Pediatric Endocrine Society (PES) Board Review Course in Pediatric Endocrinology – 2025
"Thyroid Physiology and Congenital hypothyroidism"

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****Below is a copy of the ABP content specification outline. If the information was reviewed in the presentation, then the slide number from the talk is listed after each specification (and at times with some additional information). Specifications that were not covered in the talk are expanded on below if necessary.****

3. **Thyroid Hormones (Thyroxine (T4) and Triiodothyronine (T3))**

A. Physiology

1. Ontogeny/embryology
a. Know the embryology of the formation and migration of the thyroid gland and the developmental genes involved – **slides 2-5**
b. Know the pattern and timing of hypothalamic-pituitary- thyroidal function in the fetus – **slide 8**

2. Synthesis/processing
a. Understand the synthesis of thyroid hormones, including iodide metabolism, uptake, organification, incorporation into thyroglobulin, coupling, and proteolytic secretion – **slides 11-12**

3. Regulation and secretion
a. Be aware of the changes in thyroid hormone concentrations in the immediate neonatal period and the first weeks after birth – **slides 9-10**
b. Appreciate the occurrence of the immediate TSH surge in first hours of postnatal life – **slide 9**

4. Transport
a. Know whether thyroidal hormones cross the placenta – **slide 13**
b. Be aware of the various proteins in blood which bind thyroid hormones and their relative clinical importance – **slide 13**

5. Metabolism
a. Know that thyroid hormone transport into tissues is facilitated by thyroid hormone transporters, including MCT8 – **slides 14-15**
b. Understand the metabolism of thyroid hormone, its regulation, and its physiologic significance – **slides 16-17**

6. Receptors/action
a. Know that TSH acts through the a seven-transmembrane receptor that signals through Gs alpha to increase cAMP – **slide 18**
b. Know that thyroid hormone receptors belong to the nuclear (steroid) hormone receptor superfamily, and that multiple isoforms exist – **slide 18**
c. Understand the role of the surge of thyroid hormone in thermal homeostasis, especially in the newborn period – **slide 9 →** *increased TSH results in increased T4 and T3 concentrations*

B. Pathology

1. Thyroid hormone deficiencies

a. Fetal hypothyroidism
1. Pathophysiology
a. Be aware that transplacental passage of certain substances including radioiodine, iodides, propylthiouracil and methimazole administered to the mother may affect fetal thyroid development and/or function – **slide 19**

2. Clinical implications
a. Know the concentrations of thyroid hormones and their metabolites throughout fetal development – **slides 8 and 10**
b. Know value of ultrasonography in detecting thyroidal enlargement in the fetus – **slide 20**
c. Know efficiency of fetal brain deiodination in the face of fetal hypothyroidism – **slide 21**
d. Know that maternal hypothyroidism is associated with increased fetal loss and with mild cognitive delay in the infant – **slide 21**
e. Know that when there is hypothyroidism in the mother and the fetus, severe mental retardation is likely in the fetus – **slide 22**

b. Congenital hypothyroidism
1. Pathophysiology
a. Be aware of potential effects on the breast-fed infant of antithyroidal agents ingested by the mother – **slide 24**
b. Recognize that worldwide iodide deficiency is the most common cause of congenital primary hypothyroidism and of preventable mental retardation – **slide 23**
c. Know the various metabolic defects in synthesis of thyroid hormones that occur – **slides 28-30**
d. Know the inheritance of biosynthetic errors – **slide 28** (*and see later table in outline*)
e. Based on knowledge of embryology, understand the various anatomical abnormalities causing congenital hypothyroidism (agenesis, maldescent, lingual thyroid) – **slide 27**
f. Know the approximate incidence of the various causes of congenital hypothyroidism – **slide 25**
g. Recognize the possibility of isolated TSH deficiency – **slide 35**
h. Know that children with Down syndrome may manifest mild primary hypothyroidism – **slide 25**

2. Clinical implications
a. Clinical manifestations
1. Know the pattern of osseous maturation in the neonate and the impact of thyroid hormone deficiency on the process – **slide 34**
2. Recognize that congenital central hypothyroidism is often associated with other pituitary hormone deficiencies – **slides 45-46**
3. Be aware of intracranial anatomical defects which may accompany TRH or TSH deficiencies – **slide 46**
4. Be aware that congenital hypothyroidism is the most common disease screened for in newborns – **slide 25**
5. Be familiar with the clinical significance of the effect of prematurity on thyroid function in the neonate – **slide 26**

6. Know the clinical characteristics and inheritance patterns of TSH unresponsiveness syndromes – **slides 6-7**

7. Know the clinical findings of congenital hypothyroidism and when they become manifest – **slides 32-33**

8. Know the clinical findings of Pendred syndrome and recognize that mutations in the affected gene are an important cause of sensorineural deafness – **slides 30-31**

b. Diagnosis

1. Know the changes in hormonal concentrations suggesting deficiency of either TRH or TSH – **slide 35**

2. Be aware of procedures for delineating errors of thyroid hormone synthesis – **slide 37**

3. Be aware of techniques for defining the anatomy of the thyroid (scans and ultrasound) – **slides 38-42**

4. Be aware that maternally transmitted TSH receptor-blocking antibodies can be a cause of transient congenital hypothyroidism – **slides 43-44**

5. Be aware of laboratory findings suggesting agenesis of the thyroid – **slides 38 and 42**

<u>Labs</u> – very elevated TSH and very low total or free T4; low to undetectable Tg

<u>Imaging</u> – absent thyroid uptake or absent gland on ultrasound

6. Be aware that maternally transmitted TSH-receptor-blocking antibodies can inhibit TSH-induced iodine uptake and therefore result in apparent absence of the thyroid gland on scanning – **slides 39, 43-44**

c. Treatment

1. Be aware of the half-life of transferred blocking antibodies – **slide 43**

2. Be able to develop a safe management plan for infants born to mothers with TSH receptor blocking antibodies – **slide 43**

3. Be aware that the recommended dosage of thyroxine per kg of body weight for congenital hypothyroidism changes with the age of the child – **slide 47**

4. Know how to interpret concentrations of thyroxine and TSH in monitoring treatment of congenital hypothyroidism – **slide 47**

5. Recognize the variability of TSH suppression in the young infant receiving treatment for congenital hypothyroidism with thyroxine – **slide 47**

6. Be aware of the advantages of maintaining high-normal concentrations of thyroxine in serum for optimal outcome in treating congenital hypothyroidism – **slides 47-48**

7. Know potential side effects of overtreatment of congenital hypothyroidism (premature craniosynostosis and advanced bone age) – **slide 49**

8. Know that soy formula, fiber, and iron can inhibit thyroid hormone absorption – **slide 48**

9. Know that mild hypothyroidism frequently normalizes and that treatment may not be necessary – **slide 50**

d. Prognosis

1. Be familiar with the prognosis for future cognitive development in congenital hypothyroidism and the factors that affect this prognosis – **slide 48**

e. Prevention

1. Know how to apply the genetics of biosynthetic errors in counseling

--- *All of the permanent forms of congenital hypothyroidism due to biosynthetic errors are autosomal recessive. Therefore, with the same parents, there is a 1 in 4 chance (25%) of it occurring in each newborn*

Genetic mutations that result in congenital hypothyroidism (CH)

Central hypothyroidism	Chromosome	Mode of inheritance
Thyrotropin β chain (TSHβR)	1p13	Autosomal recessive (AR)
POU1F1 (a.k.a. PIT1)	3 p11	AR
PROP-1	5q	AR
LHX3	9q34	AR
Thyroid dysgenesis		
TSH receptor (TSHR)	14q21	Autosomal dominant (AD) or AR
NKX2.1 (a.k.a. TTF11)	14q13	AD
FOXE1 (a.k.a. TTF-2)	9q22	AR
PAX8	2q14.1	AD
NKX2.5	5q35.1	AD
Thyroid dyshormonogenesis		
Thyroid peroxidase (TPO)	2p25	AR
Thyroglobulin (TG)	8q24.22	AR
Na-I symporter (NIS; SLC5A5)	19p13.1	AR
Pendred syndrome (PDS)	7q31	AR
Dual oxidase 2 (DUOX2)	15q21.1	AD (transient CH) or AR (permanent CH)
TSH resistance		
TSH receptor (TSHR)	14q21	AR or AD
G_s protein α subunit (GNAS)	20q13	AD

2. Know the methodology involved in thyroid screening of the neonate including measurement of thyroxine and TSH concentrations – **slides 35-36**

3. Be able to cite advantages and disadvantages of various systems of neonatal thyroid screening – **slide 36**

4. Know the appropriate diagnostic approaches for children with various abnormalities on newborn screening – **slide 35**

5. Be aware of various transient abnormalities in thyroid function which may be detected by neonatal screening

Screening too early: elevated TSH → repeat TSH is normal
Preterm infant: low total or free T4 → repeat T4 or free T4 is normal
Transient causes: maternal TRAb, excess iodine from mother or in the immediate newborn period (Wolff-Chaikoff effect)

6. Recognize that congenital hypothyroidism may not be detected in a small number of infants by neonatal screening

--- small number of cases (<10%) may be detected on a second newborn screen; potential to be missed if only one screen is performed. Some cases will not be picked up on newborn screen depending on the severity and type of defect (e.g. MCT8, NIS, dehalogenase, mild thyroid hypoplasia). Some infants may be missed if born at home and did not have a newborn screen performed.