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Neonatal effects of thyroid diseases in pregnancy and approach to the infant with increased TSH: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report

Gebelikte tiroid hastalıklarının neonatal etkileri ve TSH yüksekliği olan bebeğe yaklaşım: Türk Neonatoloji ve Çocuk Endokrinoloji ve Diyabet Dernekleri uzlaşı raporu

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Abstract

Thyroid functions in the fetus and newborn carry importance in terms of the baby's health and development of the central nervous system. Maternaliodine deficiency, exposure to iodine, thyroid diseases (Hashimoto thyroiditis, Graves') and drugs used by the mother affect thyroid functions in the fetus. Reflections of these effects are observed immediately after delivery. Investigation of the mother in terms of thyroid diseases during pregnancy, recognition and appropriate assessment of the required conditions, screening of all newborns in the first days of life in terms of congenital hypothyroidism, timely and appropriate evaluation of the screening results, early diagnosis and appropriate treatment of cases of congenital hypothyroidism, assessment and management of cases of transient thyroid hormone disorders and close monitoring of the thyroid functions and development of patients in whom treatment has been initiated with a diagnosis of hypothyroidism are crucial in terms of developmental outcomes of the babies who have thyroid function disorders or hypothyroidism. This guideline was written with the objective of guiding pediatricians, neonatologists and pediatric endocrinologists in the issue of assessment, diagnosis and management of thyroid function disorders and thyroid diseases concerning the fetus and baby during gestation and neonatal period.

Keywords: Congenital, hypothyroidism, thyroid diseases, maternal thyroid problems, newborn

Öz

Fetus ve yenidoğanda tiroid fonksiyonları bebek sağlığı ve merkezi sinir sisteminin gelişimi açısından önem taşımaktadır. Annede iyot eksikliği, iyoda maruziyet, tiroid hastalıkları (Hashimoto tiroiditi, Graves' hastalığı), annenin kullandığı ilaçlar fetusun tiroid işlevlerini etkiler. Doğumdan hemen sonra da bu etkilerin yansımaları görülür. Gebelikte annenin tiroid hastalıkları açısından incelenmesi gereken hallerin tanınması ve sağlıklı değerlendirilmesi, tüm yenidoğanların yaşamın ilk günlerinde konjenital hipotiroidi için taranması, tarama sonuçlarının zamanında ve sağlıklı değerlendirilmesi, konjenital hipotiroidili olguların erken tanısı, erken ve yeterli tedavisi, geçici tiroid hormon bozukluklarının değerlendirilmesi ve yönetimi, hipotiroidi tanısı ile tedavi başlanan hastaların tiroid fonksiyon ve gelişimlerinin yaşamın ilk yıllarında yakın izlemi bu dönemde tiroid fonksiyon bozuklukları ya da hipotiroidisi olan bebeklerin gelişimsel sonuçları açısından son derece önemlidir. Bu kılavuz çocuk hekimleri, yenidoğan ve çocuk endokrinoloji uzmanlarına gebelik ve yenidoğan döneminde fetus ve bebeği ilgilendiren tiroid fonksiyon bozuklukları ve tiroid hastalıklarının değerlendirilmesi, tanısı ve yönetimi konusunda yol göstermek amacıyla kaleme alınmıştır.

Anahtar sözcükler: Konjenital hipotiroidi, maternal tiroid problemleri tiroid hastalıkları, yenidoğan

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1. Thyroid functions in the gestation period

In the gestation period, daily iodine intake should be increased to 250 mcg in order to meet the requirements of both the mother and the fetus. An increase by 30% in urinary iodine loss by way of hyperfiltraton in the gestation period is another factor in terms of increase in iodine requirement. Increased placental human chorionic gonadotropin (hCG) stimulates the thyroid gland like thyrotropin (thyroid-stimulating hormone-TSH). In addition, placental estrogen provides an increase in triiodothyronine (T3) and thyroxine (T4) levels by prolonging the half-life of thyroxine-binding globulin (TBG). Detection of T4 in coelomic fluid indicates that maternal support to the fetus starts in the early gestational weeks. The fetal thyroid gland starts to uptake iodine and synthesize T4 in the 10th week. Thyroid hormone support from the mother continues until the 20th gestational week, and thereafter, T3, T4 synthesis, and an increase in TSH continue incrementally. If dyshormogenesis or agenesis is present in the fetus, maternal support prolonges until birth. The fetal thyrotropin- releasing hormone (TRH) pool initially derives from the placenta and fetal pancreas. In the 34th gestational week, fetal hypothalamus-derived TRH synthesis matures. The ability to overcome the Wolff-Chaikoff phenomenon, which consists of iodine loading, matures after the 34th week. Maternal support is interrupted and neonatal thyroid functions start with delivery. TRH-TSH release occurs in 30 minutes with delivery; the TSH level increases to 70-90 mU/L in mature babies and 30-40 mU/L in preterm babies and the T3-T4 levels increase. A physiologic hyperthyroxinemia period is experienced in the postnatal 3-4 days and this contributes to metabolic adaptation (1-2). Thyroid function tests of pregnancy for Turkish population are shown Table 1 (3).

Table 1. Turkey data related to fT3, fT4, TSH levels in pregnancy (3)

Parameter	Mean±SD	2.5 percentile	97.5 percentile
First trimester			
fT3 (pg/mL)	3.08±0.33	2.47	3.77
fT4 (ng/dL)	1.05±0.16	0.8	1.41
TSH (mU/L)	1.31±0.51	0.49	2.33
Second trimester			
fT3 (pg/mL)	3.07±0.36	2.40	3.83
fT4 (ng/dL)	1.05±0.16	0.8	1.41
TSH (mU/L)	1.67±0.77	0.51	3.44
Third trimester			
fT3 (pg/mL)	3.06±0.34	1.92	3.56
fT4 (ng/dL)	1.04±0.16	0.8	1.39
TSH (mU/L)	2.36±0.99	0.58	4.31

TSH: thyroid-stimulating hormone

Table 2. TSH values by trimesters (1, 39)

First trimester	0.1-2.5 mU/L
Second trimester	0.2-3.0 mU/L
Third trimester	0.3-3.0 or 3.5 mU/L

TSH: thyroid-stimulating hormone

Thyroid functions are evaluated by trimeters in the gestation period (Table 2) (1).

A urine iodine level below 150 µg/dL in the gestation period is considered a criterion of iodine deficiency. A thyroglobulin level above 30 ng/mL supports iodine deficiency. However, there are studies indicating that the thyroglobulin level is not a reliable variable as an evaluation criterion for iodine deficiency. If the thyroid volume is above 18 mL in pregnancy, it is considered a criterion for goitre; if it is above 22 mL, it is definite that goitre is present (4).

2. Fetal neonatal reflections of maternal diseases

A. Iodine deficiency: Iodine deficiency present in the prenatal period or that occurs during pregnancy has a series of negative effects in the mother, fetus, newborn or in later periods of life (Table 3) (4). Salt restriction during pregnancy because of hypertension or preeclampsia and eclampsia lead to iodine deficency. Maternal smoking increases thiocyanate levels and this decreases iodine levels in both urine and breastmilk. The period between the 13th and 19th gestational weeks during which the brain T3 receptors increase, is known as the critical period in terms of the fetus (4).

Definition: Urine iodine levels below 150 µg/L in the gestation period show iodine deficiency. Urine iodine levels below 100 µg/L are diagnostic in newborns. A level of 50-100 µg/L indicates mild iodine deficiency, 20-50 µg/L indicates moderate iodine deficiency, and a level below 20 µg/L indicates severe iodine deficiency. An increase in thyroglobulin levels may be observed, but it may not always be reliable in terms of indicating iodine deficiency in gestation (9). Thyroid functions should be checked starting from the 12nd gestational week (4).

Treatment: Women should have a daily iodine intake of at least 250 µg. Oral iodine tablets (100, 200 µg tablets) or one drop of lugol solution per month can be given to pregnant women for whom iodized salt intake has been limited. However, it has been concluded that studies that were conducted to elucidate if iodine supplement

Table 3. Maternal, fetal, neonatal and long-term effects of iodine deficiency (4)

Maternal-Fetal
• TInsufficient fertilization, preeclampsia, anemia, shoulder presentation at birth, early and late abortus (constitute 6% of all abortus), stillbirth, low birth weight (6.8% in the general population, 22% in iodine deficiency), congenital malformations including mainly meningocele, microcephaly, neurologic or goitrous cretinism, cerebellar developmental defects, delayed myelinization, increased sensitivity of the thyroid gland to nuclear radiation after the age of 12 weeks, gradually increasing thyroid volume in smoker mothers, occurence of goitre and nodule
Newborn
• Increased perinatal mortality, goitre, neonatal hypothyroidism, increased frequency of thyroid dysgenesis, transient hyperthyrotropinemia, increased recall rate in congenital hypothyroidism screening, increased sensitivity of the thyroid gland to nuclear radiation
Advanced ages
• Children with sequela showing a picture of cretinism, attention-deficit/hyperactivity disorder, autism

was beneficial in pregnancy were insufficient according to metaanalysis results (5). In iodine deficiency in newborns, iodine can be given at a dose of 150 µg/day in babies weighing below 2500 g and at a dose of 100 µg/day in babies weighing above 2500 g. Kurtoğlu et al. (4) administered thyroxine to one group and thyroxine + 100 µg iodine to another, and it was found that the results were not different. There are controversial studies related to the benefit of iodine supplementation in preterm babies.

B. Iodine overload: Excessive use of iodized salt during pregnancy, iodized antiseptics, iodine-rich seeweed soups, contrast-enhanced radiologic investigatons, iodized cough syrups, and other medications may cause iodine overload. A dietary iodine intake above 500 µg daily during pregnancy leads to iodine overload.

Iodine overload causes maternal-fetal hypothyroidism and goitre by leading to Wolff-Chaikoff phenomenon in the mother and fetus. It may lead to a picture of maternal hyperthyroidism if the mother has multinodular, uninodular goitre. Perinatal-postnatal iodine overload is mostly related to the use of iodized antiseptics during cesarean delivery, perineal incisions or umbilical care. In addition, it is also used for prophylaxis of "ophthalmia neonatorum" in some centers, but its use is not recommended because its efficiency in preventing gonococcal infections is not high. Iodine overload may also occur by way of breastmilk (2).

Diagnosis: An iodine level above 200 µg/L in the pregnant mother's urine, in the baby's urine, and in breastmilk is diagnostic. In newborn babies, fT4 is found to be low and TSH and thyroglobulin levels are high.

L-thyroxine treatment is given temporarily for hypothyroidism emerging in newborn babies. If hyperthyroidism occurs in the newborn, which is observed rarely, treatment is planned according to the clinical picture.

C. Thyroid autoantibodies: TSH receptor (TSHR)-stimulating or blocking antibodies found in the mother cause a picture of fetal hypothyroidism or hyperthyroidism. Antithyroid peroxidase (anti-TPO) antibodies cause hypothyroidism by disrupting thyroid hormone synthesis and may cause abortus in the mother (6). A separate assessment protocol is not needed for babies of mothers who have Hashimoto's thyroiditis.

D. Drugs: Maternal use of antithyroid drugs, propronalol and D-penicillamin may cause fetal hypothyroidsm (2).

E. Maternal hyperthyroidsm: Maternal hyperthyroidism is observed in 0.4-4% of pregnancies. Graves' disease constitutes 85-92% of the cases. More rarely, toxic adenoma, subacute thyroiditis or thyroxine intake may be found. Gestational thyrotoxicosis is manifested as multiple pregnancy, hyperemesis gravidarum, nausea, vomiting, and hydatiform mole.

Graves' disease may occur in the prenatal period, during pregnancy or in the postpartum period. In patients who have previously undergone thyroidectomy or received radioactive ablation treatment, an increase in TSHR antibodies is observed in pregnancy. Graves' disease causes a series of problems in the mother and fetus (Table 4) (7).

The TSHR antibodies affecting the mother and fetus in Graves' disease are immunoglobulin G antibodies, which begin to cross the placenta in the 17-20th weeks. In this period, 10% of the maternal antibodies cross the placenta, whereas 50% cross the placenta in the 26-28th weeks and 100% cross the placenta after the 32nd week. The clinical

Table 4. Maternal and fetal effects of Graves' disease (7)

Maternal
Abortus, preterm delivery, congestive heart failure, thyroid crisis, ablaptio placenta, pregnancy-related hypertension, preeclampsia and drug-related adverse effects
Fetal
Prematurity, SGA, IUGR, goitre, hypothyroidism, stillbirth, hyperthyroidism, transient central hypothyroidism, drug-related or independent congenital malformations, increased risk for cerebral palsy in babies of mothers who have hyperthyroidism before pregnancy (the risk does increase in Graves' disease with onset in pregnancy)
Postnatal
Neonatal hyperthyroidism, transient hypothyroidism, the risk of convulsion, attention deficit and hyperacitivity is increased in babies of mothers with Graves' disease diagnosed after pregnancy compared to the general population

SGA: small for gestational age; IUGR: intrauterine growth retardation

picture begins in this period because the response of fetal TSH receptors matures after the 20th week, but marked fetal hyperthyroidism is found in the 26-28th weeks. TSHR antibodies produced in the mother may be stimulating or blocking. In cases where stimulating antibodies are dominant, fetal hyperthyroidism is observed. However, it should be kept in mind that antibodies may change character in time and be converted to the opposite group.

Methimazole or propylthiouracil is used to treat Graves' disease. Propylthiouracil is used in the first 3 months instead of methimazole because of the teratogenic effects of methimazole, and subsequently propylthiouracil is not continued and one switches to methimazole because propylthiouracil is hepatotoxic (8). Radioactive iodine treatment is contraindicated and thyroidectomy may be considered in cases of severe thyrotoxicosis. Beta-blocker treatment is considered if the mother has tachycardia, sweating and palpitation. The risk for abortus increases in mothers who are given propranolol. In the fetus, a risk in terms of bradycardia, intrauterine growth retardation, low APGAR score, respiratory depression, hypocalcemia, hyperbilirubinemia, and hypoglycemia may emerge.

The doses of antithyroid drugs are adjusted according to the degree of disease control, but propylthiouracil should not be given at a dosage above 600 mg/day and methimazole should not be given at a dosage above 40 mg/day. The drug dose is reduced or may even be discontinued towards the end of pregnancy. Congenital malformations including aplasia cutis, coanal atresia, esophageal atresia, Potter syndrome, and dysmorphic face may occur due to use of methimazole in the first trimester. However, malformations related to hyperthyroidism or propylthiouracil have also been reported. Fetal goitre and hypothyroidism may be observed depending on the dose of thionamides. In the mother, impaired liver function tests, arthralgia, leukopenia, and rash may occur. Maternal T4, TSH and TSHR antibodies are measured and goitre is investigated by fetal ultrasonography (US) in the 26-28th weeks of gestation. In the presence of fetal goitre, the fetus may have hypothyroidism or hyperthyroidism. Hypothyroidism should be considered if Doppler US shows peripheral blood perfusion and hyperthyroidism should be considered if intensive blood perfusion is found in the center and periphery. In addition, fetal thyroid functions are evaluated by performing cordocentesis. Another finding that supports the diagnosis is specification of fetal bone age. Normally, the fetal distal femoral epiphysis is visible at about the 31st week. Observation of the distal femoral epiphysis in a fetus who is in about the 28th gestational week supports hyperthyroidism, and absence of the distal femoral epiphysis in the 33rd gestational week supports hypothyroidism. TSH receptor antibodies should be measured in the 26-28th gestational week. It is known that antibody measurement is more important especially in patients who previously had Graves' disease, those who do not have a picture of thyrotoxicosis, and those receiving levothyroxine treatment. A TSH receptor antibody level above 3-fold of the normal value is important (normal <1.75, limit 5 IU/L) (7).

F. Fetal hyperthyroidism and hypothyroidism: Fetal hyperthyroidism is observed frequently in babies of mothers with Graves' disease, but may also be observed in babies of mothers with Hashimoto's thyroiditis. It occurs in relation to TSH receptor antibodies beginning from the 20th gestational week, but marked fetal thyrotoxicosis is observed from the 26-28th gestational week. Fetal signs and symptoms including tachycardia (>160/min), heart failure, increased fetal movements, fetal hydrops, goitre, advanced bone age, intrauterine growth retardation (IUGR), premature delivery, and fetal death are observed. fT4, TSH, and TSHR antibodies are measured with cordocentesis, but it should be kept in mind that cordocentesis

poses a 1% risk of fetal loss, fetal bradycardia, infection, and fetal and cord hemorrhagia, and a 5% risk of preterm labor. If fetal hyperthyroidism is present, beta blockers are initiated in association with antithyroid drugs in the mother; the dose is adjusted according to fetal growth and tachycardia, a methimazole dosage of 10-20 mg/day is administered, a fetal heart rate of about 140/min is targeted, but there is a possibility of overdose if only the heart rate is considered as a criterion. In severe cases, blocking + replacement treatment is used. In this protocol, thyroid replacement is performed while giving high-dose methimazole to the mother.

A picture of fetal goitrous hypothyroidism may occur in the presence of blocking TSHR antibodies or due to high-dose treatment. Compression to the trachea and esophagus and polyhydramniosis may be observed due to goitre. The diagnosis is made with ultrasonography and cordocentesis. Intraamniotic levothyroxine treatment is initiated in these patients. Generally, levothyroxine at a dose of 10 µg/kg/week is given for a few weeks (7).

G. Neonatal hyperthyroidism: Neonatal hyperthyroidism is generally observed in babies of mothers with Graves' disease. More rarely, it may occur in babies of mothers with Hashimoto's thyroiditis, McCune-Albright syndrome, thyroid receptor beta gene mutations, TSH receptor activating mutations, iodine overload (considerably rare), and thyroxine overdose (iatrogenic). Another important point is that biochemical pseudohyperthyroidism may be observed in babies using biotin by way of interaction.

In babies of mothers with Graves' disease, the presence of stimulating TSHR antibodies causes the clinical picture. It may be present at birth or emerges on the postnatal 5-10th day. The serum level of maternal thionamides decreases in the newborn during this period. In babies with both groups of antibodies in the serum, stimulating antibodies predominate with a decrease in blocking antibodies, which have a shorter half-life (approximately 7.5 days) and late-onset hyperthyroidism may be observed. Although the picture of hyperthyroidism generally emerges in 3 weeks, it may also occur in 45 days or even in months.

In newborns with hyperthyroidism, tachycardia, arrhythmia, hypertension, heart failure, goitre (in 50% of cases), jitteriness, hyperexitability, exagerrated Moro reflex, apnea, prolonged acrocyanosis, inability to gain weight despite excessive appetite, hepatosplenomegaly, lymphadenopathy, steady look, palpebral retraction, exopthalmus (absent in TSHR activating mutations), periorbital edema, enlarged breasts, fever, sweating, vomiting, palmar-plantar erythema, systemic-pulmonary hypertension, cheilothorax, indirect or conjugated hyperbilirubinemia, polystemia, and thrombocytopenia are observed. The bone age is advanced and craniosynostosis may be found. A diagnosis of infantile colic, congenital infection, neonatal sepsis or urticaria pigmentosa may be made in these babies. Thyroid hormone tests and thyroid ultrasonography are helpful in the diagnosis. A TSHR-stimulating antibody level above 3-fold of the normal value in the mother in the last trimester is predictive for neonatal hyperthyroidism (normal <1.75, in patients >5.0 IU/L). In treatment, methimazole, beta blockers, and lugol solution are used. The follow-up algorithm for fetal and neonatal hyperthyroidism is shown in Figure 1 (7).

H. Maternal hypothyroidism: Increased THS is found in 2-5% of all pregnant women. In regions where iodine supplementation has been applied, the most common causes include Hashimoto's thyroiditis, thyroidectomy, and Graves' disease for which radioactive iodine treatment has been administered. Goitre and hypothyroidism are observed in pregnant women who live in regions where the problem of iodine deficiency has not been solved or in pregnant women in whom salt intake has been limited for various reasons. In addition, the rate of subclinical hypothyroidism and hypothyroxinemia is high if anti-TPO is positive in the mother. It has also been shown that the risk of abortus increases in anti-TPO–positive pregnant women. The risk of hypothyroidism is 3-fold higher if type 1 diabetes is present in pregnant women. Subclinical hypothyroidism may be observed as hypothyroxinemia or marked hypothyroidism in pregnant women. Clinical symptoms may overlap with signs of pregnancy. Gestational hypertension is observed with a rate of 8% in the general population, whereas it increases up to a rate of 25% in subclinical cases, and up to a rate of 36% in severe hypothyroidism. The probability of cesarean section increases. Maternal-fetal adverse effects including abruptio placenta, anemia, postpartum hemorrhage, preterm delivery risk (if TSH is >3 mU/L in the 16th gestational week, a 3.13-fold incrase), low birth weight, and negatively affected fetal brain development are found. In recent years, it has been recommended to consider 4 mU/L as the upper limit of normal for TSH. Treatment is given in cases of marked hypothyroidism. If hypothyroidism was present before pregnancy, the dose of L-thyroxine should be increased by 25-40% beginning from the 8th week (9). If the cause of hypothyroidsm belongs only to the mother, checking thyroid functions is not needed in the baby. However, checking should be performed on the postnatal 10-14th day if the etiology affects both the mother and the baby.

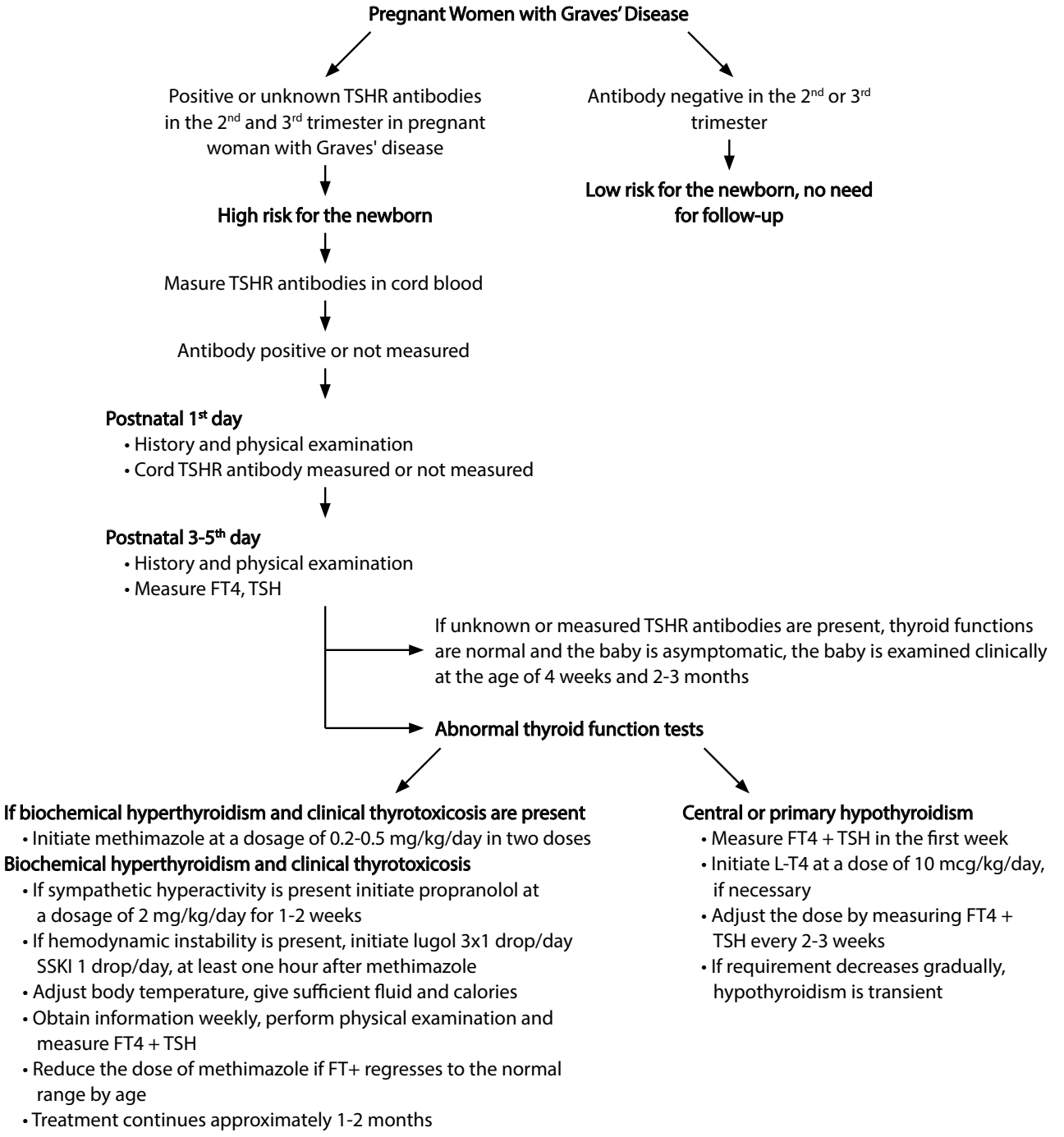

Figure 1. Algorithm of postnatal follow-up in babies of mothers with Graves' disease (7)

I. Maternal hypothyroxinemia: A FT4 level below the 2.5th or 5th percentile despite normal TSH levels in pregnant women is named hypothyroxinemia. It is found in 1-2% of pregnant women. The causes include iodine deficiency, iodine overload, pro-antiangiogenic factor imbalance, and environmental toxins (thiocyanate overload due to environmental sources or maternal smoking, pesticides, polychlorinated biphenyl (PCB), perchlorate, phytalate, bisphenol-A). If TSH is <2.5 mU/L on the primary screening, TSH should initially be remeasured every 3-4 weeks and every 6 weeks after the second half. In pregnant women, iodine, iron deficiency and environmental toxins (PCB, pesticides, thiocyanate) worsen the clinical picture; iodine and iron supplementation may also be required. In the presence of hypothyroxinemia, development of the brain and placenta is affected negatively with a decrease in glucose transporter-1 (GLUT-1) expression. The intelligence quotient (IQ) score is reduced in babies

Table 5. The American Thyroid Association (ATA) guideline for subclinical hypothyroidism and hypothyroxinemia during pregnancy (1)

Laboratory data	Levothyroxine treatment	Recommendation strength	Quality of evidence
Anti-TPO + and TSH is above the pregnancy reference values	Yes	Strong	Moderate
Anti-TPO - and TSH >10 mU/L	Yes	Strong	Low
Anti-TPO + and > 2.5 and below the upper limit	Consider	Weak	Moderate
Anti-TPO - and TSH > upper limit and <10 mU/L	Consider	Weak	Low
Anti-TPO – and TSH within the pregnancy reference values or <4 mU/L	No	Strong	High
Isolated maternal hypothyroxinemai[a]	No	Weak	Low

[a]FT4 level below the 2.5 or 5th percentile

Anti-TPO: anti thyroid peroxidase; TSH: thyroid stimulating hormone

Table 6. Follow-up guideline in babies with Down syndrome (11)

If TSH level >6 mU/L and fT4 0.7 ng/dL and/ or clinical findings are positive	Treatment is initiated
TSH 6-11, fT4 0.7-1.79 and clinical findings are absent	Treatment is unneccesary
TSH 11-20.9 mU/L, fT4 normal and clinical findings are absent	Treatment may be given or the patient may be followed up
TSH >21 mU/L	Treatment is initiated without considering fT4

in whom treatment for maternal hypothyroxinemia has been performed inadequately or not been performed at all. Different recommendations exist for the treatment of hypothyroxinemia (9).

The American Thyroid Association prepared a guideline for cases of subclinical hypothyroidism and hypothyroxinemia (Table 5) (1).

J. Fetal hypothyroidism: Transient central hypothyroidism may occur due to maternal iodine deficiency, iodine overload, thionamides, lithium, amiodarone, cobalt, use of D-penicillamin, maternal-fetal POU1F1, PROP1 mutations, blocking-type TSHR antibodies (in mothers with Graves' disease or Hashimoto' thyroiditis), and uncontrolled maternal thyrotoxicosis. Normal fetal heart rate or a fetal heart rate below 100/min, decreased fetal movements, decreased peripheral perfusion on thyroid ultrasonography, and the presence of goitre according to the Ranzini criteria are found (4). In treatment, adequate maternal intake of iodine, iron, and L-thyroxine is provided, and intraamniotic L-thyroxine injections by way of the cord are planned in severe cases. The dose of L-thyroxine is calculated as 10 mcg/kg (fetal weight) and is administered weekly for 4-8 weeks. In one study, it was shown that triiodothyroacetic acid (TRIAC) crossed the placenta easily and bound to T3 (2).

K. Down syndrome: Generally, the risk is increased in pregnancies in advanced ages. The risk of congenital hypothyroidism is increased by 30-40-fold in children with Down syndrome. Sarıcı et al. (10) found thyroid problems with a rate of 53.8% in 80 cases. Hypothyroidism was observed in 2 cases, iodine deficiency was observed in 12 cases, iodine overload was observed in 4 cases, and hyperthyrotropinemia was observed in 32 cases. The Scotland guideline is used in babies who are found to have Down syndrome (Table 6) (11).

L. Maternal systemic lupus erithematosus (SLE) and thyroid: In cases of maternal SLE, anti-TPO and antithyroglobulin (anti-TG) are increased and thyroid problems are observed with a rate of 21%. Hypothyroidism is observed with a rate of 5.7%. In a control group, it was observed with a rate of about 1%. In fetuses of mothers with hypothyroidism, heart block is more common and neonatal hypothyroidism may be observed. In one study, nephrotic syndrome was found in association with hypothyroidism in 1 of 49 subjects. The risk of autism is increased by 2.19-fold in these babies (12).

M. Neonatal hyperthyrotropinemia: An increased TSH level in association with a normal fT4 level in a newborn is named neonatal hyperthyrotropinemia. A TSH level of 6-20 mU/L after the first month is defined as persistent hyperthyrotropinemia. Its incidence varies from 1/1000 to 1/10,000. It may be idiopathic or may be related to iodine deficiency, iodine overload, Down syndrome, gestational

Table 7. Conditions where thyroid screening in pregnancy is recommended (1)

Type 1 diabetes, gestational diabetes
Morbid obesity (BMI >40 kg/m^2)
If a previous history of hypothyroidism, hyperthyroidism is present or if signs and symptoms of thyroid dysfunction are present
Presence of clinical hypothyroidism
Positive familial autoimmune disease (Vitiligo, Addison, Celiac)
If anti-TPO + and goitre is present
Similar history in previous pregnancies
Past thyroidectomy, radioactive iodine ablation, head-neck radiation
Age above 30 years
Multiple pregnancy (>2), infertility, preterm delivery, history of fetal loss
Use of amiodarone, lithium, propranolol, D-penicillamin, administration of radiocontrast substance in the last 6 weeks
Living in regions where moderate-severe iodine deficiency is prevalent

Anti-TPO: anti-thyroid peroxidase

diabetes, blocking antibodies, pseudoparathyroidism, antithyroid drugs, and low-dose radiation (<10 mCi). Sarcoidosis antibodies, maternal antithyroid antibodies, and some hormones found in radioimmunoassay (RIA) measurements may lead to increased TSH levels. Normalization of the TSH levels in the first one month indicates transient neonatal hyperthyrotropinemia. In other cases, increased TSH levels persist for 6 months. However, TSH response against TRH may be found to be increased for 3-7 years.

N. Breastmilk and thyroid: Iodine deficiency, iodine overload, radioactive substances, antithyroid drugs, thiocyanate (with smoking), perchlorate, nitrate, lead, lithium, amiodarone, cadmium, anti-TPO and TSHR antibodies may lead to thyroid dysfunction by way of breastmilk. Thionamides should be ingested 3-4 hours before nursing. Breastfeeding is recommended to be interrupted for 2-14 days for radioactive iodine and for 15 hours-3 days for technicium-99 (7).

O. Should thyroid screening be performed in pregnancy?
The general opinion of endocrine associations is that standard thyroid screening is not beneficial. It is recommended that thyroid screening should be performed in subjects in whom it will be beneficial (Table 7) (1). Management of thyroid dysfunction in pregnant women as recommended by the American Thyroid Association (ATA) is summarized in Table 7 (1).

3. Neonatal congenital hypothyroidism; the approach to babies with increased TSH:

Congenital hypothyroidism (CH) is characterized by thyroid hormone deficiency and is the most common endocrine problem in newborn babies. It may be transient or permanent (Table 8) (2, 13, 14). In recent years, it has been reported with an incidence of one in 2000-3000 live births, and this incidence increases up to one in 700-800 live births because of an increase in cases of transient CH in iodine deficiency regions.

The most common cause of permanent primary CH is dysgenesis (85%). The most common cause of dysgenesis, which leads to CH, is sublingual ectopic thyroid (13). Dyshormonogenesis, central hypothyroidism, and peripheral forms of hypothyroidism are observed considerably rarely.

The most common causes of transient CH include iodine deficiency and exposure to iodine. In our country, the incidence of transient hypothyroidism is high (1/752-1/1236) (15, 16), and the main cause is iodine deficiency. However, it should be kept in mind that iodine deficiency or excess also leads to a transient increase in TSH (T4 normal, TSH elevated, see footnote 3) and not only to CH. The incidence of CH in the screening data after 2012 in our country, which was found to be as high as 1/400, may be related to the fact that transient increases in TSH were diagnosed and treated as hypothyroidism.

1. A significant portion of the recommendations in the Workshop Report are based on the European Society of Pediatric Endocrinology (ESPE) guideline published in 2014 (this guideline was prepared with participation of representatives of the other endocrine societies). The grading used for these recommendations are based on the "Grading of Recommendations, Assessment, Development and Evaluation"

Table 8. Causes of congenital hypothyroidism

a. Permanent CH
- Primary CH
  - Dysgenesis (aplasia, hypoplasia, ectopic thyroid, hemiagenesis*)
  - Dyshormogenesis (NIS [SLC5A5] defect, TPO deficiency, hydrogen peroxide generation disorder [DUOX2, DUOXA2 gene mutations], TG deficiency)
  - TSH resistance (TSHR mutation, G protein defect)
- Central CH
  - Isolated (TSHB, TRH, TRH receptor, IGSF1, TBL1X gene mutations,)
  - MHHE (HESX1, LHX3, LHX4, POU1F1, PROP1 gene mutations)
- Peripheral
  - Thyroid hormone transport disorder (MCT8 deficiency-Allan-Herndon-Dudley sydrome)
  - Thyroid hormone metabolism disorders (Deiodinase deficiency, DEHAL1 [SECISBP2] gene mutations)3
  - Thyroid hormone resistance (Thyroid receptor [THRB THRA] mutations)

b. Transient CH
- Iodine deficiency in mother or baby,
- Exposure of mother or baby to excessive iodine
- Anti-thyroid drugs used by mother,
- TSHR blocking antibodies transferred from mother,
- Heterozygous DUOX2 and DIOXA2 mutations,
- Congenital hepatic hemangioma

*It is thought that hemiagenesis, which is included in the causes of dysgenesis, is observed very rarely; in recent years, it has emerged that the incidence of hemiagenesis might not be as low as thought (0.02-0.2%), but it does not lead to hypothyroidism. Therefore, the detection of hemiagenesis is not diagnostic for CH in the absence of hypothyroidism (low fT4) (41,42)

DEHAL1: dehalogenase 1; DUOX2: Dual oxidase 2; DUOX2A: Dual oxidasez 2A; CH: congenital hypothyroidism; MCT8: monocarboxilate transporter 8; MHHE: multiple pituitary hormone deficiency; NIS: Sodium iodine symporter; TG: thyroglobulin; TPO: thyroid peroxidase; TRH: thyrotropin-stimulating hormone; TSH: thyrotropin; TSHR: thyroid-stimulating hormone receptor

(GRADE) system. The recommendations were reported as: (1) Strong recommendations (compatible for most patients in most clinical conditions; their benefits are supperior compared to their harms); (2) Weak recommendations (recommendations that require consensus or consideration by the work group; the best choice clinical condition depends on patient values and balance of benefits and harms or is unclear). Evidence level is classified as: ⊕⊕⊕ very qualified (evidence based on prospective cohort or randomized controlled studies), ⊕⊕◯ moderately qualified (observational studies or studies with method error, controversial or indirect evidence), ⊕◯◯ poorly qualified (evidence based on case series, unsystematic clinical observations).

2. In terms of unity of terms, a normal, elevated or low TSH level, while fT4 (TT4) is low is named hypothyroidism; a slightly elevated TSH level (6-20 mIU/L), while fT4 (TT4) is normal is named elevated TSH.
3. Thyroid hormone levels should be evaluated by age (12). The American Academy of Pediatrics (AAP) recommends that the lower limit for TT4 should be 10 mcg/dL (23) (TBG deficiency should be excluded). It is not possible to propose a definite reccomendation for the reader because the fT4 level varies by different test kits. In different studies, the lower limit for the neonatal period has been reported as 0.62-1.18 ng/dL (8-15.5 pmol/L) (24,44-47). In the ESPE guideline, the reference fT4 levels were reported as <5, 5-10, and 10-15 pmol/L for severe-moderate-mild CH, respectively (13). Another problem that renders evaluation difficult is the fact that the norms reported in many laboratory reports in our country belong to the adult age group. However, fT4 levels in newborns are considerably higher compared with adults. The ideal approach is that each laboratory makes its own norm study. For evaluation, the norms specific for the neonatal period should be requested from the reporting laboratory. The upper limit of normal for thyroid stimulating hormone in the neonatal period has generally been reported to be 9.3 mIU/L (up to the 3rd month in some studies). However, a TSH level of 6-20 mIU/L

after the 14th day has been defined as mild elevation in some studies and it is considered "elevated TSH" (hyperthyrotropinemia) alone, if decreased fT4 level is absent. Elevated thyroid stimulating hormone may be "transient" or "permanent" such as in hypothyroidism (13). In our country, transient "elevated TSH" is observed frequently.

Thyroid hormones play an important role in the development of the nervous system in the first years of life. Therefore, delayed diagnosis in severe hypothyroidism leads to important and permanent mental and motor reatardation. In cases of severe hypothyroidism with delayed diagnosis, mental retardation, psychiatric disorders, spasticity, and walking and coordination disorders occur.

Clinical signs are absent in the neonatal period in more than 90% of cases of congenital hypothyroidism (17, 18). This finding has been related to remaining thyroid function, deionidase adaptation, and thyroxine transferred from the mother at the end of pregnancy. In a study conducted in our country, it was found that only 3.1% of babies with CH were diagnosed in the first month of life before neonatal screening, and the mean age at the time of diagnosis was 2 years (18). Early diagnosis and treatment of CH is based on neonatal screening in developed countries because hypothyroidism is mostly asymptomatic in the neonatal period (13).

The most common symptoms in babies who are symptomatic in the neonatal period include decreased activity, sleeping longer or more often than usual, feeding difficulties, constipation, and prolonged jaundice. The most common signs on physical examination include myxedematous facies, hoarse cry, enlarged fontanelles, macroglossia, rounded abdomen, umbilical hernia, and hypotonia. In addition, accompanying anomalies (8.4%) (18) including cardiac anomalies and some rare syndromes have been reported in cases of CH. For example, sensorineural hearing loss accompanies hypothyroidism and goitre in Pendred syndrome. Hypothyroidism is accompanied by cleft-palate, coanal atresia, hypoplastic bifid epiglottis, and spiky hair (Bamforth-Lazarus syndrome) in thyroid transcription factor 2 (TTF2-FOXE1) mutations, and by important findings that interest neonatologists (respiratory distress syndrome, hypotonia, ataxia, microcephaly, choreatetosis, global growth retardation) in thyroid transcription factor 1 (TTF1-NKX2.1) mutations (14).

Numerous studies have shown that CH screening enables normal progression of cognitive development with early diagnosis and treatment in children with severe CH and the time to normalization of thyroid hormones affects developmental outcomes (20-22). On the other hand, it was observed that a notable developmental negativity did not ocur in mild or subclinical (diagnosed only with moderately elevated TSH) hypothyroidism when studies evaluating developmental outcomes of screening were reviewed. In other words, the results found in cases of severe hypothyroidism in developmental studies cannot be extrapolated for cases of mild or subclinical CH (23). Therefore, the primary goal in CH screening is to detect cases of primary CH (1/⊕⊕⊕, 12). In our country, neonatal screening, which has been conducted on a national scale as from December 2006, is being conducted with measurements of TSH in capillary blood (heel prick), which is the most sensitive method to detect primary CH (1/⊕⊕⊕, 13). Patients whose capillary blood TSH level is found to be above the threshold value are recalled for measurement of serum TSH level. In transient CH, TSH may not be increased because of causes including drug use, immature hypothalamo-pituitary axis, severe disease, and feto-fetal transfusion. In some special populations (preterms, low and very-low-birth-weight newborns, ill preterms hospitalized in neonatal intensive care units, multiple pregnancies, especially those with the same sex, babies whose capillary blood samples were obtained in the first 24 hours) in whom thyroid hormone disorders are observed frequently and may be missed in CH screening. In these babies, it is recommended that a second blood sample should be obtained at the age of 15 days or two weeks after the first test (2/⊕⊕◯, 13). Even if hypothyroidism is found on the second evaluation, it is generally transient. Therefore, treatment should be discontinued after the age of 3 years and differentiation for permanent-transient hypothyroidism should be made.

Diagnosis of congenital hypothyroidism

In babies who have been recalled with a suspicion of congenital hypothyroidism on congenital hypothyroidism screening or have findings suggestive of hypothyroidism in the neonatal period, a detailed physical examination should be performed (to determine the clinical findings mentioned above and additionally syndromic findings, if present, 1/⊕⊕⊕, 13), and serum thyroid hormone levels should be measured. Thyroxine (fT4 or TT4) and TSH levels are mostly sufficient in the first examination.

Congenital hypothyroidism is defined with decreased levels of thyroid hormone as mentioned before. In babies who have been recalled from screening with a suspicion of hypothyroidism, the diagnosis of CH should be based

on decreased levels of serum T4 (fT4 or TT4) by age (see. footnote 3) and thyroid hormone treatment should be initiated immediately (1/⊕⊕⊕, 13). Investigations directed to etiology should not delay treatment.

The final European Pediatric Endocrine Association guideline recommends that treatment should be initiated even if fT4 is normal, if the serum TSH level is above 20 mIU/L (2/⊕⊕◯, 13). Considering the frequencies of iodine deficiency and transient TSH elevations in our country, it may be recommended that the decision should be made by a pediatric endocrinologist, if possible (the test may be repeated before one month). Treatment should be initiated if this opportunity is absent (see case example 1).

The ESPE guideline recommends two options in healthy newborns, if the TSH level is 6-20 mIU/L (elevated TSH-hyperthyrotropinemia), while the fT4 level is within the normal limits by age after the 21st day: (a) further investigations can be performed to make a definite diagnosis (including imaging methods); (b) treatment can be initiated after discussing with the family and informing that treatment would be discontinued and the patient would be reevaluated in the future or the hormone tests may be repeated 2 weeks later without initiating treatment (2/⊕⊕◯, 13). Considering that transient TSH elevation is common in our country and developmental negativity is not expected in this group, repeating thyroid hormone measurement may be preferred in terms of avoiding unnecessary treatment and evaluation may be left to pediatric endocrinologists, if possible. In such cases, the primary recommendation (additional tests-imaging) would lead to numerous unnecessary tests and increased cost, especially considering the high frequency of transient cases. In the prevention and evaluation of these cases, interrogation of the use of povidon iodine and avoidance of unnecesaary use of povidon iodine may prevent TSH elevations arising from exposure to iodine.

Severity of hypothyroidism in newborns found to have congenital hypothyroidism is important in terms of developmental prognosis. As mentioned above, normalization of the thyroid hormone levels as soon as possible in severe cases will affect developmental outcomes. In determining the severity of the disease, clinical findings (for example, posterior fontanelle size larger than 5 mm, large anterior fontanelle and large sagittal suture), thyroxine level and delayed fusion of one or both epiphyses on knee radiography may be used as markers. When babies with a TT4 level below 3 mcg/dL (40 mmol/L) at the time of diagnosis were compared with babies with normal TT4 levels, a 10-point IQ loss was reported in childhood (24).

Table 9. Thyroid hormone levels in healthy newborns (at the age of 10 days)[a] (25)

Hormone	n=82		
	2.5 p	Median	97.5p
TSH	1.19	4.95	10.72
TT4 (mcg/dL)	9.21b	13.27	19.26
fT4 (ng/dL)c	1.18	1.75	2.49
TT3 (ng/mL)	1.43	1.96	3.26
fT3 (pg/mL)	3.10	4.25	5.65

[a]Converting factor for thyroid hormones: one should multiply by 12.87 when converting from conventional units (mcg/dL and ng/dL) to SI (nmol/L and pmol/L) for TT4 and fT4. One should multiply by 1.54 when converting from conventional units (mcg/dL and ng/dL) to SI (nmol/L and pmol/L) for TT3 and fT3

[b]The lower limit for TT4 was reported as10 mcg/dL in the AAP guideline (2 SD below the normal) (43)

[c]In other studies, the 2.5 percentile was reported as 8-12 pmol/L (0.6-0.93 ng/dL) and the 97.5 percentile was reported as 25-30 pmol/L (1.94-2.33) for fT4 level in newborns (44-48)

In the study of Mutlu et al. (25), which examined thyroid hormone levels in healthy newborns, the 2.5 percentile, median, and 97.5 percentile levels for fT4 were reported as 1.18, 1.75, and 2.49 ng/dL (15.2, 22.5, and 32 pmol/L), respectively, in newborns aged 10 days (25, Table 9) and the data enabled biochemical classification of disease severity using plasma fT4 levels. Accordingly, fT4 levels of <5, 5-10, and 10-15 pmol/L can be classified as mild, moderate, and severe hypothyroidism, respectively (13). However, it should be kept in mind that normal values of fT4 levels may show variance in different laboratories (see footnote 3, Table 9).

In babies who have been diagnosed as having CH with serum thyroid hormone and TSH levels, tests directed to the etiology may be performed so long as treatment is not delayed (for example, thyroid imaging, thyroglobulin, urine iodine level in mother and/or baby). These tests may be helpful in elucidating the etiology, differentiation of transient-permanent hypothyroidism, and even in the diagnosis in borderline cases where the thyroid hormone levels are not sufficient for making a definite diagnosis of hypothyroidism (for example, TSH elevation).

Although the European Society of Pediatric Endocrinology (ESPE) guideline recommeds that both scintigraphy and USG should be performed in babies with elevated TSH (2/⊕⊕◯), this approach would increase the cost greatly and scintigraphy would lead to exposure of numerous babies to radioactive examination considering the high frequency of transient TSH elevation in our country. On

the other hand, it should be kept in mind that thyroid USG in newborns will require a high-resolution device and neonatal probe and would give erroneous results because it is an observer-dependent method (for example, surrounding adipose tissue may be confused with thyroid tissue in thyroid agenesis). It may be recommended that imaging should be used in selected cases together with pediatric endocrinologists in the early stage. Treatment should not be delayed. If scintigraphy is to be used, it should be performed in 7 days after initiation of treatment (1/⊕⊕○, 13). In patients who have been diagnosed as having hypothyroidism and in whom treatment has been initiated, USG may be performed in later months under optimal conditions. In patients in whom the gland has been found in its location on imaging, the diagnosis should be reviewed at advanced ages (1/⊕⊕○, 13).

Although screening conducted with measurements of TSH in capillary blood, as in our country, is directed to detect cases of primary hypothyroidism, it also enables the detection of some cases of secondary (central) hypothyroidsm with the reduction of threshold TSH values used in recall. In central hypothyroidism, the TSH level may be low, normal, and mildly elevated, whereas the fT4 (or TT4) level is low. Among babies who have been recalled from screening or who are being evaluated because of prolonged jaundice in the neonatal period, the possibility of central hypothyroidism should be considered in those with low fT4 (or TT4) and normal or mildly elevated (6-20 mIU/L) TSH on the primary evaluation (see case example 2). In cases of central hypothyroidism, hypothyroidism may be isolated or may be accompanied by other hormone deficiencies (growth hormone, ACTH, gonodotropins). In particular, ACTH deficiency and related adrenal insufficiency are important. In such cases, administration of thyroid hormone without correcting adrenal insufficieny may render adrenal insufficiency symptomatic by accelerating cortisol metabolism and clearance. Glucocorticoid treatment (8-12 mcg/kg/day HC or equivalent) should be initiated simultaneously with thyroid hormone treatment in cases of central hypothyroidism accompanied by adrenal insufficiency, and the family should be informed that the glucocorticoid dose should be increased in conditions of stress.

Investigations directed to the etiology should be evaluated together with pediatric endocrinologists, if possible.

Treatment of congenital hypothryoidism

Only L-thyroxine (L-T4) should be used in treatment of congenital hypothyroidism (1/⊕⊕○, 13). Treatment should be initiated as soon as possible before the first 2 weeks of life or immediately after the confirmatory test in babies who have been included in follow-up. Although the ESPE guideline recommends an initial dosage of 10-15 mcg/kg/day, it has been reported that higher doses may be used in babies with severe hypothyroidism and lower doses may be used in mild cases (1/⊕⊕○, 13). Considering that mild cases and patients in whom treatment has been initiated because of only prolonged TSH elevation are common in our country, the disease severity may be evaluated biochemically by fT4 level and the starting dosages of 5-8 mcg/kg/day, 8-10 mcg/kg/day, and 10-15 mcg/kg/day may be used in mild, moderate, and severe disease, respectively (2, 26). In patiens in whom a high strarting dose has been administered, fT4 (or TT4)/TSH levels should be measured in one week and the dose should be adjusted.

According to the ESPE guideline, L-T4 may be administered in the morning or in the evening, before or during feeding, but it should be administered in the same way daily and the dose should be adjusted by evaluating the fT4 and TSH levels. It should be kept in mind that babies who receive vitamin D supplementation may develop hypercalcemia. L-T4 should not be administered together with soya, iron, and calcium (1/⊕⊕⊕, 13). Use of tablet form is recommended. If it is to be used in liquid form, pharmaceutically produced and licenced solutions should be selected (1/⊕⊕○, 13). It has been recommended that reference drugs should be preferred to generic drugs, especially in infancy (2/⊕⊕○, 13).

Follow-up is recommended 1-2 weeks after the first dose, every 2 weeks until the TSH levels are normalized and subsequently, every 1-3 months in the first year of life and every 2-4 months up to the age of 3 years. If any abnormality is found in the hormone levels in the follow-up and an adjustment is made in the dose, the fT4 (or TT4)/TSH levels should be measured 4-6 weeks later (1|⊕○, 13). According to the ESPE guideline, blood sample for thyroid hormone measurement should be obtained at least 4 hours after the final L-T4 dose (1/⊕⊕○, 13). It has been recommended that the TSH level should be kept within the normal limits by age (not below 0.05 mIU/L) and the serum fT4 or TT4 level should be kept in the upper half of the normal reference rage by age (1/⊕⊕○, 13). Sufficient treatment throughout childhood is very important, but excessive doses should be avoided (1/⊕⊕⊕, 13). Excessive treatment has been shown to lead to developmental disorders (27).

In babies in whom investigations directed to elucidate the etiology was not performed in early infancy, treatment was initiated on the background of prematurity/

morbidity and the thyroid gland was found in its location, reevaluation is recommended after the age of 3 years with the objective of elucidating the etiology (1/⊕⊕○, 13). For a definite diagnosis, L-T4 treatment may be interrupted for 4-6 weeks and thyroid hormone levels may be measured; if hypothyroidism is confirmed, etiologic investigations may be completed. If a differentiation of permanent-transient hypothyroidism is to be made rather than making a definite diagnosis, an evaluation may be made by tapering the dose by 30% for 2-3 weeks (2/⊕⊕○, 13).

4. Hypothyroxinemia of prematurity

Definition: Hypothyroxinemia of prematurity is defined as fT4 levels below the reference values despite normal TSH level in preterm babies. A fT4 level below 0.8 ng/dL and a TSH level below 10 mU/L in the postnatal 2nd-4th weeks are diagnostic criteria (28). The incidence of preterm birth is about 12% in the general population and hypothyroxinemia occurs in 35-50% of these babies.

In the study conducted by van Wassenaer et al. (29) in which all thyoid hormone functions were monitored for 8 weeks in 100 preterm babies with a gestational age below 30 weeks, it was found that hypothyroxinemia of prematurity become prominent as the gestational age got younger, the disease did not create a statistically significant difference and the fT4 level reached the lowest value on the seventh day and started to increase after that. In the same study, it was found that no change was present in the rT3 level in ill preterms.

In a few studies which examed if hypothyroxinemia of prematurity affected development in infancy-early childhood, the results were controversial, though negativities related to hypothyroxinemia were reported (30-33). In a study from The Netherlands involving long-term results, a negative effect of hypothyroxinemia of prematurity on IQ or motor functions was not observed when 398 babies born with a gestational age below 32 weeks and a birth weight below 1500 g were examined at the age of 19 years (34). On the other hand, there is insufficient evidence indicating that thyroid hormone treatment has a positive effect on hypothyroxinemia of prematurity (28, 35-37). In a randomized, controlled study conducted by van Wassenaer et al. (28), no finding indicating that thyroid hormone treatment improved the prognosis could be obtained. However, results indicating that babies smaller than 27-28 weeks could benefit from treatment were found with a secondary examination, which was not included in the study design. Nevertheless, no finding indicating that treatment created a positive effect could be shown when babies smaller than 28 weeks who were given treatment in the same study were examined at the age of 36 months (37). In conclusion, it is currently not possible to recommend thyroid hormone treatment in very small preterm babies who have hypothyroxinemia of prematurity. This issue is still to be investigated (38).

It should be kept in mind that thyroxine treatment initiated with the objective of correcting hypothyroxinemia may have adverse effects in small preterms. In a very-low- birth-weight preterm baby, late-onset circulatory dysfunction was reported one day after thyroxine treatment (39).

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Çıkar Çatısması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Case example 1

Capillary TSH on screening test at the age of seven days: 54.6 mIU/L.

Personal history: Birth weight 4000 g, C/S; Postnatal physiologic jaundice present. Familial history: First child of third-degree consanguineous parents. No familial history of thyroid disease.

Physical examination at the age of seven days: height: 55 cm, BW: 3750 g, AF: 3x2 cm, other system findings normal. Laboratory findings (at the age of 21 days) fT4: 15.5 pmol/L (Normal [N]: 9.14-23.8), TSH: 31.3 mIU/L (N: 0.49-4.67), thyroglobulin: 35 ng/mL (N: 0-55). Very low thyroglobulin level suggests agenesis and TG deficiency; it is generally expected to increase in the gland with increased turnover under TSH stimulus in ectopy, dyshormogenesis or iodine deficiency (39), but it is found within the normal limits in this patient. The patient is being followed up without treatment.

Six days later, serum fT4: 11.1 pmol/L, TSH: 2.062 mIU/L.

One month later serum fT4: 15.27 pmol/L, TSH: 1.563 mIU/L.

Diagnosis: Transient TSH elevation

Case example 2

A 27-day-old female baby is being followed up because prolonged jaundice and idiopathic cholestasis. Personal history: birth weight: 3000 g, C/S; jaundice on the postnatal 1st day, persistent cholestasis developed after phototherapy for 10 days and a diagnosis of idiopathic cholestasis was made after investigations. Hypoglycemia developed twice during infection. Familial history: first-degree consanguineous parents, 2 spontaneous abortus and a 4-year old healthy brother.

Physical examination: height: 55 cm, BW 3100 g, pale appearance, decreased subcutaneous adipose tissue, Liver palpable 1 cm below the costal margin.

Laboratory tests: ALT 159 U/L, AST 273 U/L, ALP 417 U/L, GGT 471 U/L, BG 78 mg/dL, T. bilirubin 3.92 mg/dL, D. bilirubin 1.75 mg/dL; fT4 7.6 pmol/L (9-19.04), TSH 7 mIU/L (0.49-4.67).

The possibility of central hypothyroidism is being considered because of reduced fT4 level accompanied with neonatal cholestasis, hypoglycemia attacks during stress and mild TSH elevation. The other anterior pituitary hormones: ACTH 6.39 pg/mL (N: 9-46), cortisol 4.65 mcg/dL, PRL 85 ng/mL (1-25). Low-dose ACTH test was administered to exclude adrenal insufficiency because the basal cortisol level was found to be below 15 mcg/dL; the peak cortisol level was found as 12.2 mcg/dL (compatible with adrenal insufficiency below 19.8 mcg/dL).

Diagnosis: Central hypothyroidism, central adrenal insufficiency

In treatment, hydrocortisone and L-T4 were initiated simultaneously.

In patiens with a fT4 level below normal by age and a mildly elevated TSH level (5-20 mIU/L), central hypothyroidism should be considered in differential diagnosis in addition to primary hypothyroidism; L-T4 treatment should be initiated after exclusion of adrenal insufficiency with pediatric endocrinology consultation, because central adrenal insufficiency may accompany. If adrenal insufficiency accompanies hypothyroidism, L-T4 treatment should be given simultaneously with glucocorticoid replacement.

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