Congenital and Acquired Hypothyroidism

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Table of Contents

Introduction .......................................... 2
Thyroid Development and Physiology .............. 2
Congenital Hypothyroidism ........................ 3
Acquired Hypothyroidism .............................. 8
References ........................................... 12

Cover Illustration by May S. Cheney

NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Pediatrics.
Hypothyroidism refers to a state of decreased production and release of thyroid hormone from the thyroid gland. It is one of the most common endocrine abnormalities seen by primary care physicians and pediatric endocrinologists alike. Hypothyroidism in childhood may be congenital (present at birth) or acquired. Both forms of hypothyroidism can be further categorized as primary or central. This manual reviews clinical knowledge that is essential when caring for patients who present with laboratory or clinical evidence of hypothyroidism. The manual begins with an overview of thyroid development and physiology and then follows a case-based approach to review the causes, approach to evaluation, and treatment of congenital and acquired hypothyroidism.

THYROID DEVELOPMENT AND PHYSIOLOGY

EMBRYOLOGY AND FETAL THYROID FUNCTION

Thyroid gland organogenesis begins at 26 days gestation, with the evagination of the medial thyroid bud from the floor of the developing pharynx. By 7 weeks, the developing gland lies in the thyroid bed. Function of the gland is first detected at 10 weeks, when the thyroid becomes able to trap iodide and synthesize thyroid hormone precursors. Thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) are secreted between 15 and 18 weeks, and by 18 to 20 weeks, the thyroid gland is able to release thyroid hormone in significant amounts in response to stimulation.\(^1,2\)

The fetus has relatively low circulating levels of triiodothyronine (T\(_3\)) and high levels of reverse T\(_3\) (rT\(_3\)). Although maternal thyroxine (T\(_4\)) and T\(_3\) can cross the placenta, only a small amount enters the fetal circulation, because the placental type 3 deiodinase (D3) avidly converts maternal T\(_4\) and T\(_3\) to inactive metabolites, limiting passage to the fetus. During the first half of gestation, the fetus relies on maternal thyroid hormone to support normal development of the central nervous system (CNS). In the hypothyroid fetus, the fetal brain is partially protected against low circulating levels of thyroid hormone by upregulation of type 2 deiodinase (D2) activity, which serves to increase the levels of T\(_3\) in the CNS.\(^3\) Nevertheless, otherwise healthy infants born to mothers with inadequately treated hypothyroidism have lower developmental scores, underscoring the importance of early fetal euthyroidism.\(^4,5\)

After 30 weeks gestation, the level of fetal T\(_3\) gradually increases, the level of rT\(_3\) decreases, and fetal production of T\(_4\) and TSH increases. Most circulating thyroid hormones at this point are derived from the fetal thyroid. The ratio of TSH to T\(_4\) decreases, indicating the development and maturation of the fetal hypothalamic-pituitary-thyroid axis.\(^2,3\) Hence, in mid-gestation, levels of both T\(_4\) and T\(_3\) are low compared to a term infant, and TSH secretion is relatively high as a result of the immaturity of the negative feedback system.

NEONATAL THYROID FUNCTION

At delivery, exposure to the cold extrauterine environment causes a surge in TSH secretion, with the concentration peaking at 70 \(\mu\)IU/mL by 30 minutes after birth. This TSH surge stimulates T\(_4\) secretion. The T\(_3\) level also increases, partly as a result of direct secretion from the thyroid gland and partly as a result of increases in tissue type 1 deiodinase (D1) and the absence of the deactivating placental D3. TSH gradually declines over the first 3 to 5 days of life to levels at or below 10 \(\mu\)IU/mL, while the increased T\(_4\) and T\(_3\) levels persist for weeks to months.

THYROID HORMONE PHYSIOLOGY

Synthesis of Thyroid Hormones

Dietary iodide is actively taken up by the sodium-iodide symporter located on the basement membrane of the thyrocyte (Figure 1). The iodide is oxidized to iodine by thyroid peroxidase (TPO) and is incorporated into tyrosine residues on the thyroglobulin molecule. This process is termed *organification*. During organification, the iodinated tyrosine residues are also cross-linked to form the precursors of T\(_3\) and T\(_4\). The iodinated thyroglobulin is then stored in the colloid of the thyroid follicles. During secretion of thyroid