# Thyroid Physiology and Congenital Hypothyroidism

PES Board Review Course in Pediatric Endocrinology – 2025

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# Embryology of the formation and migration of the thyroid

- **The thyroid is the largest endocrine gland in humans**
  - **1 to 2 grams at birth**
  - **Increases by about 1 gram per year until 15 y.o.**

- **The thyroid is the first endocrine structure formed in the fetus (occurs during 1$^{st}$ trimester)**

- **Most critical events in thyroid morphogenesis occur within the first 60 days of gestation**

# Embryology of the formation and migration of the thyroid

- **Thyroid follicular cells (thyrocytes) arise from embryonic endoderm**
- **Development starts at the base of the tongue (foramen cecum)**
- **Thyroid is pulled downward by the heart during its descent into chest**
- **Various genes implicated: *FOXE1* (a.k.a. TTF2, TITF2, and FKHL15), *NKX2-1* (a.k.a. TTF1 and TITF1), *PAX8*, *NKX2-5***
- **Other genes involved: *CDCA8*, *GLIS3*, *JAG1*, *TBX1*, and *TSHR***
  - **TSH is the predominant regulator of thyroid growth and expansion**
  - **TSH not involved in thyroid gland formation and organogenesis in humans**

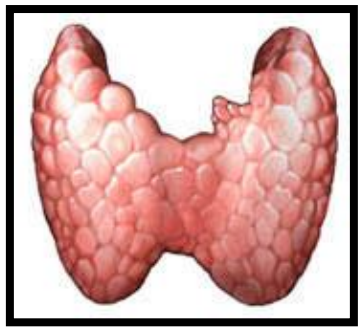
# Genes expressed in thyroid development

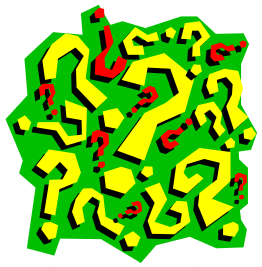
**TTF-2 (or TITF2)**
***FOXE1* or *FKHL15***
Chromosome 9q22.33
- Tongue
- Palate
- Epiglottis
- Esophagus
- Hair follicle
- Thyroid

(Bamforth-Lazarus syndrome)

**TTF-1 (or TITF1)**
***NKX2-1***
Chromosome 14q13.3
- Lungs
- Hypothalamus
- Basal ganglia
- Thyroid

(Brain-Lung-Thyroid syndrome)





Other genes (> 98%)

***NKX2-5***
Chromosome 5q35.1
- Heart
- Thyroid

***PAX8***
Chromosome 2q14.1
- Kidney
- Mid and Hindbrain
- Thyroid

# Genes expressed in thyroid development

| Gene (location) | Inheritance | Thyroid description | Associated findings |
|---|---|---|---|
| FOXE1 (9q22.33) | Recessive | Absent or hypoplastic | Bamforth-Lazarus syndrome |
| NKX-2.1 (14q13.3) | Dominant | Absent, hypoplastic, or normal | Brain-Lung-Thyroid syndrome |
| PAX8 (2q14.1) | Dominant | Absent, ectopic, hypoplastic, or normal | Unilateral renal agenesis |
| NKX2-5 (5q35.1) | Dominant | Absent or ectopic | Congenital heart defects |
| GLIS (9p24.2) | Recessive | Absent or normal | NDM, polycystic kidneys, glaucoma, hepatic fibrosis, exocrine pancreas deficiency |
| JAG1 (20p12.2) | Dominant | Absent, ectopic, or normal | Alagille syndrome |
| TBX1 (22q11.21) | Dominant | Hypoplastic | DiGeorge syndrome |
| CDCA8 (1p34.3) | Dominant | Absent, ectopic, or hemiagenesis | None |
| TSHR (14q31.1) | Recessive or dominant | Hypoplastic (mild, moderate, or severe) or normal | None |

# TSH unresponsiveness syndromes → TSH receptor (*TSHR*) defect

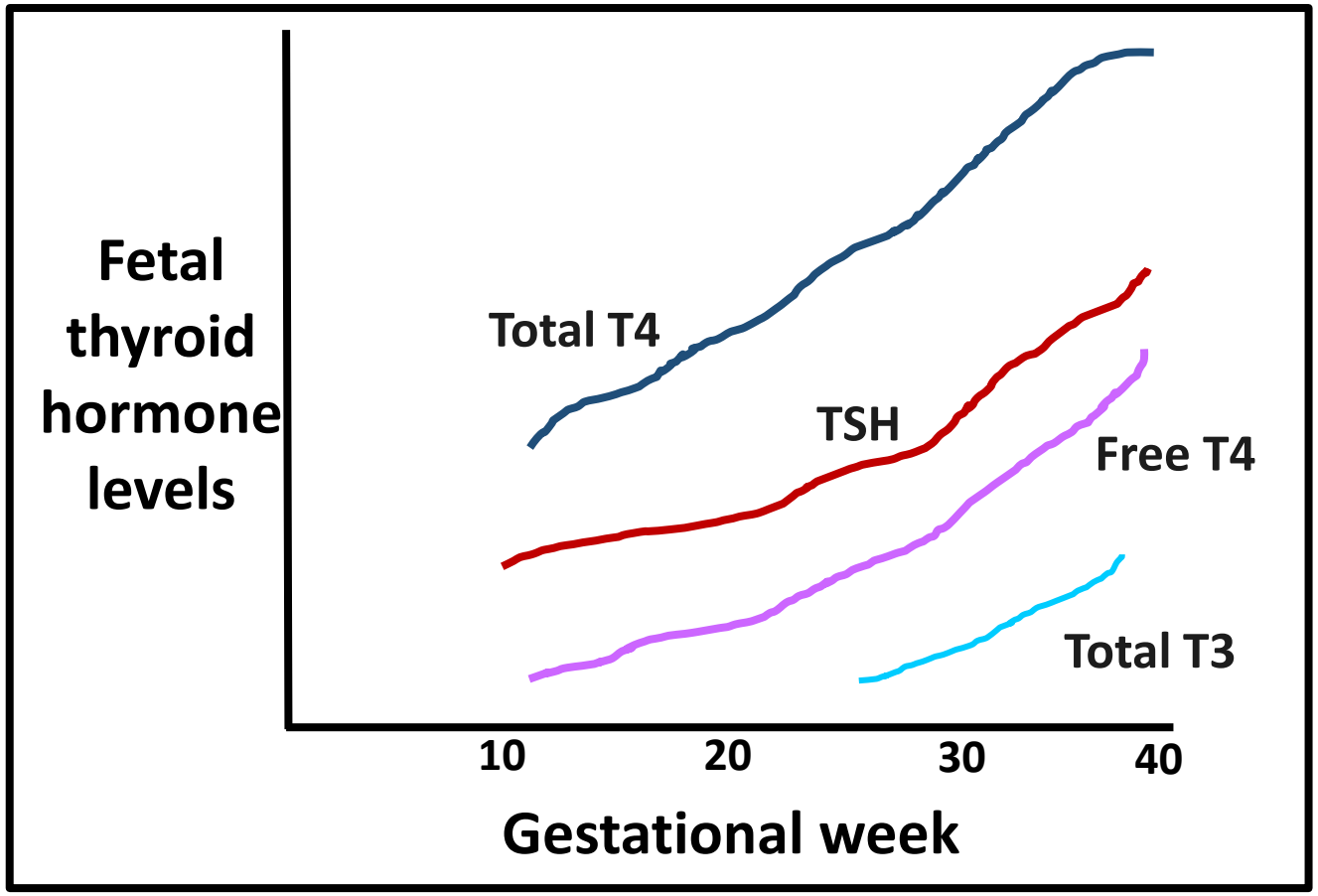
- **Complete resistance**
  - Autosomal recessive
  - Severe thyroid gland hypoplasia
  - Positive newborn screen – uncompensated
- **Moderate resistance**
  - Autosomal recessive
  - Hypoplasia or normal size
  - Variable newborn screen (+/-) – partially compensated
- **Mild resistance**
  - Autosomal dominant
  - Normal size or slight hypoplasia
  - Normal newborn screen – near to fully compensated

**TSH receptor (TSHR) mutations are not associated with true athyreosis or ectopic thyroid tissue**

# TSH unresponsiveness syndromes → Pseudohypoparathyroidism

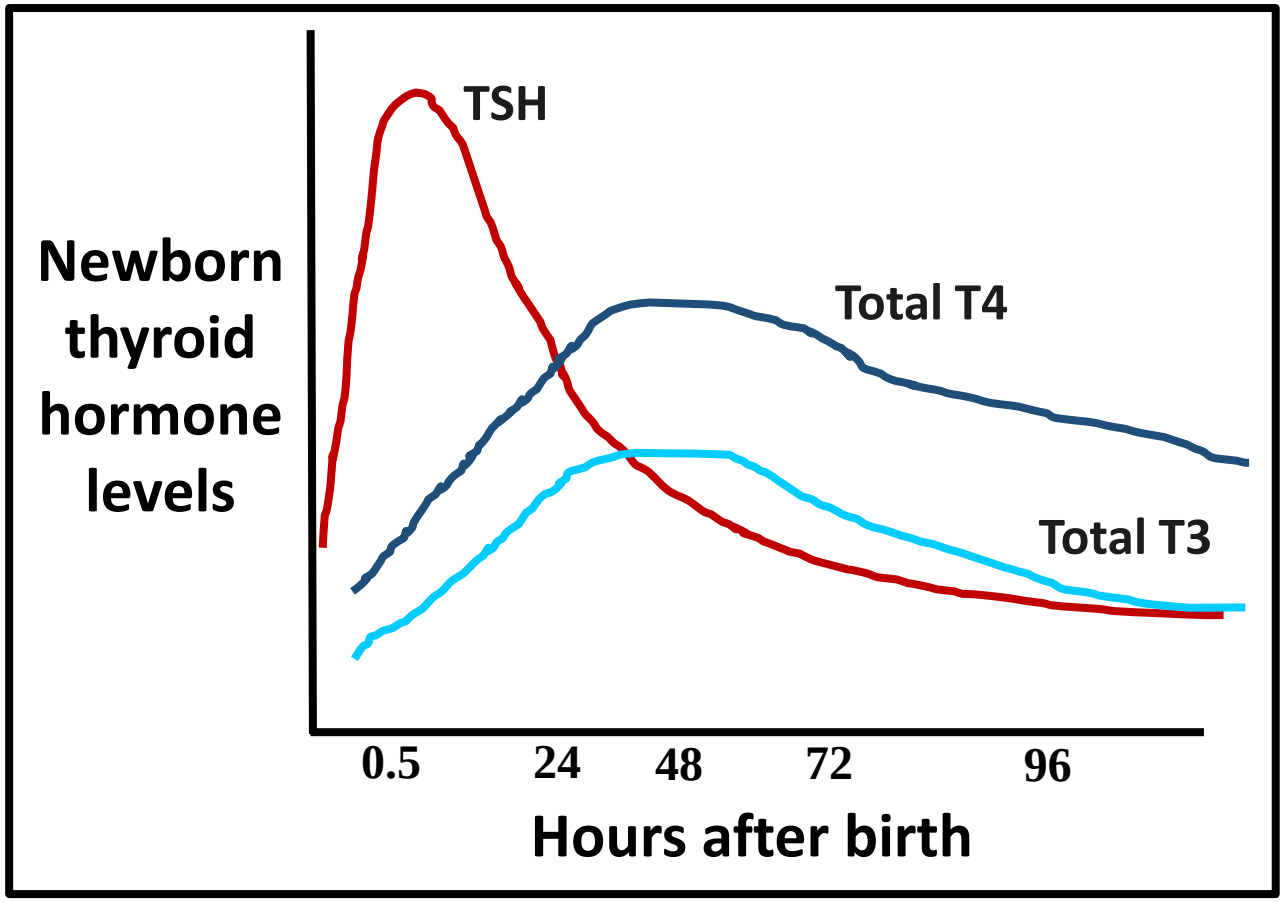
- **Inactivating mutations in the gene (GNAS) encoding the alpha subunit for the stimulatory G-protein ($G_s\alpha$)**
- **Autosomal dominant**
- **Most common form is pseudohypoparathyroidism type 1a (PHP1a)**
  - **Albright hereditary osteodystrophy (AHO) phenotype**
  - **Resistance to multiple hormones:  PTH, TSH, GHRH, LH, and FSH**

# Pattern and timing of HPT function in the developing fetus




- 4 weeks: TG synthesis
- 8-10 weeks: iodine trapping
- 10-12 weeks: TSH is detected (when hCG ↓)
- 12 weeks: T4 production
- 30 weeks: T3 production rises

# TSH surge after birth

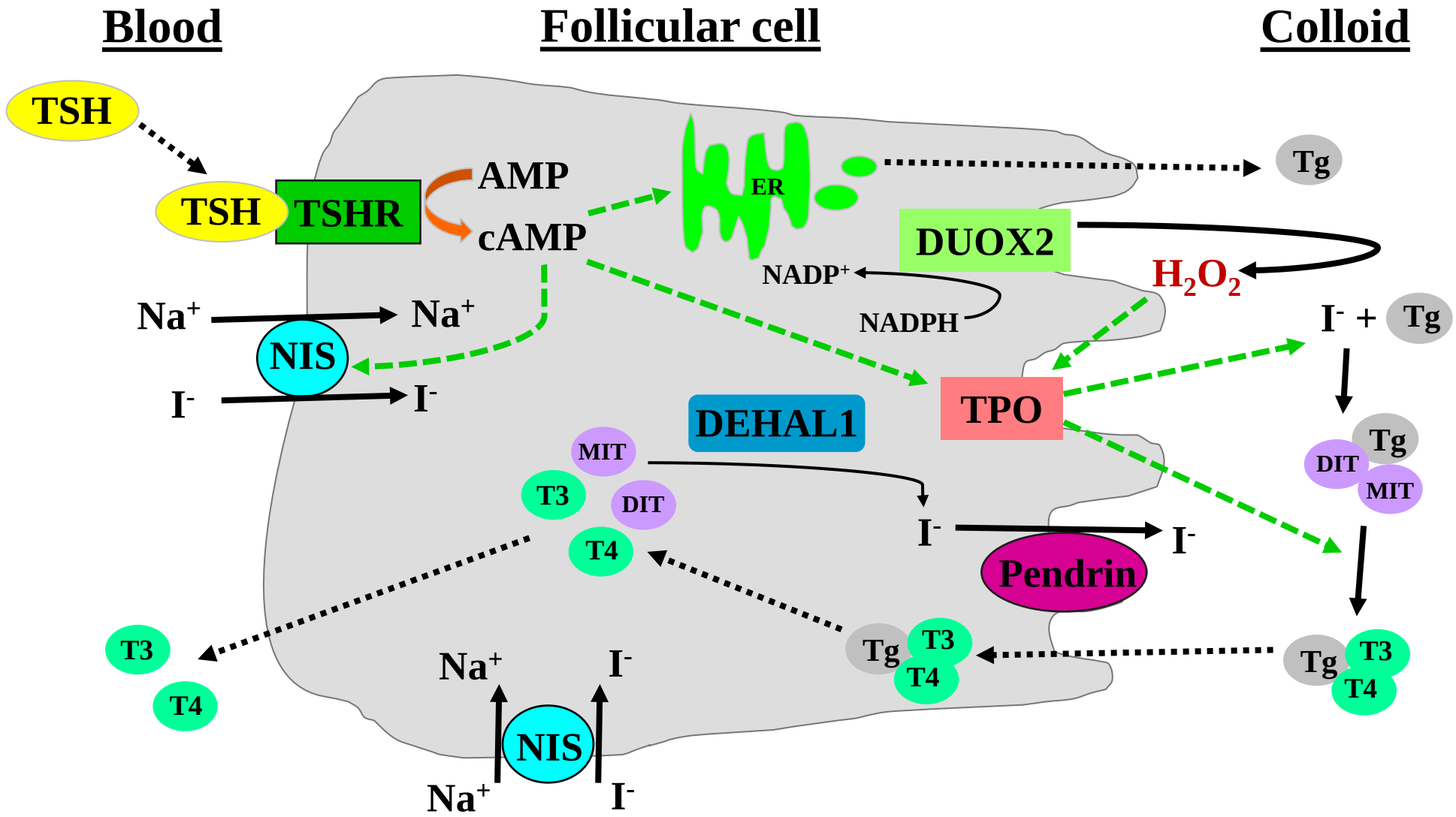



- Due to cold stress, TSH peaks to 60-70 at 30 minutes of life, and then returns to normal neonatal levels by 5 days
- T4 and T3 peak at 48-72 hours of life, and then gradually decline over several weeks

# Approximate thyroid function values

| Age | Total T4 (mcg/dL) | Free T4 (ng/dL) | Total T3 (ng/dL) | TSH (mU/L) |
|---|---|---|---|---|
| Cord blood | 7.4 – 13.0 | 1.7 – 4.0 | 15 – 75 | 1 – 17 |
| 1 to 5 days | 11.8 – 22.6 | 2.2 – 5.3 | 32 – 216 | 1 – 39 |
| 1 to 4 weeks | 7.0 – 16.6 | 0.8 – 2.0 | 160 – 340 | 1.7 – 9.1 |
| 1 to 12 months | 7.2 – 16.5 | 0.8 – 2.0 | 110 – 280 | 0.8 – 6.4 |
| 1 to 5 years | 7.3 – 15.0 | 0.8 – 2.0 | 105 – 269 | 0.8 – 6.4 |
| 5 to 10 years | 6.4 – 13.3 | 0.8 – 2.0 | 83 – 213 | 0.4 – 4.0 |
| 10 to 15 year | 5.6 – 11.7 | 0.8 – 2.0 | 83 – 213 | 0.4 – 4.0 |
| Adult | 4.3 – 12.5 | 0.8 – 2.0 | 70 – 204 | 0.4 – 4.0 |

# Thyroid hormone synthesis/processing



# Thyroid hormone synthesis/processing

1) TSH binds to the TSH receptor → cAMP activation
2) Sodium-Iodide symporter (NIS) → iodide trapping
3) Iodide diffuses to the apex and enters the colloid via Chloride-Iodide transporter (Pendrin)
4) Oxidation of iodide to iodine by $H_2O_2$
5) Organification – iodine is bound to tyrosine residues in TG to form iodothyronines (MIT and DIT)
6) Coupling: MIT + DIT = T3 and DIT + DIT = T4
7) Endocytosis – TG enters follicular cell from colloid
8) Hydrolysis – release DIT and MIT; secretion of T3 and T4
9) Deiodination – recycling of iodide

# Thyroid hormone transport

- **Placenta acts as a protective barrier to the fetus**
  - **↑ Type III monodeiodinase activity (inactivation)**
  - **About a 1/3 of maternal T4 crosses the fetus at term**

- **Majority (>99%) of thyroid hormone is bound to proteins**
  - **Bound to TBG, transthyretin, or albumin**
  - **Amount in serum: albumin > transthyretin >> TBG**
  - **Binding to T4: TBG >> transthyretin >>> albumin**
  - **T3 is less tightly bound to proteins than T4**

# Thyroid hormone transport

- **Thyroid hormone acts mostly intracellularly and is transported across the plasma membrane**
  - **MCT8**
  - **MCT10**
  - **OATP1C1**

- **MCT8 is the most important plasma membrane transporter**

# MCT8 deficiency

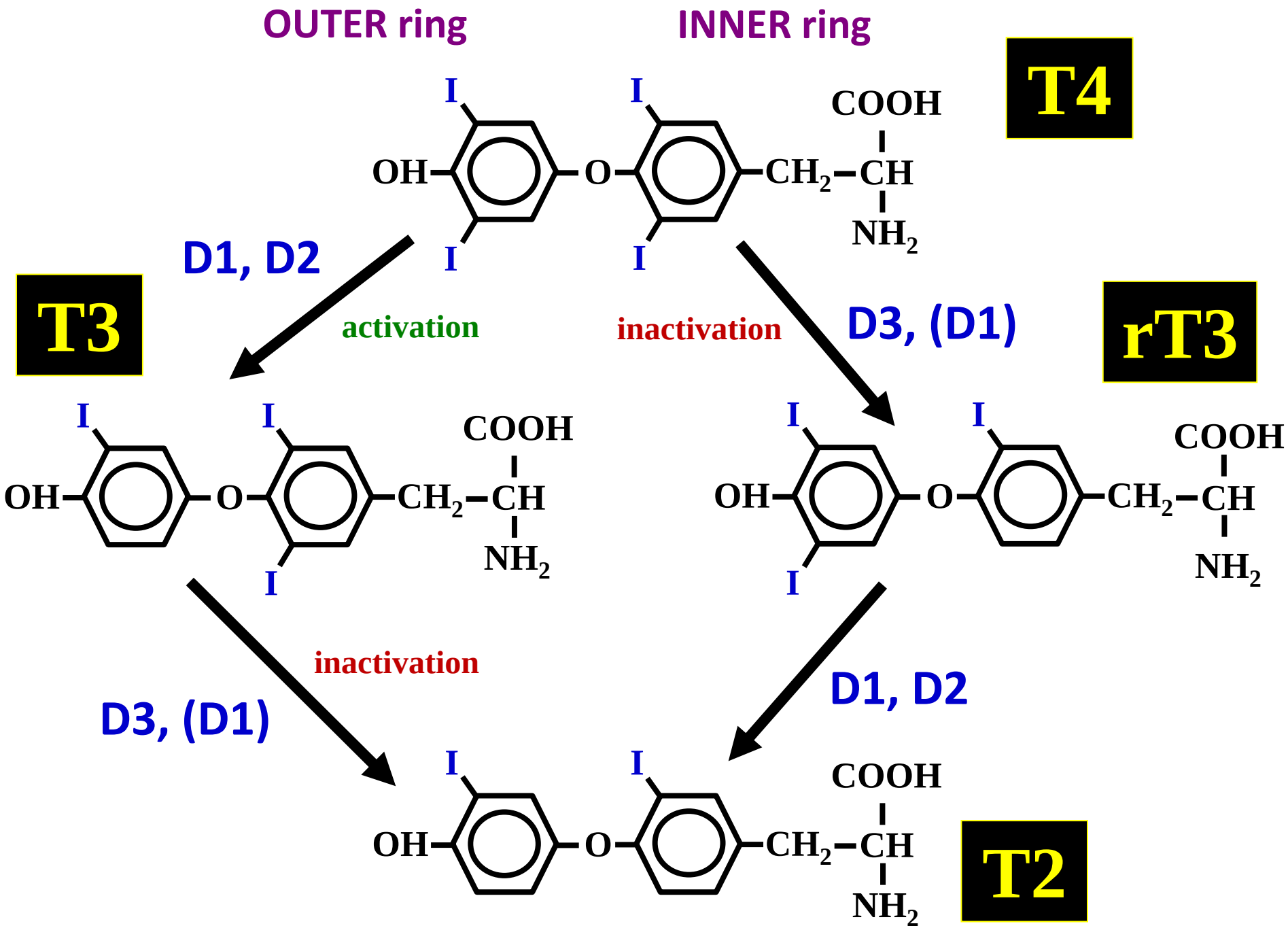
- **Genetic mutations in *SLC16A2***
- **Allen-Herndon-Dudley syndrome**
- **X-linked**

- **Impaired T4 and T3 transport into cells**
  - **Defects in brain and other tissues**
- **Severe intellectual disability, developmental delays, hypotonia, dysarthria, ataxia**
  - **Neurological abnormalities <u>not</u> reversed with T4**

- **TFTs (by 1 m.o.): ↓ T4, ↑↑ T3, ↓↓rT3, normal or slightly ↑TSH**

# Metabolism of thyroid hormone

- **Type 1 deoidinase (D1): inner and outer ring**
  - **Activation**
  - **Liver, kidney, muscle**
  - **Activity decreased in sick euthyroid**
- **Type 2 deiodinase (D2): outer ring**
  - **Activation**
  - **Brain, pituitary, adipose**
- **Type 3 deiodinase (D3): inner ring**
  - **Inactivation**
  - **Placenta, brain, and most other tissues**


OUTER ring
INNER ring
T4
D1, D2
activation
T3
inactivation
D3, (D1)
rT3
inactivation
D3, (D1)
D1, D2
T2
I
OH
O
CH2
CH
COOH
NH2

# Receptors and Action

- **TSH acts through a 7-transmembrane receptor that signals through Gs alpha to increase cAMP production leading to downstream effects**
- **Thyroid hormone receptors belong to the nuclear (steroid) hormone receptor superfamily**
- **Various isoforms:**
  - **TRα1 – CNS, heart, skeletal muscle**
  - **TRα2 – widely distributed in tissues**
  - **TRβ1 – liver, kidney**
  - **TRβ2 – pituitary, brain**

# Transplacental passage affecting fetal thyroid production

- **Radioactive iodine**
  - **Given after 8-10 weeks gestation is trapped by and destroys the fetal thyroid gland**
- **IV contrast**
- **Topical iodine-containing antiseptics**
- **Amiodarone**
- **Iodine-containing nutritional supplements**
  - **Excess iodine resulting in fetal hypothyroidism**
- **Maternal Graves (blocking antibodies, MMI > PTU)**

# Fetal thyroid enlargement

- **Fetal thyroid enlargement can be detected by prenatal ultrasound**
- **Goiter is non-specific for hypothyroidism or hyperthyroidism**
- **Goiter can be large enough at birth to cause airway compression**

# Fetal hypothyroidism

- **Fetal brain type 2 deiodinase is preferentially increased with hypothyroidism (T4 → T3)**

- **Maternal hypothyroidism is associated with increased fetal loss**
  - **Pre-eclampsia**
  - **Placental abruption**
  - **Miscarriage**
  - **Preterm birth**

# Maternal hypothyroidism and the fetus

- **Fetus does not make a significant amount of T4 until the 2nd trimester; entirely dependent on the maternal thyroid supply in the 1st trimester**
- **Some studies (controversial) have shown that offspring have lower IQ with maternal hypothyroidism**
- **#1 cause of combined maternal and fetal hypothyroidism is iodine deficiency**

# Congenital hypothyroidism and iodine deficiency

- **Recognize that worldwide iodide deficiency is the most common cause of primary hypothyroidism and of preventable intellectual disability**
- **Iodine RDA: approximately 150 mcg/day (increased in pregnancy)**
- **Only 75% of the world's population uses iodinated salt (almost 2 billion are iodine deficient)**
- **Endemic goiter**

# Breast feeding and anti-thyroid drugs

- **Very small amount of anti-thyroid drugs are secreted in breast milk (methimazole > PTU)**

- **Breast feeding is safe at low to moderate doses of anti-thyroid drugs**
  - **PTU: ≤ 300 mg/day (ATA says ≤ 450 mg/day)**
  - **Methimazole: ≤ 20 mg/day**
  - **Mothers should take the medication immediately following a feed and in divided doses**

- **Infants of affected mothers should be screened with thyroid function tests – reassuring data but limited number of patients**

# Incidence of congenital hypothyroidism

- **Overall incidence of CH:  1 in 2000 to 1 in 4000**
- **Increased incidence in Down syndrome (28x)**

- **Dysgenesis:  1 in 3,500**
  - **75-85% of cases of CH**
- **Dyshormonogenesis:  1 in 20,000**
  - **about 15% of cases of CH**
- **Transient**
  - **10-15% of cases of CH**
- **Central**
  - **less than 5% of cases of CH**

**Congenital hypothyroidism is the most common disease screened for in newborns**

# Effect of prematurity on thyroid function in the neonate

- **Cord T4 and free T4:  lower in preterm infants; proportional to weight and gestational age**
- **Lower TSH surge (vs term infant)**
  - **Accompanied by lower T4 and T3 rise after birth**
- **Hypothyroxinemia of prematurity**
  - **Immaturity of the HPT axis**
  - **Sick euthyroid syndrome or a reflection of the stress and illness of the infant**
  - **Unclear benefit to treat with LT4**

# Thyroid dysgenesis

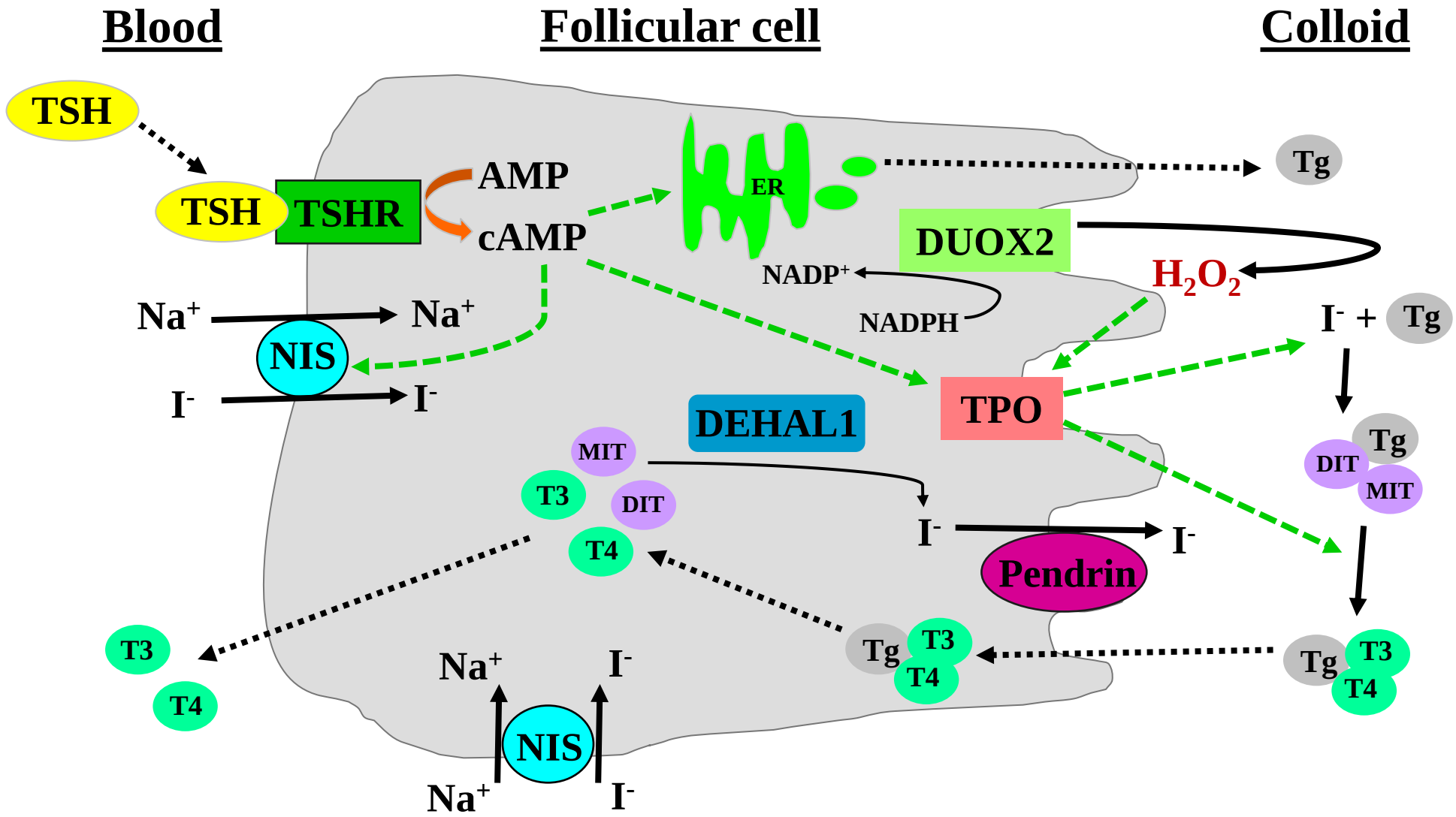
- **2% of cases are familial; 98% are sporadic**
- **Few genes have been implicated (*see slides #4 and #5*)**

- **Agenesis – failure to develop**
- **Hemiagenesis**
- **Ectopic – failure to migrate; most commonly sublingual (can also be lingual)**
- **Hypoplastic – small but in the normal location**

# Thyroid dyshormonogenesis

- **Several different steps can be affected**
- **The most common cause of dyshormonogenesis is due to an organification defect**
- **Inheritance pattern:  autosomal recessive**

# Thyroid hormone synthesis/processing



# Genetic defects in synthesis/processing

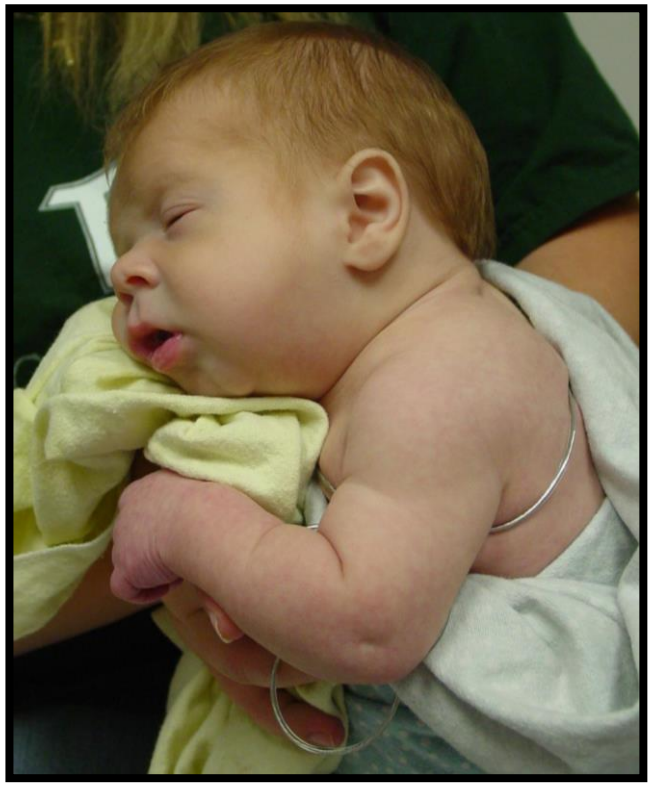
| Process | Affected substance | Gene (location) | Features |
|---|---|---|---|
| Iodide trapping | Sodium iodide symporter (NIS) | SLC5A5 or NIS (19p13) | Decreased radionuclide uptake |
| Iodide transport into follicular lumen | Pendrin | SLC26A4 or PDS (7q31) | Sensorineural deafness (Pendrin syndrome) |
| Matrix for hormone synthesis | Thyroglobulin | TG (8q24) | Very low Tg levels |
| Iodine organification and coupling reaction | Thyroid peroxidase | TPO (2p25) | #1 cause of dyshormonogenesis |
| $H_2O_2$ generation | Thyroid oxidase (THOX) | DUOX2 (15q13.3 | Transient (AD) or permanent (AR) |
| Intrathyroidal iodide recycling | Iodotyrosine deiodinase | IYD or DEHAL1 (6q25.1) | Newborn screen is usually normal |

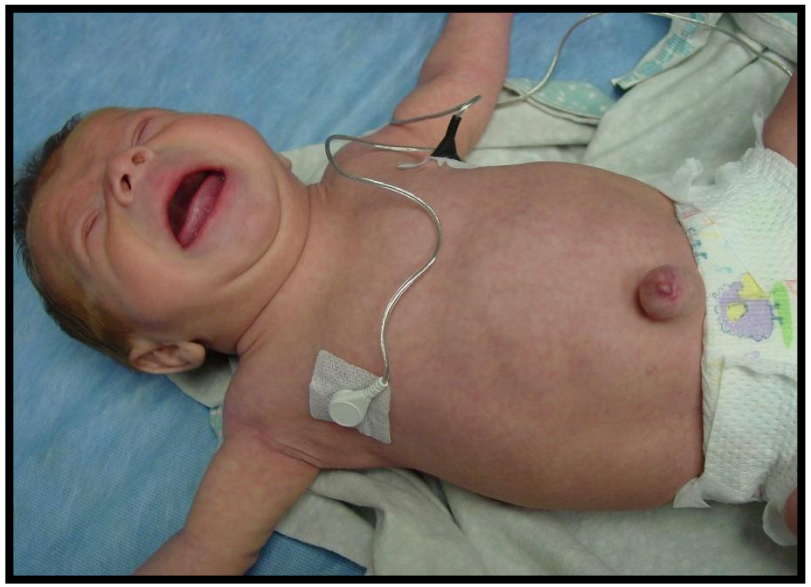
# Pendred syndrome

- ***SLC26A4*** **or** ***PDS*** **gene is expressed in the thyroid and cochlea**
  - **Encodes for the protein pendrin**
- **Defect in the transport of iodine from the follicular cell to the colloid**
- **Usually presents with goiter in late childhood or adolescence – most are euthyroid**
- **Variable thyroid disease within the same family with the same mutation**
- **About 10% of cases of childhood sensorineural deafness**

# Clinical findings of congenital hypothyroidism

- **Nonspecific, subtle signs and symptoms of CH are sometimes present in the newborn period**
- **Symptoms: lethargy, decreased activity, cold to touch, constipation, feeding problems**
- **Signs: mottled skin, jaundice, macroglossia, umbilical hernia, distended abdomen, hoarse cry, dry skin, large fontanelle with wide sutures, hypotonia, delayed/slow reflexes, goiter**
- **Obvious features are not noted until 3 m.o.**





# 3 m.o. full-term male

- “Sleeps all of the time”
- “Never smiles or looks at me”
- “Very floppy”

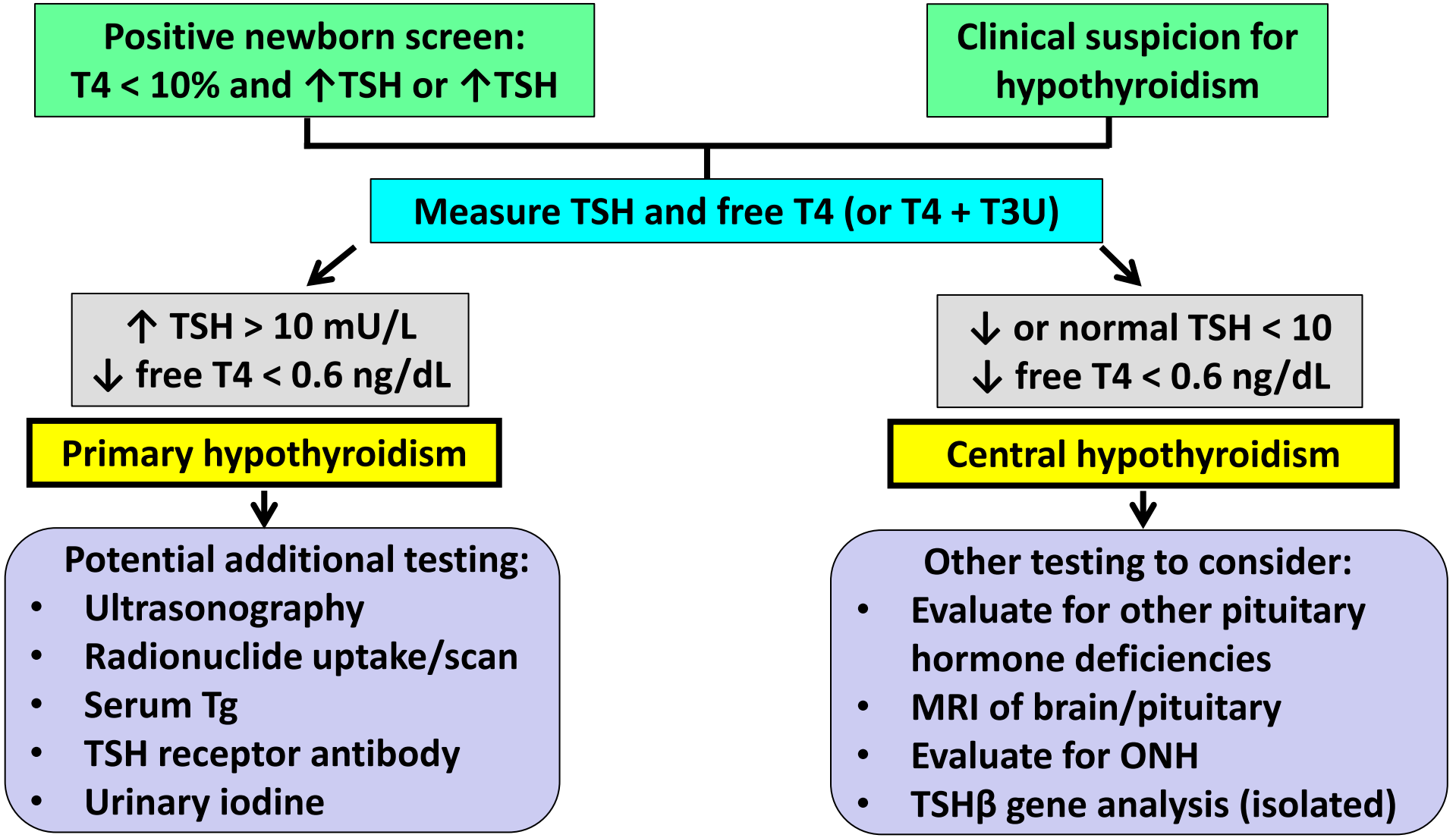
- 1 stool per week
- Hoarse cry
- Gags and chokes on feeds
- Low heart rate alarms

- Never had a newborn screen
- TSH > 400 → athyreosis

# Patterns of osseous maturation in neonate

- **Commonly ossified bones at birth:**
  - **Knee – distal femoral epiphysis → ossification center appears at about 36 weeks gestation**
  - **Knee – proximal tibial epiphysis**
  - **Foot – cuboid bone**
- **Thyroid hormone deficiency delays this process**
- **Also see delayed closure of the fontanelles (especially the posterior)**

# Diagnostic algorithm of congenital hypothyroidism



# Advantages/disadvantages of neonatal thyroid screening systems

| Thyroid disorder | Primary T4 with follow-up TSH | Primary TSH |
|---|---|---|
| Primary congenital hypothyroidism | Very good | Very good |
| Central congenital hypothyroidism | Some | Not good |
| Mild congenital hypothyroidism | Not good | Good |
| Delayed rise in TSH (e.g. preterm, acutely ill term infant) | Good (but should get a follow-up test in cases with a low T4 and normal TSH) | Good (but only if get a routine 2nd test) |
| MCT8 mutation | Not very good | Not good |

# Delineating errors in thyroid hormone synthesis

- **Genetic testing can confirm specific mutations**

- **Iodine trapping defect (NIS)**
  - **Decreased or absent I-123 uptake**
- **Oxidation/organification defect**
  - **Increased I-123 uptake**
  - **Positive perchlorate discharge (>10%) test**
- **Thyroglobulin defect**
  - **Low serum Tg levels**
- **Iodotyrosine deiodinase (DEHAL)**
  - **Low serum/urinary iodine levels**

# Techniques for defining thyroid anatomy

- **Radionuclide scans (scintigraphy)**
  - **Tc99m**
  - **I-123**
- **Ultrasonography**
  - **with or without Color Doppler**
- **Serum thyroglobulin levels**
  - **Lowest in agenesis**
  - **Intermediate in ectopic**
  - **Highest in infants with normally positioned glands**

# Thyroid scintigraphy

## Tc99m

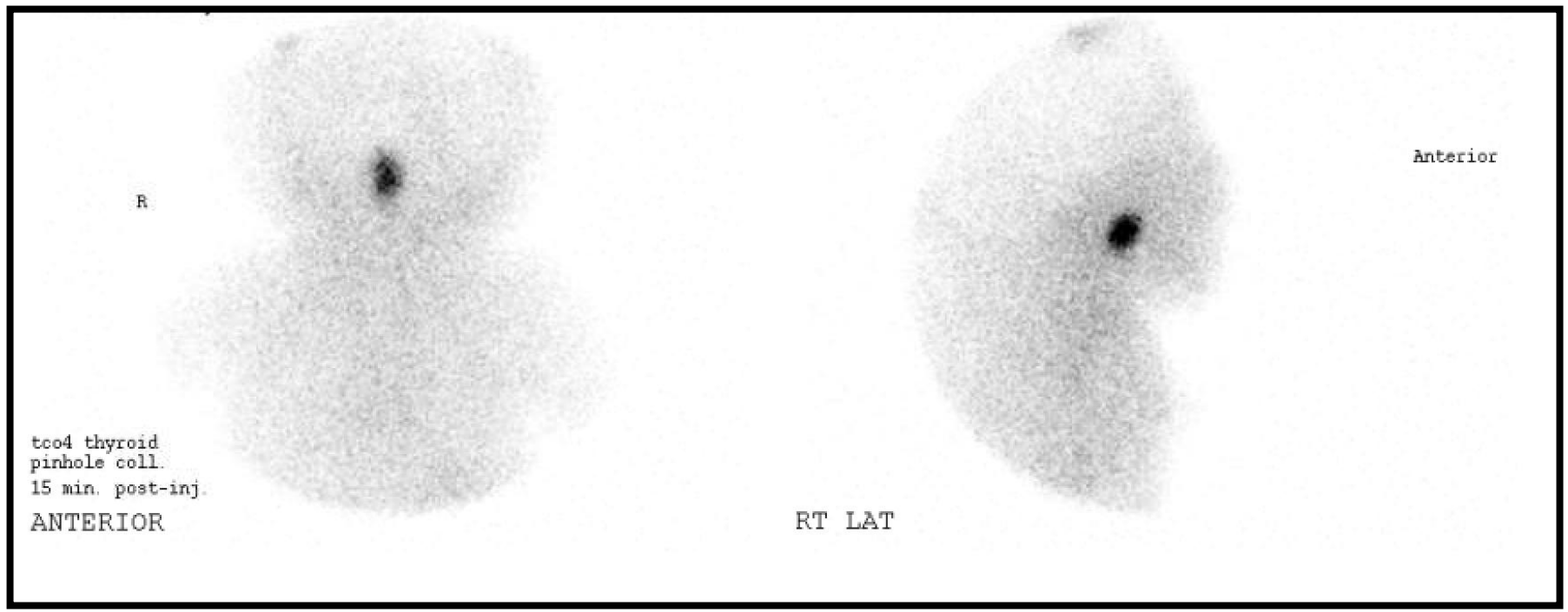
- Less expensive
- IV administration
- ½ life = 6 hours
- Only reflects thyroid trapping ability – enters the cell via NIS but cannot be organified
- Detects dysgenesis

## I-123

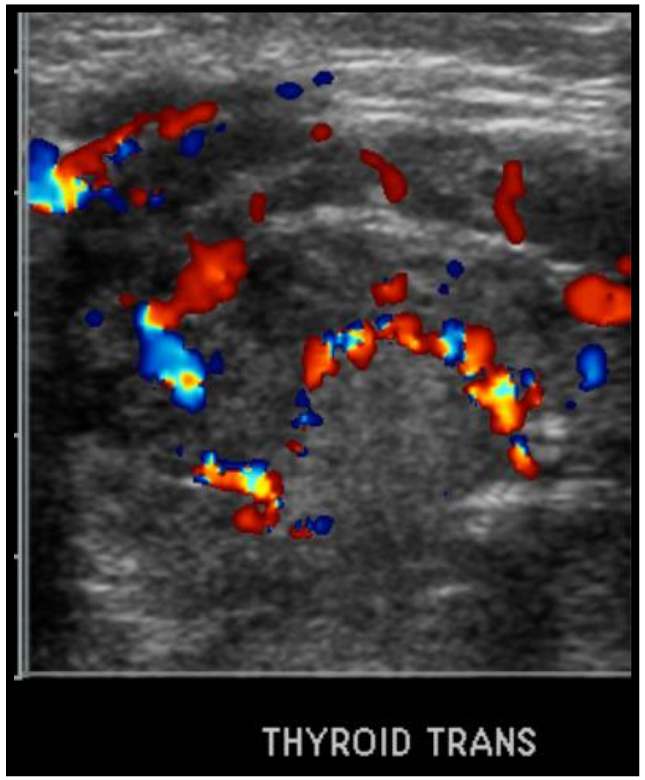
- More expensive
- Oral administration
- ½ life = 13 hours
- Also enters via NIS but then is organified
- Detects dysgenesis and also organification defects

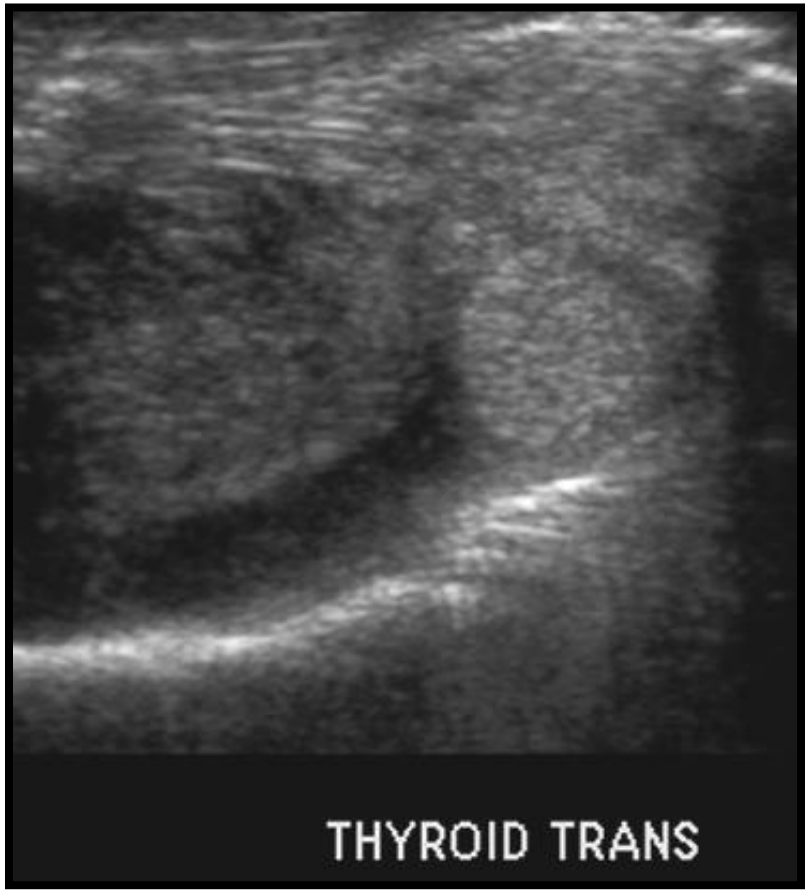
**Absent radionuclide uptake may occur in conditions with a normally positioned thyroid gland, such as TSHβ gene mutations, TSH receptor inactivating mutations, iodine trapping defects (e.g. NIS), and TSH receptor blocking antibodies.**

# Sublingual thyroid gland

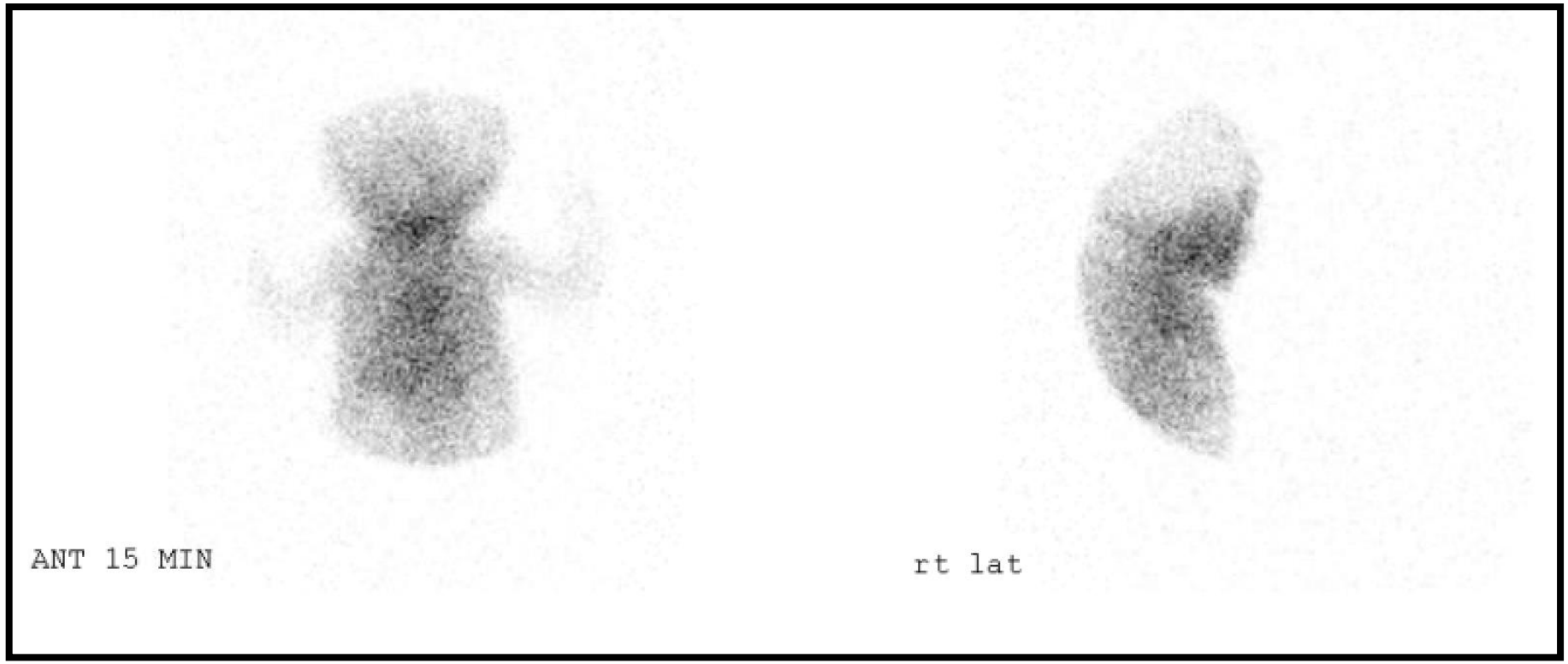


# Sublingual thyroid gland



# Absent thyroid gland



# Maternal TSH receptor antibody (TRAb)

- **TRAb (a.k.a. TBII)**
  - **Graves disease – both blocking and stimulating**
  - **Hashimoto – blocking antibodies in about 10% of women**

- **IgG antibody that readily crosses the placenta**
  - **Transient hypothyroidism**
  - **Incidence: 1 in 180,000**
  - **Half-life:  3 to 4 weeks**
  - **Usually disappear from infant by 3 to 6 months but dependent on the antibody amount and potency**
    - **Trial off when TRAb is negative but safest to treat until 2-3 y.o.**

# Maternal TSH receptor antibody (TRAb)

- **Maternal TRAb can inhibit TSH-induced iodine uptake and result in apparent absence of the thyroid gland (on Tc99m and I-123 scans)**
- **Similar findings are seen in cases of permanent CH such as agenesis, iodine trapping defects (i.e. NIS), TSH β gene mutations, and inactivating mutations of the TSH receptor**
- **Thyroid ultrasound will reveal a normal thyroid gland in the normal location**

# Congenital central hypothyroidism

- **Often associated with other pituitary hormone deficiencies**
  - **GH deficiency: hypoglycemia in newborn period**
  - **ACTH deficiency: hypoglycemia**
  - **LH/FSH deficiency: micropenis and cryptorchidism in males**
  - **ADH deficiency: least common**
- **Rare to have isolated TSH deficiency**
  - **TSH β subunit gene mutation**
  - **TRH gene mutation/deficiency**
  - **TRH receptor inactivating mutation**

# Congenital central hypothyroidism

- **Be aware of intracranial anatomical defects which may accompany TRH or TSH deficiencies**
- **Midline brain abnormalities**
  - **Absent septum pellucidum**
  - **Absent corpus callosum**
  - **Holoprosencephaly and hydranencephaly**
  - **Septo-optic dysplasia**
- **Cleft lip/palate**
- **Single central maxillary incisor → hypopituitarism (and GHD)**

# Treatment of congenital hypothyroidism

- **Initial dosage of LT4 is 10-15 mcg/kg/day**
- **Goal is normalize the T4 level within 2 weeks and TSH within a month (i.e. < 10)**
- **Serum T4 or free T4 should ideally be in the upper half of the reference range during the first 3 years of treatment**
  - **TSH may inappropriately be elevated because of relative pituitary resistance→ need to use T4 or free T4 levels to titrate dose in this situation**

# Treatment of congenital hypothyroidism

- **Infants with low serum T4 (< 10 mcg/dL) and a TSH > 15 mU/L during the first year of life have lower IQ values than patients with T4 concentrations that are held constant at higher concentrations**

- **Avoid concomitant administration of LT4 with**
  - **Soy**
  - **Fiber**
  - **Iron**
  - **Calcium carbonate**
  - **Simethicone**

# Treatment of congenital hypothyroidism

- **Know the potential side effects and consequences of overtreatment with LT4**
  - **Premature suture closure; craniosynostosis**
  - **Advanced bone age**
  - **Lower cognitive outcome**

# Mild congenital hypothyroidism frequently normalizes and treatment may not be necessary

- **More commonly seen in screening programs with lower TSH cutoffs**
- **Clues to suggest that it may resolve:**
  - **TSH trending toward normal (screen → serum)**
  - **Free T4 is normal to upper part of normal range**
- **Reasonable to follow trend of TFTs at weekly intervals – need to start LT4 at 4 weeks of life if TSH > 10**

# ABP outline – handout

- **Additional ABP specifications and information are contained in the handout**