به نام خداوند جان و خرد

Congenital Hypothyroidism

Screening, Diagnosis and Management

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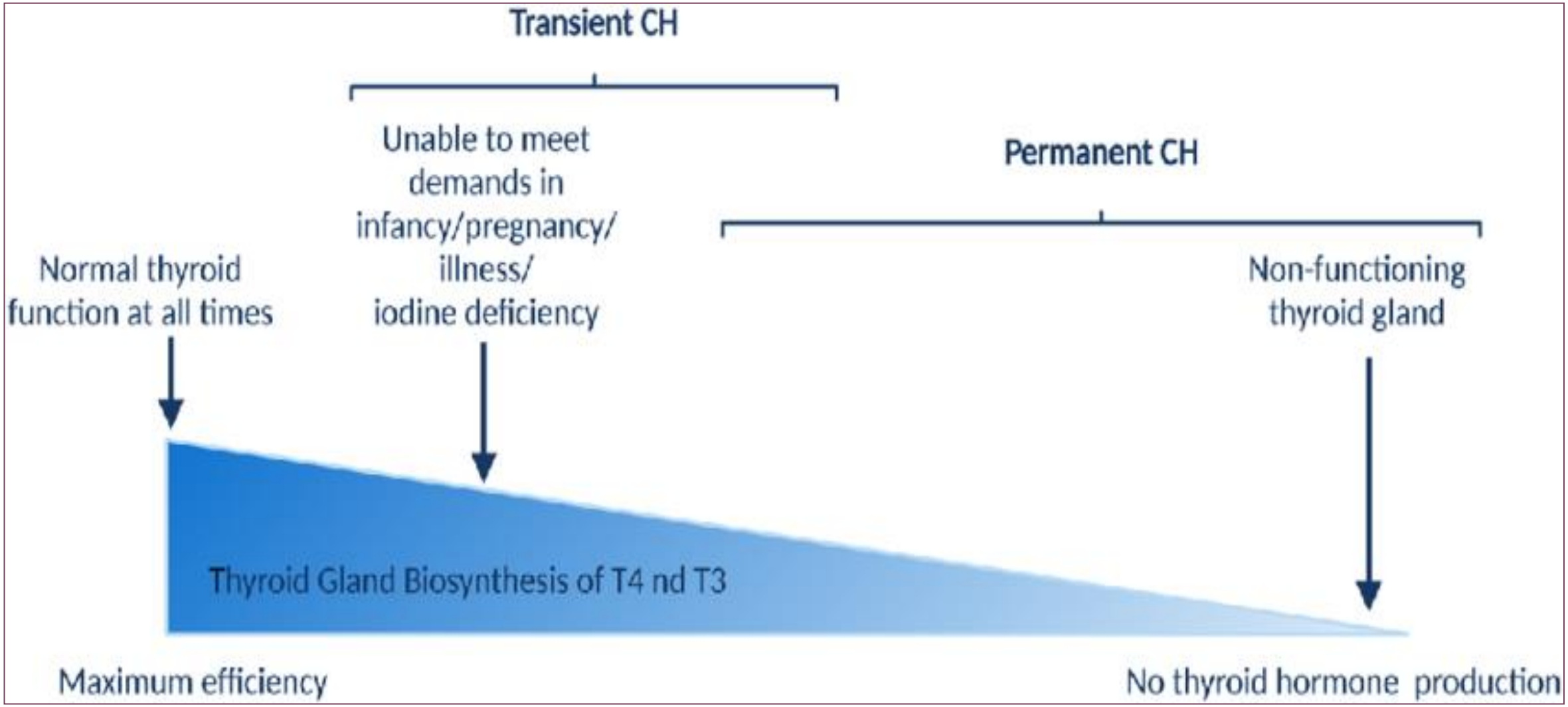
- **Congenital Hypothyroidism**
- **Screening**
- **Diagnosis (**Term & Premature)
- **Management**
- **History of the National Screening Program in IRAN**

AGENDA

Congenital Hypothyroidism

- The thyroid hormone plays an essential role in **energy metabolism**, **growth**, and **neurodevelopment**.
- Specifically, the thyroid hormone acts on **neuronal differentiation**, **synapsis development**, and **myelination** in the prenatal and newborn periods, regulating central nervous system development.
- **Congenital hypothyroidism** (CH) is one of the most common preventable causes of **intellectual disability** worldwide.
- CH is an inborn condition in which thyroid hormone (TH) levels are insufficient for the normal development and function of body tissues.
- Untreated CH leads to **Intellectual Disabilities**.

AAP 2023 and https://www.ncbi.nlm.nih.gov/books/NBK558913



Association between the efficiency of thyroid hormone biosynthesis

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Common Signs and Symptoms of CH

- Prolonged jaundice
- Decreased activity
- Sluggishness
- Increased sleep
- Feeding difficulty
- Constipation
- Sensitivity to cold
- Dry and itchy scalp
- Hhypotonia
- Large fontanels
- Umbilical hernia
- Myxedematous faces
- Macroglossia
- Distended abdomen
- Pallor

Classification and Etiology of Congenital Hypothyroidism	
Primary Hypothyroidism	• Thyroid Dysgenesis (Ectopia, Athyreosis, Hypoplasia, Hemiagenesis) • Thyroid Dyshormonogenesis • Resistance to TSH binding or signaling
Central Hypothyroidism	• Isolated TSH deficiency (TSH β subunit gene mutation) • Thyrotropin releasing hormone deficiency • Thyrotropin releasing hormone resistance • Hypothyroidism due to deficient transcription factors involved in pituitary development of function
Peripheral Hypothyroidism	• Resistance to thyroid hormone • Abnormalities of thyroid hormone transport
Syndromic Hypothyroidism	• Pendred syndrome (hypothyroidism, deafness, goiter) • Bamforth Lazarus Syndrome (hypothyroidism, cleft palate, spiky hair) • Ectodermal dysplasia (hypothyroidism, hypohidrotic, ciliary dyskinesia) • Kocher-Deber- Semilange Syndrome (hypothyroidism, muscular pseudohypertrophy) • Benign chorea (hypothyroidism) • Choreoathetosis (hypothyroidism, neonatal respiratory distress) • Obesity-Colitis (hypothyroidism, cardiac hypertrophy, developmental delay)
Transient Hypothyroidism	• Maternal intake of anti-thyroid drugs • Transplacental passage of maternal TSH receptor blocking antibodies • Maternal and neonatal iodine deficiency or excess • Heterozygous mutations of THOX2 or DUOXA2 • Congenital hepatic hemangioma/hemangioendothelioma

National Screening Program for Congenital Hypothyroidism in Iran

Newborn Screening

- **Newborn screening** refers to tests that are performed in the first few days of a newborn's life and separate newborns who may be sick (**suspicious cases**) from newborns who are probably not sick.
- It has both **false positives** and **false negatives**.

- Newborn screening can be used as a prevention activity in various diseases, such as endocrine, metabolic, genetic, hematologic and infectious diseases.
- After screening and determining suspicious cases, **tests to confirm the diagnosis** should be done to confirm the disease.

Newborn Screening (NBS)

- **Newborn screening tests** play a vital role in an effective disease recognition.
- Prompt diagnosis by **newborn screening (NBS)** leading to **early** and **adequate treatment** results in grossly **normal neurocognitive outcomes** in adulthood.
- Clinical and laboratory follow-up of children with CH is essential for **appropriate management.**

AAP 2023 and https://www.ncbi.nlm.nih.gov/books/NBK558913

History

- The national program was designed in 1383.
- It was implemented as a pilot in 3 provinces of Isfahan, Bushehr and Fars in 1384.
- Revision and finalization was done in 1384.
- It was integrated into the country's health system in 1384.
- The number of screening centers = 6426
- Focal points physicians = more than 550
- Screened Neonates = more than 24 million
- Diagnosed patients = more than 70000 (both transient and permeant cases)

The Process of Carrying out the Program in Iran

- Education of expectant mothers during pregnancy
- Sampling on the **3rd-5th day of the baby's birth** by heel prick on S&S 903 filter paper
- Sending filter paper containing blood from **sampling centers** to **the newborn screening laboratories** (33)
- Measurement of **TSH** concentration using a punched sample filter paper
- Urgent **recall** of **suspicious cases**
- **Re-sampling** of the heel in special cases

The Process of Carrying Out the Program in Iran …

- Performing serum tests to confirm the diagnosis (**Free T4** or **T4**, **T3RU**, **TSH**).
- Rapid initiation of **replacement therapy** with levothyroxine tablets by the **focal point** of the program or the first doctor available.
- Introduction to a **Focal Point Physicians** in the city (if the treatment has not been initiated by her/him).
- Conducting tests and etiological measures if possible (provided that it does not cause time loss and delay in starting the treatment of patients).
- **Long-term care** of patients based on national guidelines.
- Conducting **specialized consultations** needed.

Re-screening

- Premature newborn (at **2**, **6** and **10** weeks)
- Birth weight less than 2500 grams
- Birth weight more than 4000 grams
- Twins and multiples
- Hospitalized infants or those with a history of hospitalization
- History of receiving or exchanging blood
- Babies who have taken special drugs (Dopamine, Corticosteroids, …)
- Screening test results TSH= 5-9.9 mU/L
- Inappropriate sample

Normal Variation of T4, FT4 and TSH

- **Before 4 weeks of age**
  - **T4**= 10.7 ± 1.4 µg/dl
  - **Free T4**= 2.03 ± 0.3 ng/dl
- **After 4 weeks of age**
  - **T4**=7-16 µg/dl
  - **Free T4**= 0.8-2 ng/dl
- **1 to 4 weeks of age**
  - **TSH**= 1-6 mU/L

Uptodate 2021

Interpretation of Confirmatory Serum Testing Results

- **Elevated TSH and Low Free T4** or **T4**

Elevated TSH with low FT4 on the confirmatory serum testing **Primary Hypothyroidism.**

- **Elevated TSH and Normal Free T4** or **T4**

This pattern of confirmatory serum results is termed **hyperthyrotropinemia** or **subclinical hypothyroidism** and represents a **mild primary thyroid abnormality.**

Interpretation of Confirmatory Serum Testing Results …

- **Normal TSH and Low Free T4** or **T4**

This pattern of thyroid function tests is observed in patients with **Central Hypothyroidism**, **Prematurity**, **Low Birth Weight**, **Acute illness**.

- ✓Anticonvulsants
- ✓TBG deficiency
- ✓Birth asphyxia
- ✓Dopamine
- ✓High-dose glucocorticoids

Interpretation of Confirmatory Serum Testing Results …

- **Delayed TSH elevation and Low Free T4** or **T4**

Primary Hypothyroidism and **delayed TSH elevation**, common in infants who are preterm, Low Birth Weight and acutely ill.

✓ Free T4 or T4 and TSH should be retested at 2 - 4 weeks later

Uptodate 2020

Interpretation of Confirmatory Serum Testing Results …

- **TSH = 6-10 mU/L**

  after the age of 1 month

✓ Retested TSH at 2 & 4 weeks later

- If TSH >10 , **Start treatment**
- Otherwise, it will be considered for 3 months and TSH will be checked.

دستورالعمل برنامه کشوری و Uptodate 2021

Diagnosis, Initial Dose, and Time interval between visits (Term Neonates)

- **T4 < 6.5** µg/dl
- **TSH > 9.9** mU/L

- **Initial Dose: 10-15** µg/kg/day

- **Scheduled Set Visiting Patients**

  - ✓ 2-4 weeks after levothyroxine initiation
  - ✓ Every 2 months in the first 6 months of life
  - ✓ Every 3 months in the 6 to 36 months of life
  - ✓ Every 3 to 6 months for children with Permanent CH

Therapeutic Goals

- **To Ensure Normal Growth & Development:**
  - ✓ T4 = 10-16 µg/dl
  - ✓ Free T4 = 1.4-2.3 ng/dl
  - ✓ TSH = 0.5-2.0 mU/L

  During the first 3 years of life

- **After Initiating Treatment**
  - ✓ FreeT4 or T4 should increase into **the upper half of the reference range within 2 weeks**

  and/or
  - ✓ TSH should decrease to **0.5-2** mU/L in **the shortest possible time** (preferably within 4 Weeks)

Premature Newborn

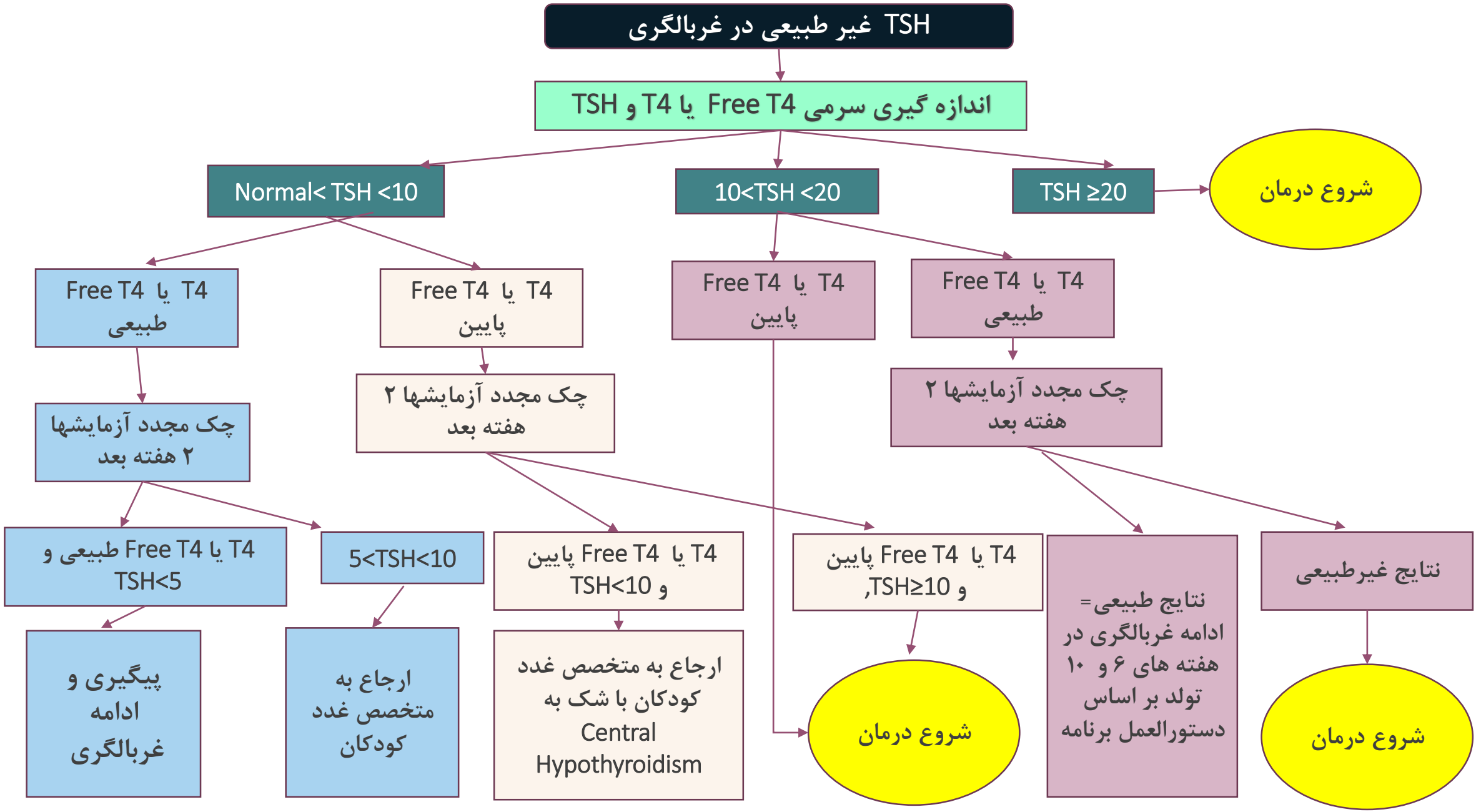
Pre-Term Newborn

- **Congenital hypothyroidism** (CH) is a disorder highly prevalent in premature neonates and it originates from **maternal factors**, **perinatal** and **labor complications**, **genetic abnormalities**, **thyroid malformations** as well as side effects of **medications** and **therapeutic actions**.

Martyna Klosinska et al. 2022

Thyroid Tests in Pre-term Neonates

Normalization of Free T4 in Pre-term Neonates			
Gestational age at birth		**Weight at birth**	
≤ 30 weeks	**>30 weeks**	**< 1000 gr**	**1000 – 2500 gr**
4 weeks after birth	1-2 weeks after birth	4-12 weeks after birth	1-2 weeks after birth


TSH غیر طبیعی در غربالگری
اندازه گیری سرمی Free T4 یا T4 و TSH
Normal< TSH <10
10<TSH <20
TSH ≥20
شروع درمان
Free T4 یا T4 طبیعی
Free T4 یا T4 پایین
Free T4 یا T4 پایین
Free T4 یا T4 طبیعی
چک مجدد آزمایشها ۲ هفته بعد
چک مجدد آزمایشها ۲ هفته بعد
چک مجدد آزمایشها ۲ هفته بعد
Free T4 یا T4 طبیعی و TSH<5
5<TSH<10
Free T4 یا T4 پایین و TSH<10
Free T4 یا T4 پایین و TSH≥10,
نتایج طبیعی= ادامه غربالگری در هفته های ۶ و ۱۰ تولد بر اساس دستورالعمل برنامه
نتایج غیرطبیعی
پیگیری و ادامه غربالگری
ارجاع به متخصص غدد کودکان
ارجاع به متخصص غدد کودکان با شک به Central Hypothyroidism
شروع درمان
شروع درمان

Normal range In premature newborns

TSH(mu/l) ±sd	T4(μg/dl) ±sd	FreeT4(ng/dl) ±sd	Age of specimen	Gestation(week)
6.8±2.9	5.4±2	1.28±0.4	cord	23-27
3.5±2.6	4±1.8	1.47±0.6	7	
3.9±2.7	4.7±2.6	1.45±0.5	14	
3.8±4.7	6.1±2.3	1.5±0.4	28	
7±3.7	6.3±2	1.45±0.4	cord	28-30
3.6±2.5	6.3±2.1	1.82±0.7	7	
4.9±11.2	6.6±2.3	1.65±0.4	14	
3.6±2.5	7.5±2.3	1.71±0.4	28	
7.9±5.2	7.6±2.3	1.49±0.3	cord	30-34
3.6±4.8	9.4±3.4	2.14±0.6	7	
3.8±9.3	9.1±3.6	1.98±0.4	14	
3.5±3.4	8.9±3	1.88±0.5	28	
6.7±4.8	9.2±1.8	1.41±0.3	cord	>37
2.6±1.8	12.7±2.9	2.7±0.6	7	
2.5±2	10.7±1.4	2.03±0.3	14	
1.8±0.9	9.7±2.2	1.65±0.3	28	

Normal range±2SD

Treatment Pre-term Patients

- CH is treated with **enteral L-T4** at a starting dose of **8 - 12** mcg/kg per day
- **10-15** µg/Kg In Severe CH.
- The goal of initial L-T4 therapy is to normalize serum FT4 and TSH concentrations **as quickly as possible**.
- Rapid normalization of serum T4 or Free T4 levels leads to **improved neurocognitive outcomes**.
- Dose adjustment is often needed **2 weeks** after starting L-T4 treatment.
- L-T4 dose requirements can be affected by **chronic illness**, **organ dysfunction**, **medications,** or **changes in weight**, **dietary soy intake**, **L-T4 absorption**, or **serum estrogen concentrations.**

Up to date 2021 and AAP 2023

Dose Adjustment

- **Levothyroxin dose** should be **adjusted** according to the infant's
  - Clinical response
  - Free T4 / T4
  - TSH
- **Free T4, rather than the total T4**, has to be measured periodically to assess the concentration of the biologically relevant unbound or free form of circulating T4.
- Serum Free T4 and TSH should be determined at least 4- 6 hour after the last dose.
- Reduction of Levothyroxine dose **should not be** based on **a single increase** in FreeT4 during treatment.
- Lab. evaluations should be carried out **4–6 weeks after any change** in Levothyroxine dose.

Horm Res Paediatr 2014

Treatment Failure

- Child is not receiving the medication
- Absorption of thyroxin is incomplete
- Malabsorption
- Drug exposure to high temperature
- Soy Formulas (within 1 hour)
- Tablet is not appropriately active
- Expired date tablet
- Increased degradation (anticonvulsants)
- Drug Interaction:
  - Ferrous Sulfate
  - Aluminum Hydroxide
  - Colic" drops (Simethicone)
  - Calcium
  - Bile Acid Sequestrants
- Large hemangiomas with high deiodinase activity

UptoDate 2021

Adverse Effects of Overtreatment

- **Prolonged overtreatment** (>3 months) should be avoided
- Persistently **high FreeT4 > 2.4** ng/dL **or T4 >16** mcg/dL with **suppressed TSH**

  <0.5 mU/L may adversely affect:

  - Weight loss
  - Restlessness
  - Attention Disorders
  - Brain development disorders
  - Cognitive development alterations
  - Premature Craniosynostosis

Up to date 2021

Specific Recommendations

- In newborn with **Cardiac Insufficiency**, starting Levothyroxine dose should be at 50 % of the target replacement dose and should be further increased in accordance with FreeT4 levels after 2 weeks.
- **Sick Neonates** with CH in ICU, unable to receive medication via enteral route, or those under NPO status during pre or postoperative care will require **IV** Levothyroxine therapy (50% to 75% of the oral dose).

Curr Opin Endocrinol Diabetes Obes 2020

Follow-Up

- **Management Card**
- **Scheduled Set Visiting Patients**
- **Determination of**
  - **Permanent and**
  - **Transient types**

Conclusion

The national newborn Screening program for Congenital hypothyroidism is one of the most successful health programs for infants and children in Iran and has given health as a gift to patients.

Thank You