Thyroid Function Screening in Newborn: A Literature Review

Vennia Riskia Tristianti

ABSTRACT

The thyroid hormone has a vital role in the growth and maturation of many target tissues, especially the brain and bone. Abnormalities of thyroid gland function in neonates not only cause metabolic disorders such as thyroid disorders in adults but also cause tissue abnormalities whose growth and maturation depend on thyroid hormone. Furthermore, they are at high risk for permanent mental retardation if they do not get treatment immediately. Thyroid function abnormalities often do not show typical clinical signs and symptoms at birth, even though the duration of early intervention is very short to prevent mental retardation. Therefore, it is important to detect thyroid abnormalities in infants early through thyroid hormone screening in neonates. Most states use TSH for primary screening, with T4 as the second level of testing. Testing before the recommended time will detect a physiological TSH spike, causing a falsely abnormal result. The earlier the detection and treatment of hypothyroidism, the better the patient's prognosis.

Keywords: Hyperthyroidism, hypothyroidism, screening, newborn, thyroid.

I. INTRODUCTION

Fetal thyroid hormone needs are still dependent on the mother through the placenta, until then the gland is able to supply thyroid hormone for itself. The thyroid gland in the fetus is developing and can provide its own thyroid hormone at further maturation in the third trimester of pregnancy. At birth, the extraterine environment is cooler than the intrauterine environment, so the neonate releases a surge in thyroid stimulating hormone (TSH). The thyroid hormone has an important role in the growth and maturation of other target organ tissues, especially the bones and brain [1]. Abnormality of thyroid gland function in neonates not only causes metabolic disorders such as thyroid disorders in adults but will cause tissue abnormalities whose growth and maturation depend on thyroid hormone [2].

The severity of the resulting disorder depends on the age this disorder occurs. For example, in congenital hypothyroidism in newborns, thyroid hormone deficiency causes hyperbilirubinemia and delayed bone maturation, which means the liver and bones are immature. Furthermore, they are at high risk of permanent mental retardation if they do not receive thyroid hormone therapy immediately [2]. Newborn baby with congenital hypothyroidism is one of the most preventable causes of Intellectual disability or mental retardation [3]. In addition, although cases are rarer, Untreated neonatal hypothyroidism can cause long-term problems, namely premature closure of the cranial sutures [4]. Currently, more than 70% of infants worldwide are not screened postnatally [2]. Thyroid function disorders often do not show the typical clinical signs and symptoms at birth, despite the fact that the duration of the intervention is very short to prevent mental retardation. Therefore, it is essential to be able to detect thyroid abnormalities in infants early through thyroid hormone screening in neonates [3].

II. THE OVERVIEW OF THYROID GLAND

The thyroid gland is a gland located in the neck, consisting of two lobes, which are connected by the isthmus. The thyroid gland crosses the midline of the upper trachea at the second and third tracheal rings. Anatomically, the thyroid gland lies behind the sternohyoid and sternothyroid muscles, enclosing the cricoid cartilage and the tracheal ring. The thyroid gland is inferior to the larynx's thyroid cartilage at the C5-T1 level. Ligaments connect each thyroid lobe to the trachea. The thyroid is attached to the trachea with the help of a ligament called the lateral suspensory ligament or Berry's ligament [5].

The thyroid gland is responsible for the production of iodothyronines. The iodothyronines products include T4, T3, and rT3. The main secretory products are inactive thyroxine, or T4, and prohormone triiodothyronine, or T3. Later T4 must be converted to T3 in the periphery by deiodinase type 1 (D1) in tissues with high blood flow, such as the kidneys and liver. Then in the brain, by deiodinase type 2 (D2), T4 will be converted into active T3, which is produced by glial cells [6]. Then reverse T3 (rT3) is an inactive form and is formed based on type 3 deiodinase activity on T4. Both hormones are stimulated to release in the anterior lobe of the pituitary gland by TSH [7]. The hypothalamic-pituitary axis regulates the release of TSH. The hypothalamus secretes thyroid releasing hormone (TRH), then TRH will stimulate the thyrotrophs in the anterior pituitary to secrete TSH. The release of TSH stimulates thyroid follicular cells to secrete T4 (80%) and T3 (20%). T4 that has been released into the circulation can be
converted into T3 through the deiodinase process. High circulating levels of T4 and T3 provide negative feedback on TSH levels to decrease TSH production. If T3 and T4 levels are low, feedback is obtained to increase TSH levels from the anterior pituitary [8].

III. THE ROLE OF THYROID HORMONES IN NEWBORNs

In infants and neonates, thyroid hormone has an essential role in the development of the fetal growth center, endochondral ossification, linear bone growth, and maturation of the epiphyseal bone center after birth. T3 stimulates the nervous system to stay awake, alert, and responsive to external stimuli. The thyroid also plays a role in peripheral reflexes, gastrointestinal motility and tone, reproductive health, and other endocrine organ functions. It enables the regulation of normal reproductive function in both males and females by regulating the ovulatory cycle and spermatogenesis [7].

Thyroid hormones also regulate pituitary function. The production and release of growth hormones inhibit the production and release of prolactin. In addition, thyroid hormone increases renal clearance by stimulating renal blood flow (RBF) and glomerular filtration rate (GFR). Cardiac output, stroke volume, heart rate, basal metabolic rate (BMR), heat production, resting respiratory rate, and ventilation are also influenced by thyroid hormones [7].

IV. THYROID FUNCTION SCREENING IN NEWBORN AND THEIR EFFECTIVENESS IN ESTABLISHING THE DIAGNOSIS

Detection and treatment of hypothyroidism in neonates should be done as early as possible to improve brain function and reduce the progressive decline in cognitive function in children. These observations were made in the mid-20th century, universal newborn screening for congenital hypothyroidism was performed in all 50 states in the 1970s and the publication of recommended guidelines [9]. Screening for the detection of congenital hypothyroidism in newborns is generally effective after 24 hours, but ideally it is done two to four days after birth at term or before seven days after premature birth [3], [9]. TSH and T4 are usually used for primary screening for thyroid hormone abnormalities. Screening performed before the recommended time will detect a physiological increase in TSH so that it reads as a false abnormal result. In newborns at term, within 30-60 minutes, there is a spike in TSH levels of 60-80 mU/L, then it will decrease rapidly until it reaches levels of 20 mU/L on the first day of birth, and will continue to decline to levels 6-10 mU/L at 7 days of age [9]. Newborn screening is positive if the TSH level is 20 mU/L. To establish the diagnosis, neonates with a positive TSH screening result should be confirmed by re-examination of serum TSH and FT4. A new diagnosis can be made when high TSH and low FT4 levels are obtained. Infants who were not screened for the diagnosis were made by assessing clinical symptoms and examining serum TSH and FT4 [3].

Infants ≥ 2 weeks of age with a TSH level ≥ 10 mU/L are considered abnormal and should be treated. If the baby is not treated, the TSH and FT4 should be repeated at 2 weeks and 4 weeks. Patients should be treated immediately if the TSH and FT4 on re-examination are not normal. If the TSH and FT4 are found to be abnormal, they must be treated. Follow-up examinations can be done, such as radiological scintigraphy and thyroid ultrasound, to check for the presence or absence of the thyroid gland, thyroid gland size, or thyroid ectopic [3].

In cases of neonatal hyperthyroidism, it is essential to be screened primarily during pregnancy. Patients with a TBII level of >40–70% (n<10–15%) and maternal TSHR-stimulating antibody level of 350–500% (n<125%) are at risk of delivering a baby with hyperthyroidism [10]. Neonates are at high risk of developing hyperthyroidism, especially infants of mothers with Graves' disease, family history of congenital hyperthyroidism, and infants whose intrauterine surveillance reveals fetal signs of hyperthyroidism. Laboratory and clinical examinations are recommended in the first two weeks of life. If possible, in high-risk infants, TRAb levels are determined from cord blood. Elevated FT4 levels at 3-7 days of age can be used to screen for hyperthyroidism [10].
Fig. 3. Congenital hypothyroid screening algorithm [3].

Fig. 4. Congenital hyperthyroid screening algorithm [3].

Fig. 5. Genes involved in congenital hypothyroidism [12].

Fig. 6. Three months infant with congenital hypothyroidism [11].
TABLE I: CLINICAL MANIFESTATIONS DUE TO GENETIC DISORDERS ASSOCIATED WITH CONGENITAL HYPOTHYROIDISM [12]

<table>
<thead>
<tr>
<th>Primary congenital hypothyroidism</th>
<th>Central congenital hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAX8</td>
<td>IGSF1</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>Macro-orchidism, delayed pubertal testosterone rise, PRL deficiency, transient GH deficiency</td>
</tr>
<tr>
<td>NKK2–1</td>
<td>TBLIX</td>
</tr>
<tr>
<td>Cleft palate, bifid epiglottis, choanal atresia, spiky hair (Bamforth-Lazarus syndrome)</td>
<td>Hearing deficits</td>
</tr>
<tr>
<td>FOXE1</td>
<td>LEPR</td>
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<tr>
<td>Congenital heart disease</td>
<td>Severe early-onset obesity, delayed puberty</td>
</tr>
<tr>
<td>NKK2–5</td>
<td>POU1F</td>
</tr>
<tr>
<td>Glial abnormalities</td>
<td>Combined pituitary hormone deficiency</td>
</tr>
<tr>
<td>GLIS3</td>
<td>PROPI</td>
</tr>
<tr>
<td>Neonatal diabetes mellitus, congenital glaucoma, developmental delay, hepatic fibrosis, polycystic kidneys</td>
<td>Combined pituitary hormone deficiency</td>
</tr>
<tr>
<td>JAG1</td>
<td>HESX1</td>
</tr>
<tr>
<td>Alagille syndrome (variable involvement of liver, heart, eye, skeletal, facial defects), congenital heart disease</td>
<td>Combined pituitary hormone deficiency, optic nerve hypoplasia</td>
</tr>
<tr>
<td>SLC26A4</td>
<td>LHX3</td>
</tr>
<tr>
<td>Sensorineural hearing loss</td>
<td>Combined pituitary hormone deficiency, cervical abnormalities, sensorineural deafness</td>
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<tr>
<td></td>
<td>LHX4</td>
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<td></td>
<td>Combined pituitary hormone deficiency, craniofacial abnormalities</td>
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<tr>
<td></td>
<td>SOX3</td>
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<tr>
<td></td>
<td>Combined pituitary hormone deficiency, micro–/anophthalmia, seizures</td>
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</tbody>
</table>

V. PATHOGENESIS OF THYROID DISORDERS IN NEWBORNS

Congenital hypothyroidism is classified into transient and permanent hypothyroidism. Transient hypothyroidism occurs due to a temporary deficiency of thyroid hormone that is found at birth, but then returns to normal levels. Permanent hypothyroidism can be classified into two categories, primary and secondary permanent (or central) [12].

Congenital hypothyroidism is usually caused by an abnormality in the thyroid gland itself (primary hypothyroidism). Based on the cause, primary congenital hypothyroidism can be classified as hypothyroidism due to failure of the thyroid gland to develop normally (dysgenesis) or hypothyroidism due to failure of a structurally normal thyroid gland to produce normal amounts of thyroid hormone (dysmorphogenesis). Thyroid dysgenesis is the most common cause of congenital hypothyroidism, and its incidence (approximately 1:4000 infants). In thyroid dysgenesis, abnormalities may include hypoplasia, spectrum of thyroid agenesis, and ectopia. The underlying cause of thyroid dysgenesis is still not widely known and elucidated. It usually occurs sporadically, with only 2-5% of cases due to an identifiable genetic mutation. Thyroid Stimulating Hormone Receptor (TSHR) and the transcription factors PAX8, NKK2–1, and FOXE1 are expressed in the developing thyroid. Disruption in any of these genes is thought to result in failure of the thyroid gland to form. This transcription factor also plays a vital role in the development of other tissues, and its mutations are associated with other syndromes such as renal abnormalities (PAX8), interstitial lung disease and choora (NKK2–1), or cleft palate, bifid epiglottis, choanal atresia and spiky hair (FOXE1) (Table I) [12].

In contrast to primary disorders in which the disease is located in the thyroid gland, central hypothyroidism is caused by disorders located in the hypothalamus or pituitary of the thyroid axis that result in inadequate production or bioactivity of TSH. Central congenital hypothyroidism is rare, with initial estimates of its incidence between 1:29,000 and 1:110,000. Central hypothyroidism can be detected by a screening program that measures T4 concentrations in all infants, together with TSH measurements simultaneously, or in a subset of infants with low T4 [12].

In neonatal hyperthyroidism, TSHR-stimulating antibodies produced by the mother cross the placenta and cause fetal and neonatal hyperthyroidism. Antibodies decrease towards the end of pregnancy, but levels in the fetus continue to rise, levels that continue to remain high leading to an increased likelihood of neonatal thyrotoxicosis. TSHR-stimulating antibodies produced in the mother cause difficulty in detecting neonatal hypothyroidism, this condition masks the clinical picture of thyroid hormone abnormalities, either hypothyroidism or hyperthyroidism according to the type of TSHR antibody. If the TSHR-stimulating and blocking antibodies are in balance in the fetus, the newborn may be initially euthyroid [13].

VI. TREATMENT AND PROGNOSIS OF THYROID DISORDERS IN NEWBORN

For cases of neonates with confirmed hypothyroidism, thyroid hormone therapy should be started immediately. Treatment is best started before the baby is two weeks old with levothyroxine (L-T4). The initial dose of levothyroxine is 10-15 g/kg BW/day, with continued doses adjusted for periodic TSH and FT4 results and the patient's age (TABLE II). The drug is given orally and should not be taken together with soy milk, iron, or calcium. Monitoring FT4 and TSH are done periodically to see the success of therapy. Target TSH levels <5 mU/L are expected to be achieved within two weeks. Then it is expected that the FT4 level is above the middle reference level for age [3].
The first few months after giving birth is the most critical period of growth and brain development stimulated by thyroid hormone [14]. Therefore, early detection and treatment are necessary. Before the screening, the IQ scores of the patients showed a significant difference compared to after the screening program. Studies show a negative relationship between age and IQ scores. The earlier detection and treatment of hypothyroidism increase the patient's IQ score [3, 14].

For Graves’ Disease neonates with biochemical hyperthyroidism, MMI therapy should be initiated at a dose of 0.2 to 0.5 mg/kg/day. To reduce the symptoms of sympathetic hyperactivity, tachycardia and hypertension, propranolol is given in the treatment of neonatal hyperthyroidism. In adult patients propylthiouracil (PTU) is usually prescribed, but PTU is not recommended in neonates and children because of the increased risk of hepatotoxicity. In severe cases with hemodynamic compromise, Lugol’s solution or potassium iodide may be considered [15].

The short-term prognosis of neonatal hyperthyroidism is usually good, but the long-term prognosis is negative, especially if not treated properly. Thyroid hormone levels are essential for normal brain development. Abnormal amounts of thyroid hormone impair neurocognitive development in neonates. Studies show a history of neonatal thyrotoxicosis leading to intellectual impairment and craniosynostosis. Further studies are needed to assess whether neonatal hyperthyroidism causes long-term complications. However, further studies are also needed to assess the impact of hypothyroidism and hyperthyroidism on the neonate and the effectiveness of their treatment [15].

VII. CONCLUSION

Thyroid hormone has vital role in the growth and maturation of many other target tissues, especially the brain and bones. Abnormal amounts of thyroid hormone in neonates not only cause metabolic disorders such as thyroid disorders in adults, but will cause tissue disorders whose growth and maturation depend on thyroid hormones. The earlier the detection and treatment of hypothyroidism, the better the patient’s prognosis.

REFERENCES