheck at 4, 6, and 10
TSH <6: With normal T4 OR free T4 follow up
>6 TSH <10 treatment should be started based on clinical symptoms and ultrasound by an endocrinologist if needed
Persistent TSH >10 at 6 weeks of age treatment

In patients with TSH levels between 6 to 10 and no positive point, physician clinical judgment defines the treatment process.

Generally, a high level of TSH indicates the need for treatment regarding its impact on the occurrence of developmental disorders.[26-28]

In premature neonates weighed <1,000 grams and aged <28 weeks of gestation, some clinicians recommend levothyroxine therapy at 4 µg/kg, but this is not a consensus on it, yet.[28-30]

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Conflicts of interest

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