Congenital hypothyroidism

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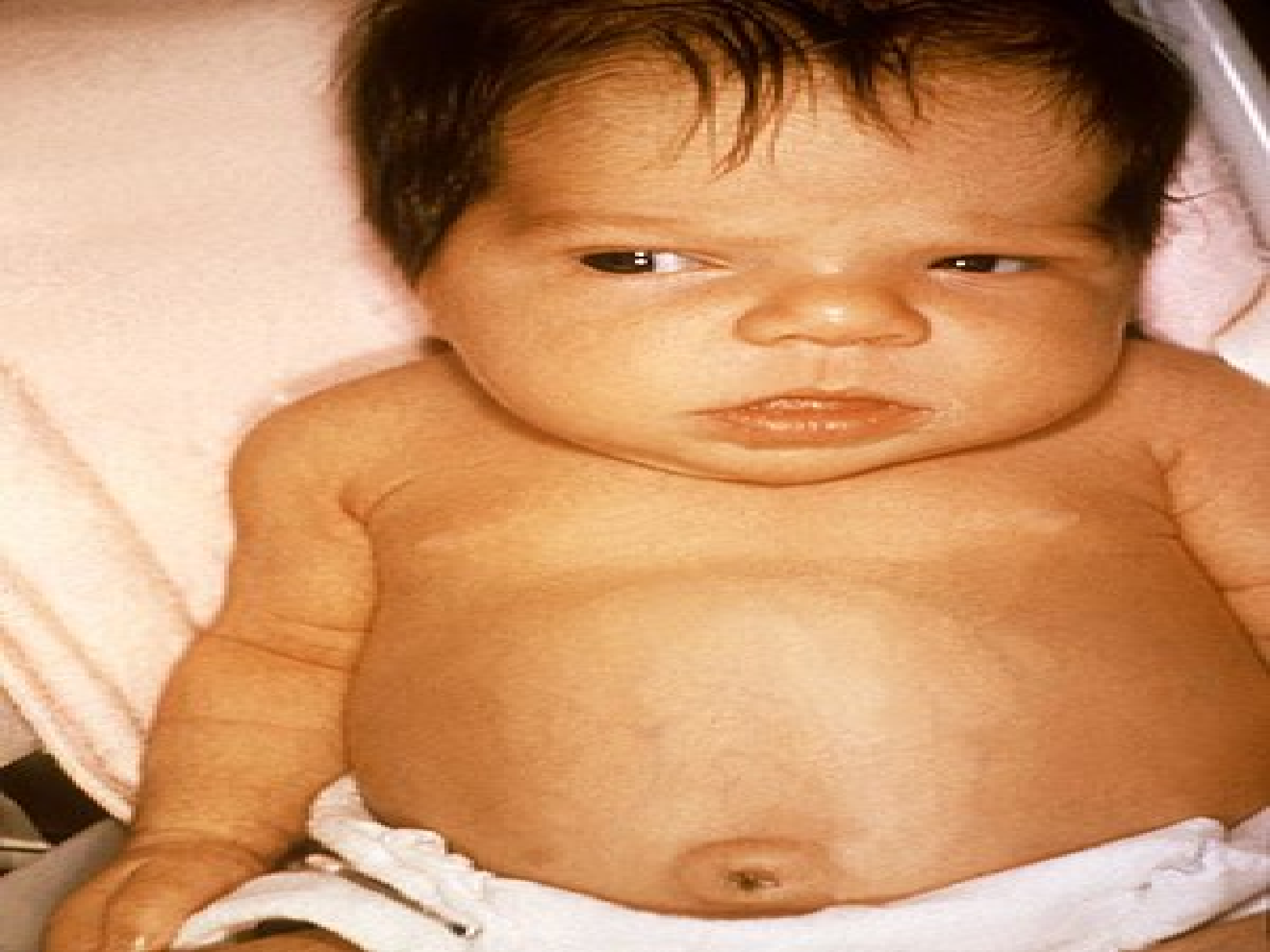


Congenital primary hypothyroidism, occurring in approximately **1:2000 to 1:4000 newborns**,. There is an inverse relationship between age at treatment initiation and intelligence quotient (**IQ**) later in life, so that the longer the condition goes undetected and untreated, the lower the IQ

Most newborn babies with congenital hypothyroidism have **few or no clinical manifestations** of thyroid hormone deficiency.

the majority of cases are **sporadic**, so it is not possible to predict which infants are likely to be affected. For these reasons, **newborn screening programs** were developed to detect this condition as early as possible by measuring either thyroxine (T4) or thyrotropin (thyroid-stimulating hormone [TSH]) in heel-stick blood specimens.

EPIDEMIOLOGY

The incidence varies by geographic location and by **ethnicity**.

he incidence appears to be increased in **twin** births (1:900) and even higher in multiple births (1:600).

The highest incidence, 1:581, was reported from the **Markazi Province in Iran**, likely related to consanguinity and a higher occurrence of autosomal recessive inborn errors of thyroid hormone synthesis

Nearly all screening programs report a female preponderance, approaching a **2:1 female-to-male** ratio

ETIOLOGY

Congenital hypothyroidism is most commonly caused by an embryologic defect in thyroid gland development (**dysgenesis**) or a defect in thyroid hormone synthesis (**dyshormonogenesis**). Most cases of thyroid dysgenesis are **sporadic**, while the dyshormonogeneses are inherited in an **autosomal recessive pattern**.

Worldwide, **iodine deficiency** remains the main cause of congenital hypothyroidism;.

Other causes of **transient hypothyroidism** include transfer of maternal antithyroid drugs, maternal thyroid-stimulating hormone (TSH) receptor-blocking antibodies, exposure to excess iodine, large hepatic hemangiomas

Congenital central hypothyroidism is most commonly caused by a defect in the embryologic development of the pituitary gland or mutations in the genes responsible for pituitary hormone synthesis.

Congenital hypothyroidism or other causes of low total T4 at birth, with thyroid function test results

Cause	Incidence	Serum free T4	Serum T4	Serum TSH
Primary hypothyroidism	1:2000 to 1:4000	↓	↓	↑
▪ Thyroid dysgenesis – Ectopia, aplasia, or hypoplasia		↓	↓	↑
▪ Resistance to TSH*		Normal or ↓	Normal or ↓	↑
▪ Inborn errors of thyroxine synthesis (dyshormonogenesis)		↓	↓	↑
▪ Gland in situ¶		↓	↓	↑
Defects in thyroid hormone transport (THCMTD)Δ	Rare	↓	↓	Normal or slightly ↑
Defects in thyroid hormone action – Resistance to thyroid hormone	1:40,000	↑	↑	Normal or slightly ↑
Central hypothyroidism	1:16,404 to 1:29,000	↓	↓	Normal or ↓
Transient hypothyroidism				
▪ Iodine deficiency (worldwide, in areas of endemic iodine deficiency)		↓ then normalizes	↓ then normalizes	↑ then normalizes
▪ Iodide excess (from topical iodine antiseptics, natural supplements, drugs, or contrast agents)		↓ then normalizes	↓ then normalizes	↑ then normalizes
▪ Maternal antibody-mediated hypothyroidism	1:180,000	↓	↓	↑
▪ Gland in situ¶		↓ then normalizes	↓ then normalizes	↑ then normalizes
TBG deficiency (causes low serum total T4 concentrations◇ but not hypothyroidism)	1:4000 to 1:8000	Normal	↓	Normal

T4: thyroxine; TSH: thyroid-stimulating hormone (thyrotropin); THCMTD: thyroid hormone cell membrane transport defect; TBG: thyroxine-binding globulin; T3: triiodothyronine.
* Resistance to TSH is usually due to a mutation in the TSH receptor.
¶ Gland in situ refers to a normal-sized or large thyroid gland in a normal location. In modern studies, this is the most common category of congenital hypothyroidism. While the underlying cause is often unknown, it likely represents a mild form of thyroid dyshormonogenesis. On follow-up, approximately one-half of thyroid gland in situ cases have transient hypothyroidism.
Δ THCMTD is characterized by high serum T3 and low reverse T3 concentrations.
◇ TBG deficiency is characterized by low serum total T4 but normal serum free T4 concentrations.

Primary hypothyroidism — Primary hypothyroidism refers to inadequate thyroid hormone production in the gland itself.

approximately **85 percent were caused by thyroid dysgenesis, while 15 percent were caused by one of the inborn errors in thyroid hormone synthesis**

the majority of these cases have permanent hypothyroidism.

Thyroid dysgenesis — The ***most common*** cause of permanent congenital hypothyroidism is thyroid dysgenesis (abnormal thyroid gland development) resulting from **agenesis, hypoplasia, or ectopy.** Thyroid ectopy accounts for two-thirds of the dysgenesis cases worldwide.

Although most cases of thyroid dysgenesis are **sporadic**, there is evidence of a familial/genetic component in approximately 2 percent of cases.

infants with trisomy 21 (**Down syndrome**) have a higher incidence of hypothyroidism detected by newborn screening programs, occurring in as many as **1:50 newborn**.

Resistance to thyroid-stimulating hormone

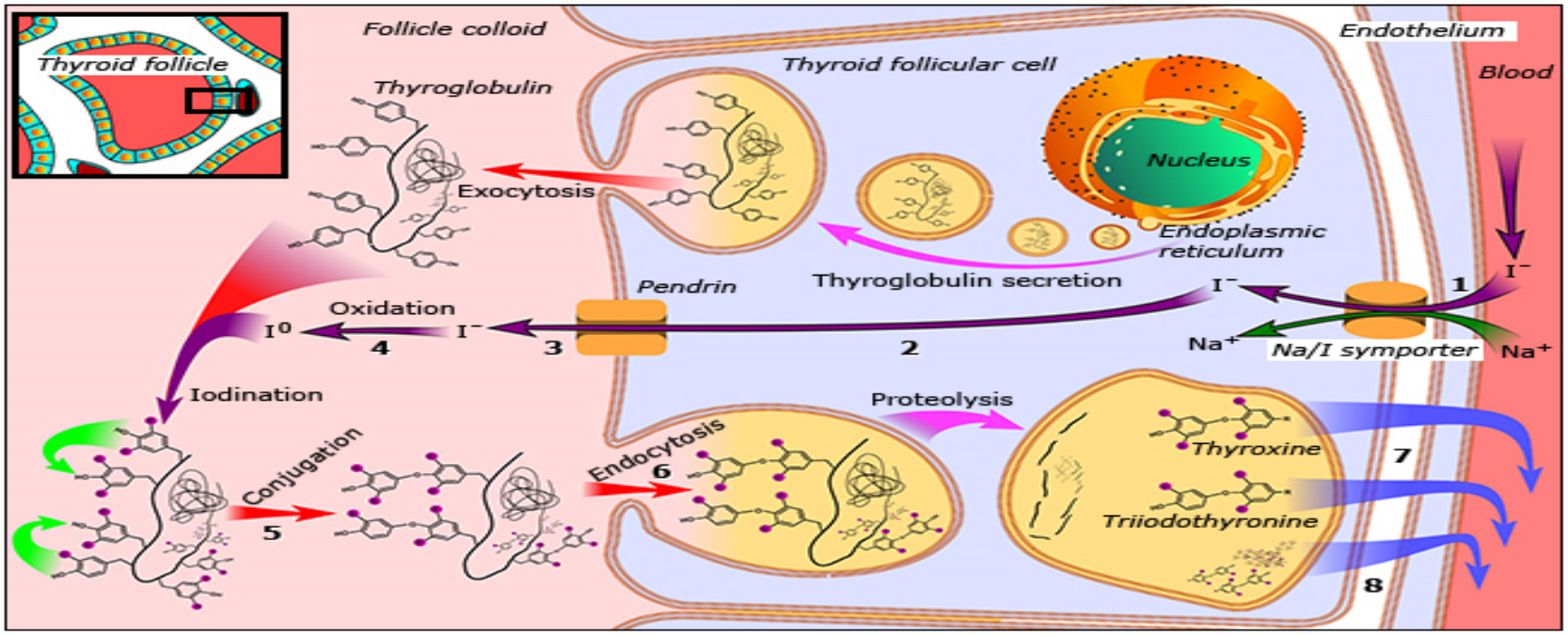
elevated serum TSH and low T4 level.

In some forms of *pseudohypoparathyroidism,* When such cases are detected by newborn screening, **the hypothyroidism is mild** and, despite thyroid hormone treatment, *linear growth slows, accompanied by excessive weight gain*. Such cases should then be screened for *hypocalcemia and elevated PTH levels* to confirm PTH .resistance.

Disorders of thyroid hormone synthesis and secretion

Hereditary defects in virtually all steps in thyroid hormone biosynthesis and secretion have been described, all of which are characterized by **autosomal recessive** inheritance

Thyroid hormone biosynthesis



Thyroid hormone synthesis includes the following steps, marked by numbers in the diagram above:
(1) I^- trapping by the thyroid follicular cells.
(2) Diffusion of I^- to the apex of the cells.
(3) Transport of I^- into the colloid.
(4) Oxidation of inorganic iodide to I^- by TPO and incorporation of I^- into tyrosine residues with thyroglobulin molecules in the colloid. DUOX2 and DUOXA2 are required for generation of hydrogen peroxide, a substrate for TPO.
(5) Combination of 2 DIT molecules to form T4 or of MIT with DIT to form T3.
(6) Uptake of thyroglobulin from the colloid into the follicular cell by endocytosis, fusion of the thyroglobulin with a lysosome, and proteolysis and release of T4, T3, DIT, and MIT.
(7) Release of T4 and T3 into the circulation.
(8) Deiodination of DIT and MIT to yield tyrosine.
T3 is also formed from monodeiodination of T4 in the thyroid and in peripheral tissues.

I^-: iodide; TPO: thyroid peroxidase; DIT: diiodotyrosine; T4: thyroxine (tetraiodothyronine); MIT: monoiodotyrosine; T3: triiodothyronine;

- Defects in **iodide transport** into thyroid follicular cells (step 1 in the figure)
- Defects in transport across the apical membrane (step 3 in the figure) responsible for **transporting iodine out of the cell and into the follicular colloid**, and in the cochlea, where it results in a sensorineural hearing loss (Pendred syndrome

- A defect in *thyroid peroxidase activity*
- Defects in the *generation of hydrogen peroxide* (step 4 in the figure), a substrate for thyroid peroxidas.
- Production of abnormal *thyroglobulin* molecules (top of figure).
- *Iodotyrosine deiodinase* deficiency

Altogether, these disorders account for approximately **15 percent** of cases of permanent congenital hypothyroidism.

Defects in thyroid hormone transport

Passage of *thyroid hormone into target organs* is facilitated by plasma membrane transporters. A mutation in one such transporter gene, , located on the X chromosome.

The defective transporter appears to impair passage of triiodothyronine (**T3**) into neurons; this syndrome is characterized by *decreased serum T4, associated with elevated T3, normal to mildly elevated TSH levels, and psychomotor retardation*

Defects in thyroid hormone action: Resistance to thyroid hormone

The incidence is approximately **1:40,000**. It is characterized by high serum T4, free T4, T3, and free T3 levels, with normal or slightly elevated serum TSH levels. Rarely, patients with high TSH levels may be detected by newborn screening programs.

Typical findings in childhood include failure to thrive and attention deficit hyperactivity disorder, but patients may have no clinical manifestations of hyperthyroidism; for most patients, no treatment is indicated

Central hypothyroidism

Central hypothyroidism refers to defects in the production of TSH due to either **hypothalamic or pituitary dysfunction**.

Newborn screening programs that employ the initial T4/follow-up TSH approach often detect central hypothyroidism but are not reliable for this purpose. **Programs based only on TSH screening alone will not identify these infants**.

It may be associated with other congenital syndromes, particularly **midline defects** such as optic nerve hypoplasia/septo-optic dysplasia or midline cleft lip and palate defects and may follow birth trauma or asphyxia.

Most infants with central hypothyroidism, have other **pituitary hormone deficiencies**. Some cases of central hypothyroidism are present in infants with **congenital hypopituitarism**.

Congenital central hypothyroidism also can be caused by insufficient treatment of **maternal Graves** hyperthyroidism during pregnancy. This form of central hypothyroidism may persist beyond **six months** of age.

Transient congenital hypothyroidism

Worldwide, the most common cause of congenital hypothyroidism that resolves during the first few months or years of life (transient hypothyroidism) is **iodine deficiency.** In iodine-sufficient countries, the most common cause is a gestational **exposure to either maternal antithyroid drugs or iodine**.

The causes of **transient hypothyroidism with goiter** in newborn infants are:

- Iodine deficiency – Iodine deficiency, particularly in preterm infants,
- Iodine exposure – Exposure of the fetus or newborn to high doses of iodine can cause hypothyroidism. This can occur in infants of mothers with cardiac arrhythmias treated with amiodarone,

Populations at risk include infants born prematurely and in preterm or term infants with congenital heart defects or other anomalies, due to exposure to iodine through the skin and/or in **contrast media** used for cardiac catheterization or lymphangiography .

- **Maternal blocking antibodies** – Transplacental transfer of TSH-receptor blocking antibodies can occur in infants of mothers with autoimmune thyroid disease .

This form of hypothyroidism usually subsides around three months of age (range one to six months) as the maternal antibodies are cleared

- **Maternal antithyroid drugs**

These drugs are cleared in days; as a result, many of these infants are euthyroid when restudied a few weeks after delivery.

- **Large hepatic hemangiomas** – Large hepatic hemangiomas, present from birth, may produce increased levels of type 3 deiodinase, resulting in "consumptive hypothyroidism

CLINICAL MANIFESTATIONS

Asymptomatic newborns

The vast majority (more than 95 percent) of infants with congenital hypothyroidism have few, if any, clinical manifestations of hypothyroidism at birth.

This is because some maternal thyroxine (T4) crosses the placenta, so that even in infants who cannot make any thyroid hormone, umbilical cord serum T4 concentrations are approximately 25 to 50 percent of those of normal infants

Symptomatic infants

Infants born in regions of the world that lack newborn screening programs typically present with symptoms and signs of hypothyroidism that develop over the first few months of life, which include lethargy, hoarse cry, feeding problems, often needing to be awakened to nurse, constipation, puffy (myxedematous) and/or coarse facies, macroglossia, umbilical hernia, large fontanels, hypotonia, dry skin, hypothermia, and prolonged jaundice (primarily unconjugated hyperbilirubinemia) .

Newborn infants with thyroid **dyshormonogenesis** may have a **goiter** detected on prenatal ultrasound or on clinical examination of the neonate, while in others, the goiter is discovered later in life.

If an infant has **central hypothyroidism**, the clinical manifestations are often related to associated deficiencies of other pituitary hormones and include hypoglycemia (growth hormone and adrenocorticotropic hormone), micropenis (growth hormone and/or gonadotropins), undescended testes (gonadotropins), and, least commonly, features of diabetes insipidus (vasopressin).

NEWBORN SCREENING

In the United States, approximately four million infants are screened annually, leading to the detection of 2000 infants per year with congenital hypothyroidism.

Timing — Blood for screening is collected onto filter paper cards after **heel prick**.

For **full-term infants**, the sample is usually collected **one to two days after birth .** Some programs also routinely obtain a second specimen between one and three weeks after birth .

For **preterm infants**, a more rigorous screening procedure is required due to developmental changes in thyroid physiology and higher rates of false-positive and false-negative results on the initial screen

Technique — Three major screening strategies have evolved:

- Initial blood thyroxine (**T4**) assay, with follow-up thyrotropin (thyroid-stimulating hormone [**TSH**]) assay **if** the blood T4 value is below a certain concentration (usually less than the 10th percentile for a given day's run in the laboratory performing the assay).
- Initial blood **TSH** assay.
- Simultaneous **T4 and TSH** assays.

Either approach detects the majority of infants with congenital primary hypothyroidism, and each has its advantages and disadvantages. Infants with a delayed rise in blood TSH concentration and those with central hypothyroidism are detected more reliably by the initial T4/follow-up TSH assay method,

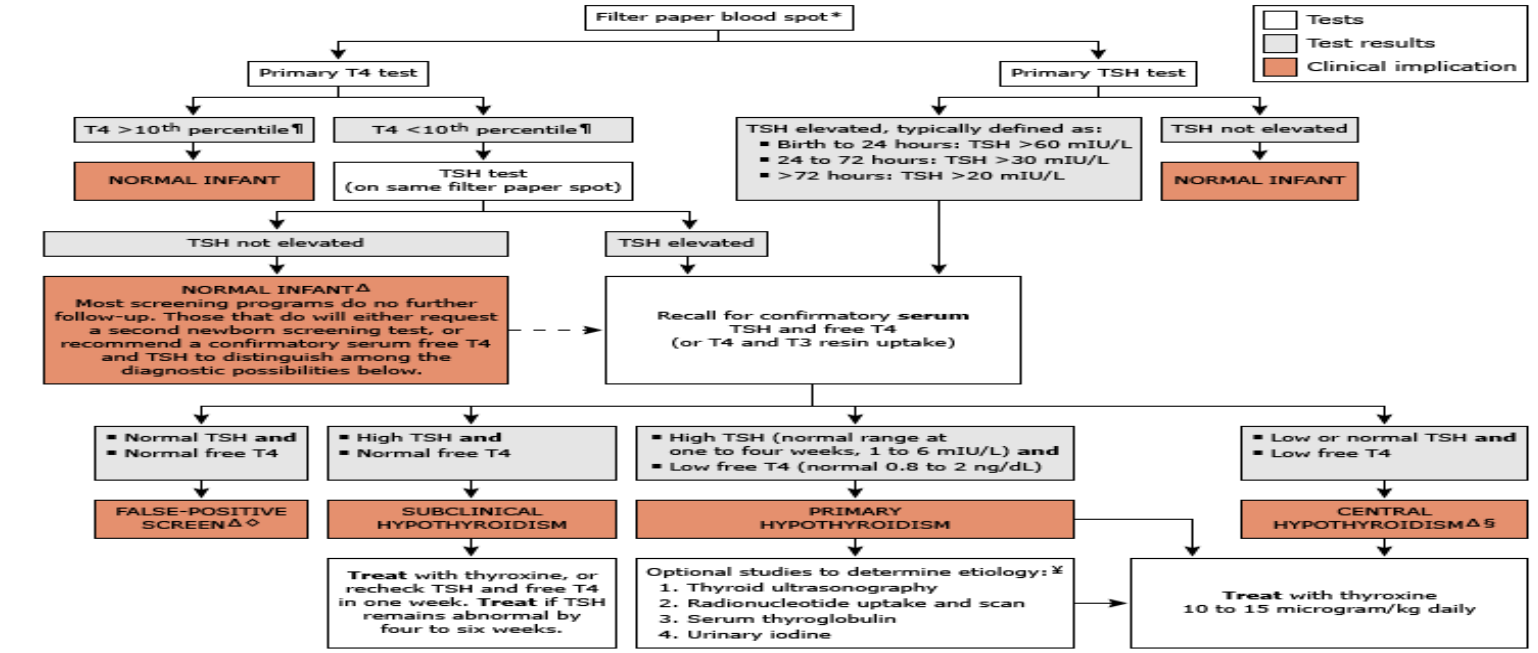
whereas infants with subclinical hypothyroidism (high blood TSH, normal blood T4) are detected more reliably by TSH testing.

Interpretation and follow-up

TSH results in **whole blood units are equivalent to approximately one-half of the corresponding serum value**. An abnormally high hematocrit may result in modest reductions in the TSH concentration on the screening test, which may be important for infants with borderline result

Infants with TSH values above certain levels on the initial newborn screen, usually >30 mIU/L in **serum units** (equivalent to >**15** mIU/L in **whole blood** units), are recalled for clinical evaluation and serum testing (algorithm 1), which occurs around one week of age. If a second test is done, the results should be interpreted using a lower TSH cutoff (**typically >10 mIU/L after one week of age)**. Unfortunately, some screening programs do not **adjust for the infant's age**, leading to false-negative results for infants with mild hypothyroidism

Algorithm for screening and diagnosis of congenital hypothyroidism [1,2]



This algorithm shows the pathway for newborn screening using either a primary T4 technique (left-hand pathway) or primary TSH technique (right-hand pathway). A third technique employed by some newborn screening programs is to perform these tests simultaneously for the initial screen; in those programs, infants with abnormal results either proceed directly to confirmatory serum testing or undergo a second screening test before referral. The exact protocol varies by program.

T4: thyroxine; TSH: thyroid-stimulating hormone (thyrotropin); T3: triiodothyronine.
* Filter paper blood spot TSH cutoffs are expressed as serum values. To get equivalent whole blood values, divide the serum value by 2. Screening programs in North America typically report serum values, whereas screening programs in Europe often report whole blood values.
¶ For newborn screening programs that employ primary T4 screen, samples with T4 values below a certain concentration (usually less than the 10th percentile for the laboratory's samples on the same day) undergo a TSH measurement on the same filter paper blood spot.
Δ Prematurity or nonthyroidal illness may cause false-positive results on serum testing and/or the initial screen, with low T4 and normal TSH.
◇ This result usually indicates that the screen was a false positive, especially if the screening TSH was only mildly elevated. However, 1 study suggests that infants with these findings are at increased risk for developing subclinical hypothyroidism later in life[3].
§ Rarely, infants with low TSH and low free T4 are ultimately proven to have primary hypothyroidism (rather than central hypothyroidism) because the expected rise in serum TSH is delayed.
¥ Thyroid imaging studies may be useful for infants with borderline results of serum testing, or with goiter or suspected transient hypothyroidism. Measurement of the urinary iodine concentration may be useful for infants with suspected exposure to excess iodine or iodine deficiency.

References:

1. *American Academy of Pediatrics, Rose SR, Section on Endocrinology and Committee on Genetics, American Thyroid Association, et al. Update of newborn screening and therapy for congenital hypothyroidism. Pediatrics 2006; 117:2290.*
2. *Léger J, Olivieri A, Donaldson M, et al. European Society for Paediatric Endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. J Clin Endocrinol Metab 2014; 99:363.*
3. *Leonardi D, Polizzotti N, Carta A, et al. Longitudinal study of thyroid function in children with mild hyperthyrotropinemia at neonatal screening for congenital hypothyroidism. J Clin Endocrinol Metab 2008; 93:2679.*

Using this screening technique, **0.1 percent of infants in the population are recalled for further testing** and approximately **one-half of these are diagnosed with hypothyroidism**.

Infants **who "pass" an initial screening** test but are then detected with **abnormal results on the second** (and sometimes third) screen are recalled for further testing, consisting of a full set of thyroid function tests on a blood sample obtained by venipuncture. Infants with this unusual pattern of screening tests may have **equivocal serum thyroid function** tests; in selected cases, **imaging may help** make a management decision

- **False-negative results** – The likelihood of false-negative results (ie, the sensitivity of newborn screening) depends on the type of hypothyroidism and on the technique used by the screening program:
- Newborn screening using **any of the above techniques** is generally **highly sensitive for detecting infants with primary hypothyroidism**.
- Newborn screening has low sensitivity for detecting central hypothyroidism. **Central hypothyroidism is not detected by newborn screening programs that use TSH screening alone.** Moreover**, even** those programs that employ primary T4 testing fail to detect many cases of congenital central hypothyroidism because early on, these infants often have T4 levels above the cutoffs that are typically used by screening program

- Newborn screening will **miss infants with subclinical hypothyroidism if the program uses the T4-**based screening technique.
- If a screening sample is collected **later than the usual age (one to four days of life), the test may fail to detect mild hypothyroidism** unless the reference range is adjusted for the infant's age since the TSH values decrease sharply during the first week of life [101]. Many screening programs do not use age-specific cutoffs for TSH.
- The initial screening test in an affected **monozygotic (monochorionic) twin may be normal**. For unknown reasons, most monozygotic twins are discordant for congenital hypothyroidism, such that shared blood supply may temporarily normalize thyroid function in the affected twin. Most screening programs therefore recommend a **second routine screening test in same-sex twins**.

●False-positive results

•**Primary T4 with follow-up TSH screening** technique – False-positive cases occur chiefly because the T4 cutoff is set relatively high (<10th percentile), leading to capture of many normal babies. Further misidentification may **occur if the specimen is obtained early in life (<24 hours of age)** when the TSH is physiologically elevated as part of the postnatal TSH surge, which peaks at approximately 60 to 80 mIU/L, 30 minutes after delivery. For infants with **positive results of the initial screen, a screening program may either request a second heel-prick screening specimen for retesting or request confirmatory serum testing.** As noted above, there are approximately five false-positive cases for every true case of congenital hypothyroidism with this screening approach.

- **Primary TSH screening technique** – The false-positive rate is greatly influenced by the **timing of collection** of the specimen (following the postnatal TSH surge). To reduce the rate of false positives, many screening programs use age-related TSH cutoffs. As noted above, there is approximately one false-positive case for every true case of congenital hypothyroidism with this screening approach.

False-positive screens may lead to unnecessary parental **anxiety** as well as a potential rise in overall **costs** because of unnecessary recall of patients and need for further testing.

DIAGNOSIS

In the **majority of cases**, the diagnosis of hypothyroidism can be confirmed or excluded by results of **serum tests of thyroid function**, informing the decision to start thyroid hormone treatment.

If the diagnosis of hypothyroidism is confirmed, other studies (such as thyroid radionuclide uptake and scan, ultrasonography, serum thyroglobulin, tests for thyroid autoantibodies, or urinary iodine excretion) **may be performed** to identify the cause.

Serum tests of thyroid function

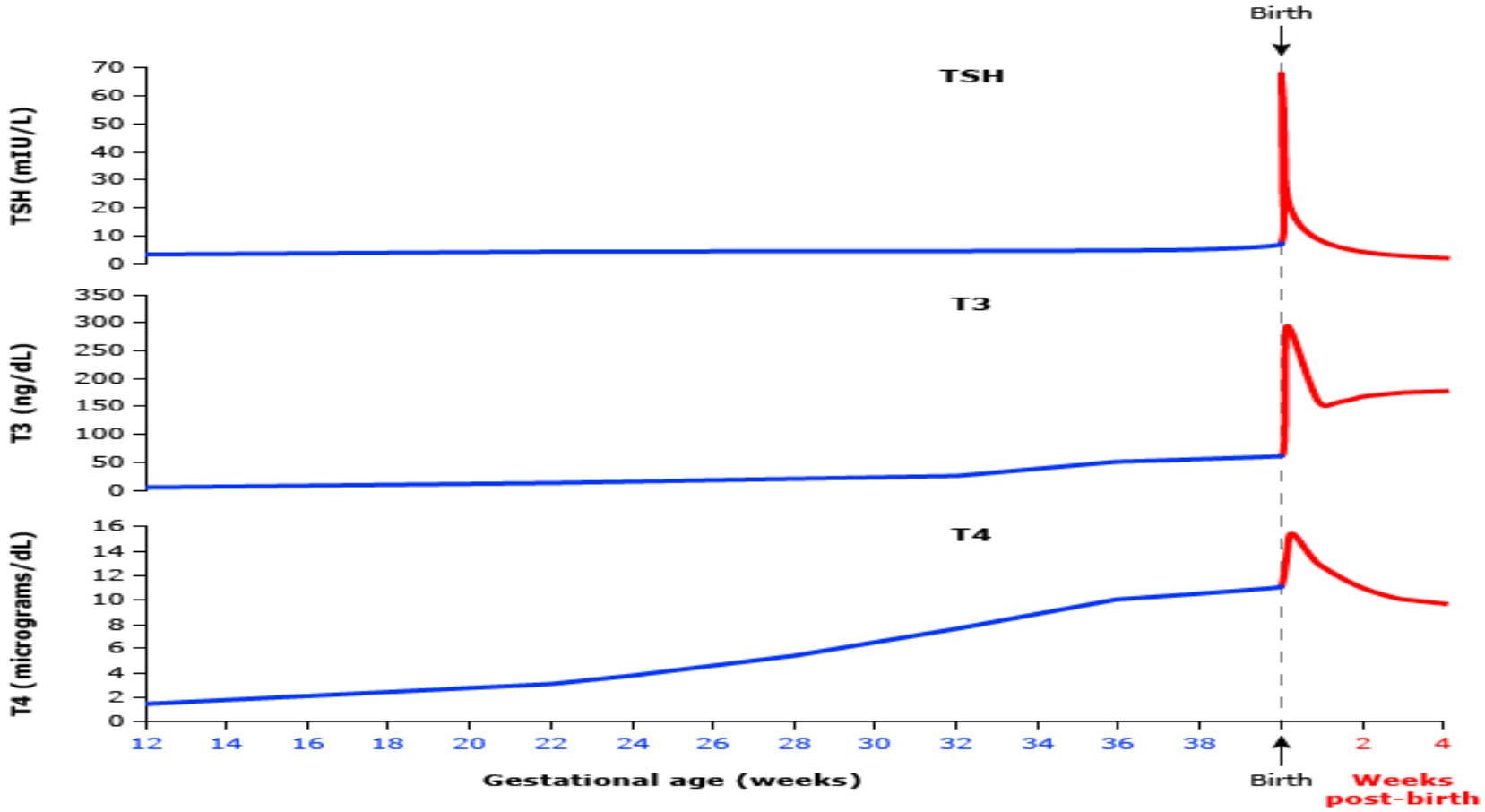
When abnormal results are reported for the newborn screen, a blood sample should be obtained by venipuncture to confirm or exclude the diagnosis of hypothyroidism, measuring TSH,free T4 or total T4 . This strategy also applies *if hypothyroidism is suspected because of clinical* symptoms (eg, if the infant had not been identified by a screening program). Results of these tests help to determine the type of hypothyroidism and treatment approach and can be interpreted as follows (algorithm 1):

High TSH, low free T4 — These results on serum testing confirm the diagnosis of **primary hypothyroidism.**

One must keep in mind that serum **T4 concentrations are higher in the first few weeks** of life in normal infants than in adults because of the surge in TSH secretion that occurs soon after birth (figure 2). Serum **TSH concentrations rise abruptly to 60 to 80 mIU/L, typically peaking 30 minutes after birth**. The serum TSH concentration **then decreases rapidly to approximately 20 mIU/L 24 hours after delivery and then more slowly to 6 to 10 mIU/L at one week of age**

A serum **TSH >10 mIU/L is elevated in infants after one week of age**. Between **one and four days of life, the normal range for serum total T4 is approximately 10 to 22 mcg/dL** (129 to 283 nmol/L) and the **normal range for serum free T4 is approximately 2 to 5 ng/dL** (25 to 64 pmol/L).

Thyroid physiology in the fetus and newborn



Normal patterns of change for TSH, total T4, and total T3 are depicted for the fetus (beginning at 12 weeks gestation) and continuing for the first 4 weeks of life in the newborn.
NOTE: To convert T3 in ng/dL to nmol/L, multiply by 0.01536. To convert T4 in mcg/dL to nmol/L, multiply by 12.87.

TSH: thyroid-stimulating hormone; T3: triiodothyronine; T4: thyroxine.

Data from:

1. *Thorpe-Beeston JG, Nicolaides KH, Felton CB, et al. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. N Engl J Med 1991; 324:532.*
2. *Fisher DA. Thyroid physiology in the perinatal period and during childhood. In: Werner's and Ingbar's The Thyroid, Braverman LE, Utiger RD (Eds), Lippincott-Raven, Philadelphia, 1996. p.974.*
3. *Williams FL, Simpson J, Delahunty C, et al. Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. J Clin Endocrinol Metab 2004; 89:5314.*

High TSH, normal free T4 or total T4 — These results on serum testing define **subclinical hypothyroidism**.

If the TSH is significantly elevated (eg, >20 mIU/L), treatment should be initiated.

In cases where the **serum TSH is marginally elevated (eg, 6 to 20 mIU/L), one option is to monitor carefully, repeating a serum TSH and free T4 in one week**.

Some infants will normalize TSH without treatment using this approach. However, **if the serum TSH remains >10 mU/L by four weeks of age, we recommend starting thyroid hormone treatment because the development of the central nervous system is critically dependent on adequate amounts of T4.**

Low or normal TSH, low free T4

These results on serum testing suggest the possibility of **central hypothyroidism** (table 1). Treatment should be promptly initiated for infants with these findings, unless the infant is premature and/or has nonthyroidal illness that explains the finding.

Premature infants or infants with nonthyroidal illness also may have normal TSH and low total and free T4 serum concentrations .

We **do not recommend treatment for these infants** unless there is other evidence of hypothalamic or pituitary disease.

It is important that gestational and postnatal normative values be used.

- **Low T4, normal free T4, and normal TSH**

This combination of findings indicates the presence of a deficiency of binding proteins, the most common of which is **T4-binding globulin deficiency, an X-linked recessive disorder** that occurs in approximately 1:4000 newborns, predominantly males.

These infants are **euthyroid and do not require treatment**.

ADDITIONAL TESTING

Additional evaluation may be helpful for **selected infants.**

In those cases where thyroid function appears to be improving and is almost normal before treatment, additional testing may facilitate a decision about whether to treat versus observe.

However, in most cases, **these tests do not change management, and we consider them to be optional**.

Thyroid imaging

Thyroid **ultrasonography or radionuclide uptake measurements and imaging ("thyroid scan")** provide information about the underlying etiology, eg, thyroid dysgenesis or one of the types of dyshormonogenesis.

We do **not** recommend either test routinely, because for most cases, the results do not alter management.

However, the tests may provide useful information in infants with the following characteristics:

- Infants with **minor abnormalities in thyroid function**, in whom it is not clear whether thyroid hormone treatment is indicated (eg, thyroid-stimulating hormone **[TSH] 6 to 10 mIU/L, with free thyroxine (free T4) in the normal reference range for age**). In such an infant, a finding consistent with some form of thyroid dysgenesis, eg, ectopically located thyroid tissue, would support a diagnosis of hypothyroidism

- **Infants with a goiter** in whom an enzymatic defect in T4 synthesis is suspected; most of these infants have normal or high uptake values in normally located.

As these defects are hereditary (autosomal recessive), this finding allows counseling about risk in future children.

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- **Infants suspected of having transient hypothyroidism** (eg, due to iodine deficiency or exposure, maternal autoimmune thyroid disease, or antithyroid drugs during pregnancy).

The presence of a normal thyroid gland on ultrasonography or scan supports a diagnosis of mild, possibly transient, hypothyroidism.

Cases of excess iodine exposure likely will have reduced radionuclide uptake until the excess iodine is cleared.

Cases of transient hypothyroidism due to transplacental passage of maternal TSH-receptor blocking antibodies typically do not have radionuclide uptake or image on scanning, but on ultrasonography, a normal thyroid gland may be visualized

Thyroid ultrasonography and color flow Doppler If the clinician chooses to do thyroid imaging, we recommend starting with ultrasound to characterize thyroid shape, size, and location. If an **ectopic thyroid gland is identified by ultrasound (typically found in the lingual, sublingual, or subhyoid areas), radionuclide imaging will not be necessary**, thus avoiding radiation exposure and expense. However, ultrasound is not as reliable as radionuclide imaging in identifying cases of thyroid dysgenesis

Color flow Doppler ultrasonography may be superior to gray-scale ultrasonography. It detected ectopic thyroid tissue in 90 percent of infants with congenital hypothyroidism and ectopic tissue detected on radionuclide imaging

Thyroid radionuclide uptake and scan

If the ultrasound study does not detect ectopic thyroid tissue, then a thyroid radionuclide uptake and scan may help to identify cases of thyroid dysgenesis.

A large gland in a normal location typically is seen with one of the enzymatic defects

Thyroid autoantibodies

For infants born to *mothers with known autoimmune thyroid disease, and in families where a previous sibling was detected with congenital hypothyroidism with a transient course,* measurement of TSH-receptor blocking antibodies (in the mother and/or fetus) may be useful in diagnosing this form of transient congenital hypothyroidism.

Serum thyroglobulinconcentration

Measurement of serum thyroglobulin has been advocated as a means to distinguish among the causes of congenital hypothyroidism. For *infants with no thyroid gland seen by imaging, a low serum thyroglobulin level is consistent with thyroid aplasia, while in infants with a large gland on imaging, a low serum thyroglobulin level points to a thyroglobulin gene defect*

Urinary iodine concentration

If there is a **history of iodine exposure, or if the infant is born in an area of endemic goiter** , measurement of *urinary iodine can confirm an excess (or deficient) state*.

In infants thought to have iodine-induced hypothyroidism, any continuing **iodine exposure should be discontinued. If thyroid function does not normalize within a few weeks, T4 therapy should be given for several months and then gradually withdrawn**.

Treatment and prognosis of congenital hypothyroidism

Congenital hypothyroidism is **one of the most common treatable causes of intellectual disability** (mental retardation).

Screening programs have been established in most developed countries to detect and treat this disorder, which affects approximately **1 in 2000 to 1 in 4000 newborn**

Rationale

Delays in diagnosis and treatment of congenital hypothyroidism will result in **impaired neurocognitive outcome, as measured by intelligence quotient (IQ**). Even after diagnosis, IQ and neurologic development may suffer if the infant has suboptimal management during the **first two to three years of life, a time when thyroid hormone is critical for normal brain developmen**t.

Thus, appropriate initial therapy and follow-up are essential to ensure optimal dosing of thyroid hormone, with monitoring and dose adjustments and support for the family to encourage close adherence to treatment

Levothyroxine

Oral levothyroxine is the treatment of choice. Although triiodothyronine (T3) is the biologically active thyroid hormone, the majority of brain T3 is derived from local deiodination of thyroxine (T4); thus, it is not necessary to use T3.

Both **the timing and dose of thyroid hormone replacement are important**:

Timing and dose — To correct hypothyroxinemia **as rapidly as possible, treatment should be initiated for any infant with a clearly positive screening test as soon as confirmatory blood samples have been drawn**, pending results

. In cases in which **screening tests are borderline, a treatment decision can be postponed** until after results of the confirmatory tests return

- **Term infants** – We suggest a starting levothyroxine dose of **10 to 15 mcg/kg/day for term infants.**

This usually amounts to giving 37.5 or 50 mcg/day since these doses can be readily prepared from the available levothyroxine tablets (25 or 50 mcg)

- **Preterm infants** – In preterm and other low birth weight infants, **we also recommend using a levothyroxine dose of 10 to 15** mcg/kg/day, though in milder cases, often characterized by delayed thyroid-stimulating hormone (TSH) elevation, a starting dose of 8 to 12 mcg/kg/day is sufficient to normalize thyroid function.

Severe hypothyroidism

For infants with severe hypothyroidism (eg, those with a **pretreatment serum total T4 <5 mcg/dL or a fT4 <0.4 ng/dL we suggest selecting a dose in the upper one-half of the recommended range (ie, 12.5 to 15 mcg/kg/day**). This is because rapid replacement with adequate doses of levothyroxine is particularly important in infants with severe hypothyroidism to prevent cognitive and psychomotor delay.

Mild hypothyroidism

In mild cases of congenital hypothyroidism (confirmatory serum **TSH 5 to 20 mU/L, with a borderline low or normal range fT4), we suggest starting at a levothyroxine dose of 8 to 10 mcg/kg/day**.

Administration

Only levothyroxine **tablets,** available as 25 or 50 mcg, should be used. There is limited experience with liquid preparations, and levothyroxine suspensions prepared by individual pharmacists may result in unreliable dosing.

The levothyroxine tablet should be crushed; mixed with **breast milk, formula, or water**; and fed to the infant.

The **absorption of levothyroxine** is somewhat reduced by administration with food and formula. However, requiring that the medication be given separately from meals may be difficult for the family and reduce compliance . ***Thus, instead of requiring that it be administered on an empty stomach, we ask the family to be consistent in how they administer the medication, in both time of day and with or without food***.

The levothyroxine dose then can be **adjusted** based on serum fT4 (or T4) and TSH levels.

Coadministration of levothyroxine with any of the following may reduce drug absorption and should be avoided:

- Soy formula
- Preparations with *iron or calcium*
- *Antacids (aluminum hydroxide) or infant "colic" drops (simethicone)* [18]

Although the US Food and Drug Administration (FDA) considers all forms of levothyroxine to be bioequivalent, a prospective randomized crossover study concluded that **generic and brand-name levothyroxine are not bioequivalent for children with severe congenital hypothyroidism** , while another retrospective study found no differences.

if an infant is switched from brand to generic, or from one brand to another brand, or one manufacturer of generic to another manufacturer of generic levothyroxine, **we recommend checking serum TSH and fT4 after six weeks to determine if a dosing adjustment is required**

Treatment goals

The **overall goals of treatment are to assure normal growth and neurodevelopmental outcome. This is achieved by restoring the serum fT4 (or T4) and TSH concentrations to the normal range as rapidly as possible, followed by dose adjustment to ensure continued clinical and biochemical euthyroidism**.

- **FT4 or T4** – Target is serum **fT4 or T4 concentration in the upper one-half of the normal range for age**:
  - For **serum fT4**, the target varies with the assay method used in the testing laboratory. For example, if the reference range for a specific fT4 assay method is 0.8 to 2.3 ng/dL , the aim of treatment would be to keep the serum fT4 between 1.4 and 2.3 ng/dL
  - For **serum T4**, the target is 10 to 16 mcg/dL (130 to 206 nmol/L).
- **TSH** – Target is **serum TSH in the normal range (ie, 0.5 to 5.0 mU/L) and, optimally, the lower end of this range (ie, 0.5 to 2.0 mU/L).**

The **serum fT4 (or T4) concentration typically reaches the target range within one to two weeks after initiating levothyroxine therapy. Serum TSH may take two to four weeks to reach the target range**, depending on the degree of elevation prior to treatment.

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despite what appears to be a normal levothyroxine dose, some infants with congenital hypothyroidism will manifest ***persistent mild serum TSH elevations (5 to 20 mU/L) despite serum fT4 (or T4) values in the target range***.

This appears to be the result of transient mild thyroid hormone resistance, due to resetting of the pituitary-thyroid feedback threshold because of intrauterine hypothyroidism

Prolonged overtreatment (>3 months) should be avoided because it can lead to complications. Persistently high serum fT4 or T4 concentrations for age (especially if **the fT4 is above 2.4 ng/dL** or **T4 is above 16 mcg/dL** combined with suppressed **TSH concentrations (<0.5** mU/L), may adversely affect the tempo of brain development; have adverse effects on cognitive development, temperament or attention span; and cause premature craniosynostosis.

Laboratory monitoring and dose adjustment

We recommend monitoring of serum fT4 (or T4) and TSH at the following intervals to ensure optimal levothyroxine dosing:

- Two weeks after the initiation of levothyroxine treatment and every 2 weeks until serum TSH level is normalized.
- Every one to two months during the first 12 months of life and monthly for those with moderate to severe hypothyroidism. Infants in this age group typically need frequent dose adjustments due to their rapid growth], and those with moderate to severe hypothyroidism are particularly likely to require dose adjustments.

- Every one to three months between one and three years of age.
- Every 6 to 12 months thereafter until growth is complete.
- Four to six weeks after any change in dose or after changing brands of levothyroxine (eg, changing from one generic to a different generic brand).
- At more frequent intervals when compliance is questioned or abnormal results are obtained.

Despite treatment using recommended levothyroxine doses, some infants will manifest thyroid function test results that make it difficult to know whether continuing the same dose or a dose increase or decrease is indicated. The two primary **thyroid test patterns** include:

- **fT4 in the upper part of the reference range and TSH mildly elevated.** Such findings may be explained by:
- Making up *several missed doses* of levothyroxine just before scheduled blood test monitoring. If this history is obtained from the parents, no dose increase in indicated, but we would recommend rechecking thyroid function tests in one month.

- *Mild underdosing* – Lacking a history of making up missed doses, we recommend making a small dose increase and rechecking serum fT4 and TSH in four weeks; those patients who were mildly underdosed will be euthyroid with this dose adjustment.
- *Thyroid hormone resistance* In this situation, if the levothyroxine dose is increased to normalize TSH, patients may manifest thyrotoxic clinical features.

- **fT4 elevated and TSH in the normal reference range**. Such findings may be explained by:
- The elevated fT4, though higher than this patient's "genetic set point," is required to generate normal T3 levels (for example, in patients with thyroid aplasia who lack the 20 percent of T3 produced by the normal thyroid gland).
- The fT4 reference range reported for this assay is not appropriate for a neonate or infant, who tend to have somewhat higher normal reference ranges.
- The "elevated fT4" may actually be normal for this patient (ie, >2 standard deviations used to establish the reference range) but at the "genetic set point" for this patient.

In each of these cases, **no decrease in the levothyroxine dose is indicated, because TSH is normal; the chief laboratory finding of overtreatment is a suppressed serum TSH level.**

LONG-TERM MANAGEMENT

in the first few decades following initiation of newborn screening, **approximately 90 percent of cases had permanent congenital hypothyroidism requiring lifelong treatment.**

Beginning around the year 2000, the *incidence of congenital hypothyroidism increased from 1:4000 to 1:2000; this increase was due to detection of milder cases of hypothyroidism, including cases in preterm or low birth weight infants* with "delayed thyroid-stimulating hormone (TSH) elevation," in which the hypothyroidism is usually transient. With the detection of these milder cases, follow-up studies showed that approximately *70 percent were permanent, while 30 percent had a transient form of hypothyroidism*.

Assessment of permanent versus transient hypothyroidism

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Permanent hypothyroidism

- **Thyroid dysgenesis** or a confirmed defect in thyroid hormone biosynthesis or secretion **(dyshormonogenesis**) Thyroid dysgenesis is likely if ***ultrasonography*** *shows absent thyroid tissue or an ectopic gland or if a* ***scan*** *shows an ectopic gland.* If an initial radionuclide scan shows absence of thyroid tissue, this should be confirmed by ultrasonography because a scan can appear to show aplasia in infants with TSH receptor-blocking antibodies, a transient form of hypothyroidism.

These tests are considered **optional at initial diagnosis** because in most cases, the results are not required for management decisions. Some clinicians elect to perform these studies **after age three years in cases where permanent hypothyroidism has not been established**.

- **Central hypothyroidism**

– Most infants with confirmed central hypothyroidism have **permanent hypothyroidism**, in particular, those with *other documented pituitary hormone deficiencies and those with demonstrated congenital midline defects (*eg, optic nerve hypoplasia/septo-optic dysplasia).

Approximately **20 percent of cases of congenital central hypothyroidism have isolated TSH deficiency** without a known congenital anatomic defect. In these cases, **we recommend reevaluation after age three years to confirm that the hypothyroidism is permanen**t

If the cause of congenital hypothyroidism is unknown, the patterns of thyroid function tests can provide supportive evidence. **Permanent hypothyroidism is likely if the patient has ever had a rise in the serum TSH concentration to above 10 mU/L after the first year of life in the setting of insufficient levothyroxine replacement**.

Transient hypothyroidism

Transient hypothyroidism has several causes, and, likely, duration depends on the cause:

- *Maternal autoimmune thyroid disease* with transplacental transfer of maternal TSH receptor-blocking antibodies – Maternal TSH receptor-blocking antibody levels *typically fall and disappear between six weeks to six months of age*.

Thyroid hormone *treatment may be discontinued at this point, although it is also reasonable to treat until age two to three years of age before discontinuing treatment and confirming normal thyroid function*.

- ***Excessive iodine exposure to the fetus or newborn*** – The majority of cases of hypothyroidism caused by iodine excess will recover *normal thyroid function within a few weeks of discontinuing the iodine*; such cases require ***monitoring*** *of TSH and free thyroxine (fT4) to confirm recovery to euthyroidism but generally* ***do not*** *need treatment*

- *Iodine deficiency* – Cases of iodine deficiency are quickly corrected by adequate iodine ingestion.
- "*Consumptive hypothyroidism*" associated with hepatic hemangiomas – Cases of "consumptive hypothyroidism" associated with large hemangiomas generally resolve by several months to one year of age, but they **require levothyroxine treatment until the hemangioma resolves.**

- *Pattern of "delayed TSH elevation" in preterm infants*

Some preterm infants have **delayed serum TSH elevation**, characterized by low serum T4 values on initial newborn screens and delayed elevation in screening TSH values (eg, TSH rising to >20 mU/L [serum]. For infants with this pattern, we **recommend levothyroxine treatment, with a trial off after two to three years of age**

If the cause of congenital hypothyroidism is unknown,

transient hypothyroidism is likely if initial *imaging by ultrasound showed a normally located (eutopic), normal-sized thyroid gland and **if** the infant has never had an abnormal TSH elevation while on levothyroxine treatment, **never** required an increase in dose, **or** requires a relatively low dose to maintain euthyroidism (eg, <2.5 mcg/kg/day)* .

Trial off of treatment

If permanent hypothyroidism has not been established by one of the above findings and the child is three years or older, the possibility of transient hypothyroidism can be evaluated by a **trial of discontinuing levothyroxine therapy for 30 days**:

- If a low serum fT4 (or T4) and high TSH concentration are found, permanent hypothyroidism is confirmed and treatment **should be restarted**.

- If the serum fT4 (or T4) and TSH values remain normal, the hypothyroidism was probably transient. In this case, the child can be **observed off of levothyroxine.**
- If the results of thyroid function tests are inconclusive, **careful follow-up** and subsequent retesting are indicated.

Management of patients with transient hypothyroidism

if transient hypothyroidism is likely and thyroid function **tests are normal after a 30-day trial off of levothyroxine, the child can be observed off of levothyroxine. The child should be examined periodically.**

Laboratory assessment of thyroid status should be performed if the child develops any clinical features suspicious for hypothyroidism, such as slowing of growth.

Patients with permanent hypothyroidism

Patients in whom congenital hypothyroidism **proves to be permanent will require thyroid hormone replacement throughout life**.

These patients are managed by titrating the levothyroxine dose based on periodic measurements of serum TSH and fT4 (or T4), as for an adolescent or adult with acquired hypothyroidism.

PROGNOSIS

In general, **these infants grow and develop normally**. The psychometric outcome is much improved over the prescreening era, but some *infants with severe hypothyroidism or those who are inadequately treated in the first two or three years of life have intelligence quotients (IQs) below* those of normal children.

Neurodevelopment and functional outcomes

The long-term neurodevelopmental and functional outcome of individuals with congenital hypothyroidism is *generally good for infants who are treated early (beginning at two to six weeks of life*) and optimally through the first three years of life; their global IQs are similar to those of normal infants

- **Inadequate treatment including noncompliance**

Suboptimal levothyroxine dosing during infancy and the first few years of life ***adversely affects neurocognitive outcomes***. In one study, infants who were inadequately treated in the first three years of life (estimated levothyroxine dose <5 mcg/kg/day) had worse cognitive outcomes compared with the larger, adequately treated group (mean **IQ score 87 versus 105**).

- **Severity of disease** – Some screening programs report that more severely affected infants, as judged by a *lower serum T4 concentration or immature skeletal maturation at diagnosis, have lower IQ scores later in life*

- **Early versus delayed treatment**

infants who started "*early" (12 to 30 days of age) had IQ scores 15.7 points higher than infants who started "later" (>30 days of age*)

As most infants are now started at an earlier age and treated with higher levothyroxine doses, future results may be better.

- **High versus low starting dose of** levothyroxine

evidence suggests that children treated with the recommended *starting dose of 10 to 15 mcg/kg/day have a better IQ outcome* than children started on lower doses

Other neurologic sequelae — A small proportion of infants with congenital hypothyroidism, including those with *normal IQ scores, can have other neurologic problems, such as gross and fine motor incoordination, ataxia, increased or decreased muscle tone, short attention span, speech defects,.*

Sensorineural hearing loss was reported in up to 20 percent of children with congenital hypothyroidism

We recommend routine hearing tests in infants with congenital hypothyroidism;

Growth — Long-term follow-up of children with congenital hypothyroidism detected by newborn screening shows that treated children have normal growth patterns and *normal adult height*