Hypothyroidism
in children

Contributors:

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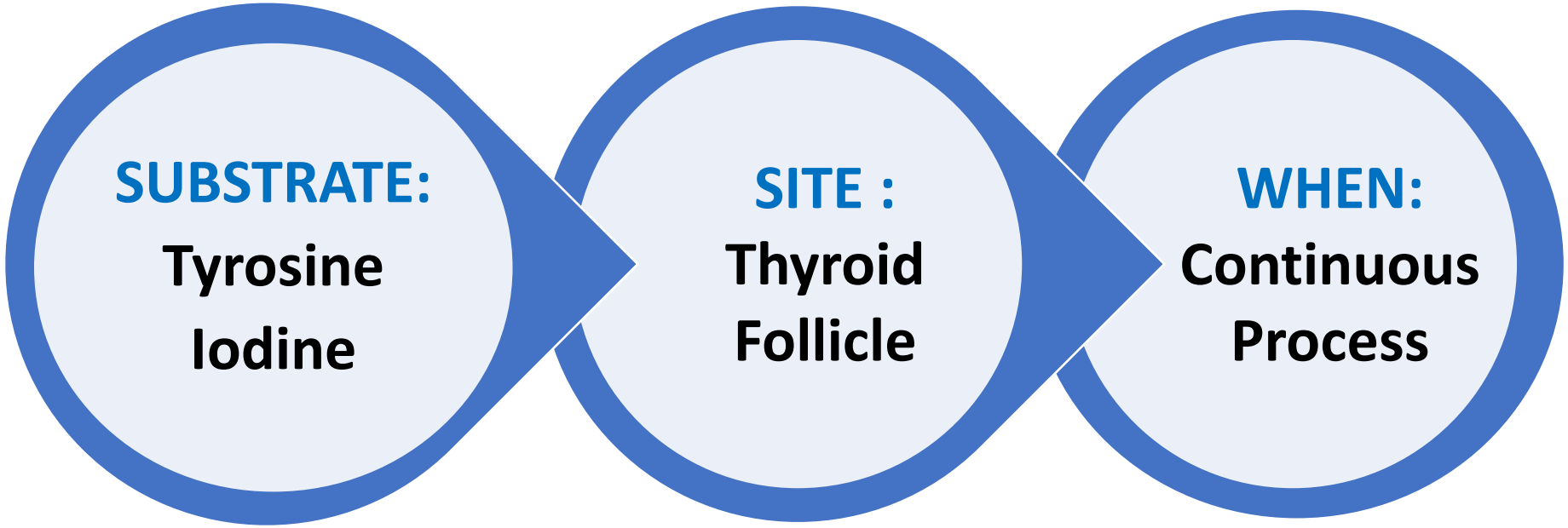
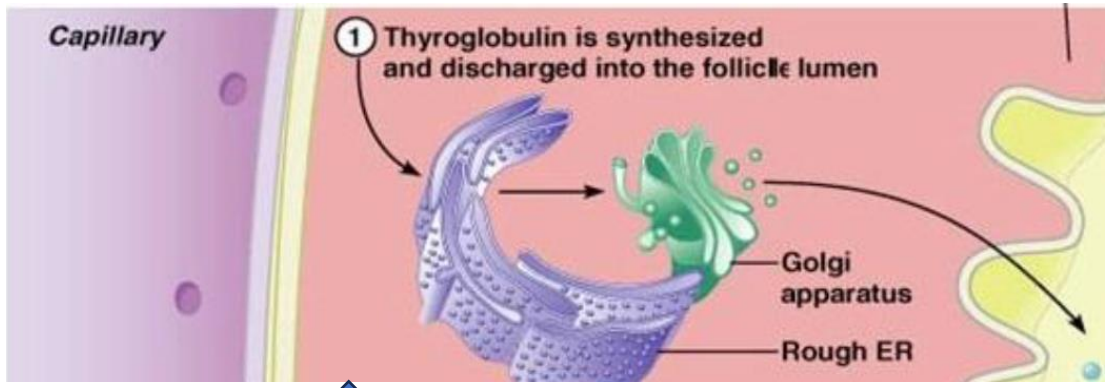
Synthesis of thyroid hormones

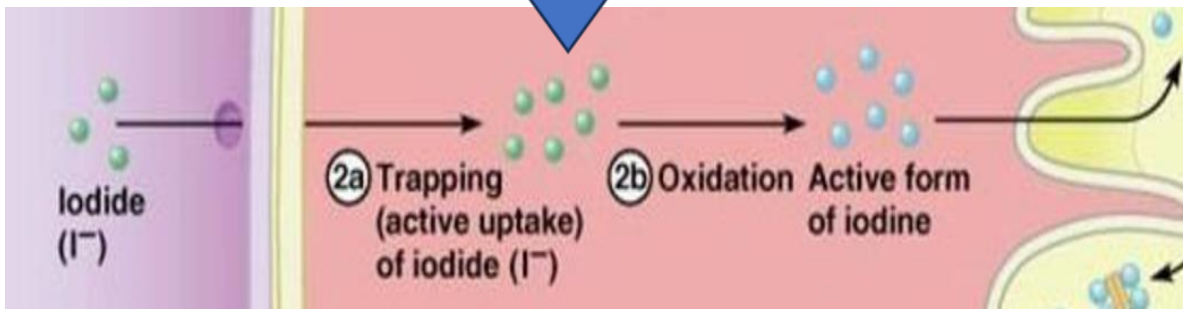




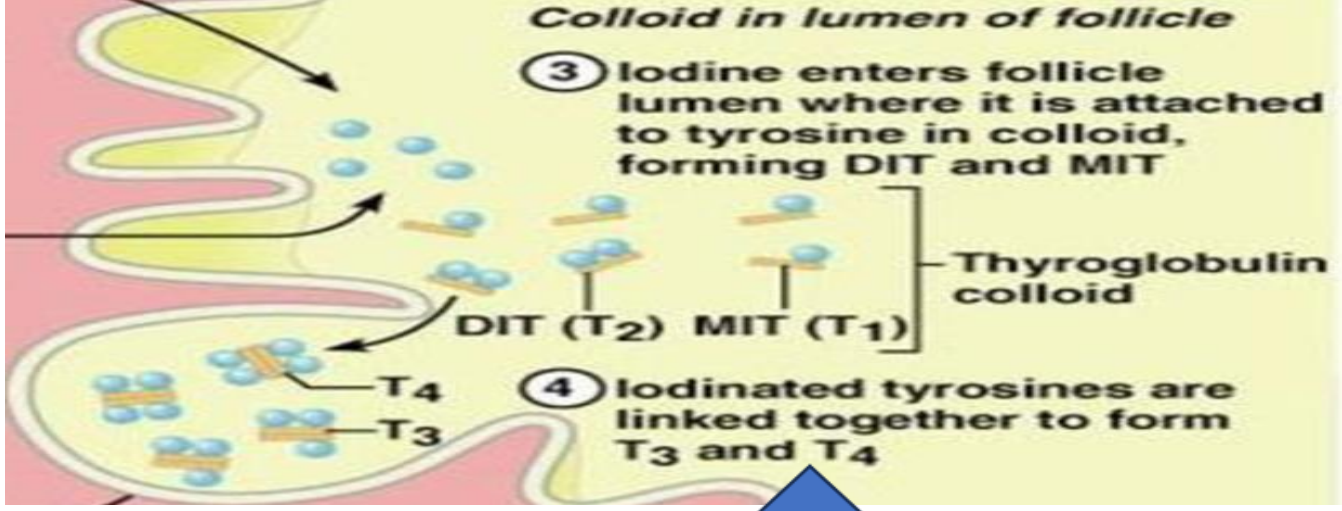
Thyroglobulin synthesis

Iodide trapping

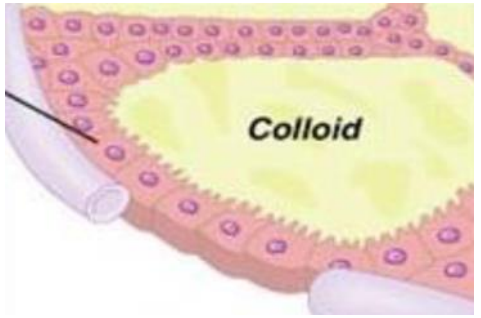
Transport of iodine and oxidation



quizlet.com/532096587/biochemistry-biosynthesis-and-functions-of-thyroid-hormones-and-thyroid-disorders-flash-cards/



Thyroid cell follicle



Iodination of tyrosine (organification of thyroglobulin)

Coupling reactions:

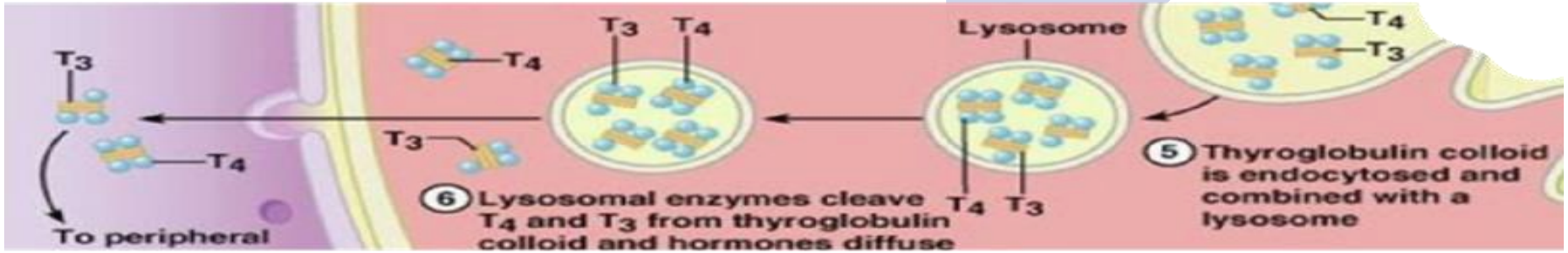
Tyrosine + I = Mono-iodotyrosine (MIT)

MIT + I = Di-iodotyrosine (DIT)

DIT + MIT = Tri-iodothyronine (T3)

DIT + DIT = Tetra-iodothyronine or Thyroxine (T4)

Release of thyroid hormones



T3 Production

- **Only 20% of T3 is directly produced in thyroid gland**

- **Remaining 80% of T3 produced is formed by 5'-deiodination of T4 in extrathyroidal tissues**

- **Extrathyroidal T3 production:**

  Sites: Liver, kidney

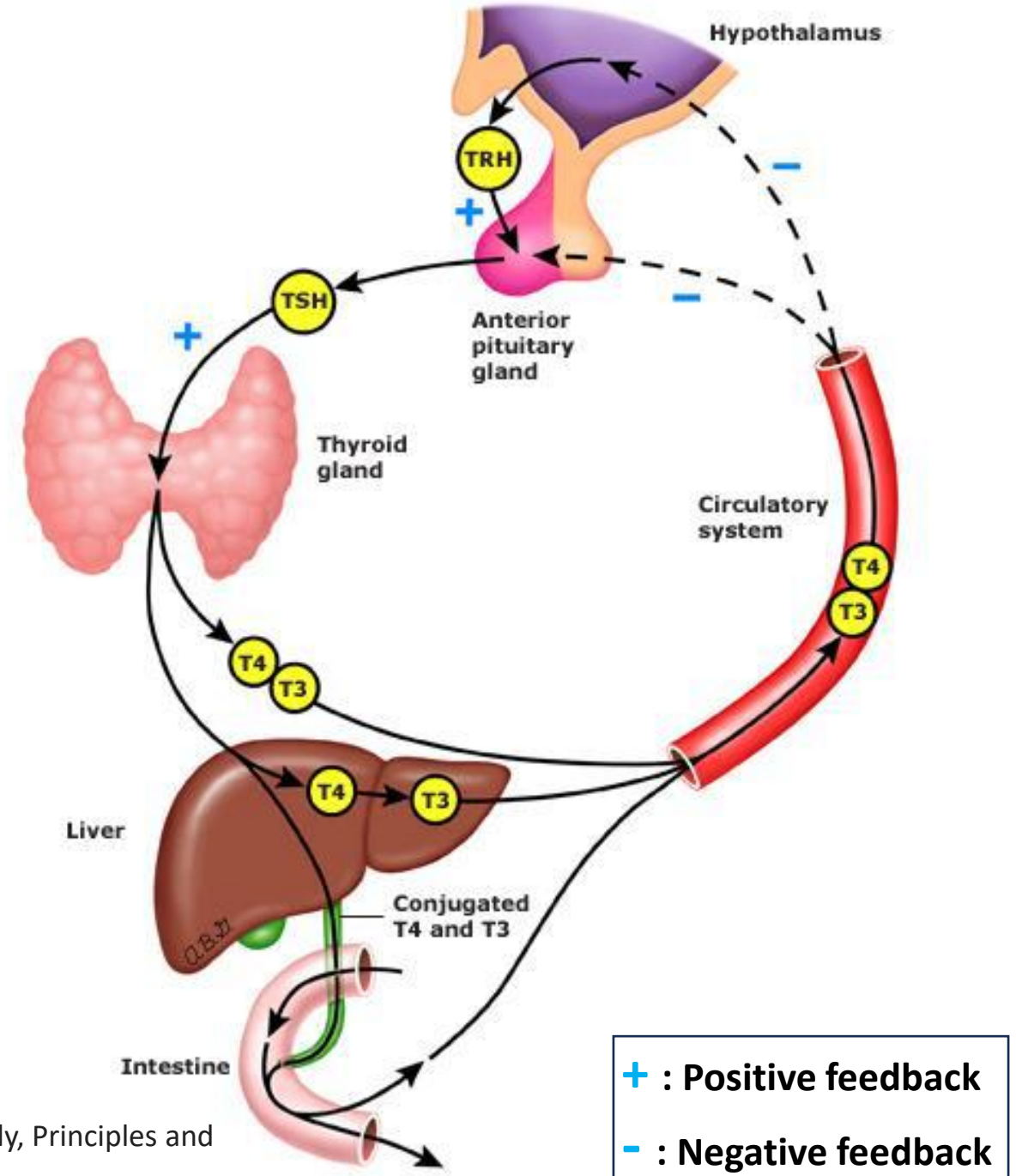
  Other sites: Muscle, brain, pituitary, skin, placenta

Serum Binding Proteins

More than 99.95% of T4 and 99.5% of the T3 in serum are bound to several serum proteins:

- **Thyroxine-binding globulin (TBG)**
- **Albumin**
- **Lipoproteins**

Regulation of Thyroid Hormones



Wu, et al. (2011). Surgical Disorders of the Thyroid in the Elderly, Principles and Practice of Geriatric Surgery. Springer, New York, NY.

Normal thyroid physiology in the fetus

- **First half of pregnancy**

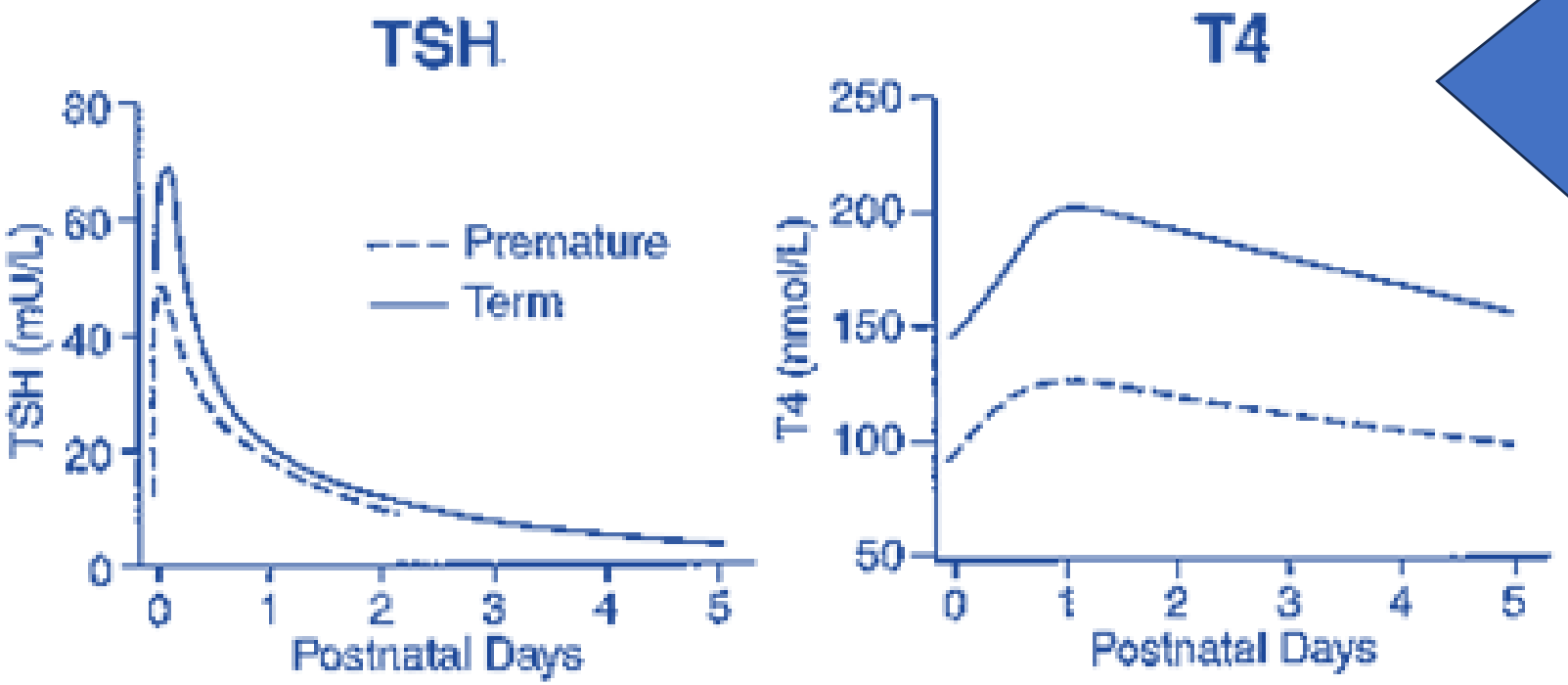
T4 in fetus is of maternal origin

- **Second half of pregnancy**

T4 production switches over from maternal to fetal origin

Maternal T4 partially protects a hypothyroid fetus in-utero.

Postnatal thyroid function



Brook's clinical Pediatric Endocrinology, 6th Edition, 2009

Serum TSH rises abruptly within 30 to 60 mins after delivery due to:

- **Stress during labor**
- **Clamping of umbilical cord**
- **Exposure to cold environment outside the uterus**

T4 Surge is seen on day 1-2

MEAN ± SD FOR TSH AND T4 OF PRETERM AND TERM INFANTS 0-28 DAYS

Age ± SD	Cord (Day 0)	Day 7	Day 14	Day 28
T_4 (mcg/dL)				
23–27*	5.44 ± 2.02	4.04 ± 1.79	4.74 ± 2.56	6.14 ± 2.33
28–30	6.29 ± 2.02	6.29 ± 2.10	6.60 ± 2.25	7.46 ± 2.33
31–34	7.61 ± 2.25	9.40 ± 3.42	9.09 ± 3.57	8.94 ± 2.95
>37	9.17 ± 1.94	12.67 ± 2.87	10.72 ± 1.40	9.71 ± 2.18
FT_4 (ng/dL)				
23–27	1.28 ± 0.41	1.47 ± 0.56	1.45 ± 0.51	1.50 ± 0.43
28–30	1.45 ± 0.43	1.82 ± 0.66	1.65 ± 0.44	1.71 ± 0.43
31–34	1.49 ± 0.33	2.14 ± 0.57	1.96 ± 0.43	1.88 ± 0.46
>37	1.41 ± 0.39	2.70 ± 0.57	2.03 ± 0.28	1.65 ± 0.34
TSH (mIU/L)				
23–27	6.80 ± 2.90	3.50 ± 2.60	3.90 ± 2.70	3.80 ± 4.70
28–30	7.00 ± 3.70	3.60 ± 2.50	4.90 ± 11.2	3.60 ± 2.50
31–34	7.90 ± 5.20	3.60 ± 4.80	3.80 ± 9.30	3.50 ± 3.40
>37	6.70 ± 4.80	2.60 ± 1.80	2.50 ± 2.00	1.80 ± 0.90

*Weeks gestational age

Williams FL, et al. Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. *J Clin Endocrinol Metab*. 2004;89:5314-5320.

AGE-BASED NORMAL VALUES FOR ROUTINE THYROID FUNCTION TESTS[14]

Age	Free T_4 (ng/dL)	TSH (mIU/L)	T_4 (mcg/dL)	T_3 (ng/dL)	Reverse T_3 (ng/dL)	TBG (mcg/mL)
Day of birth	0.94–4.39	2.43–24.3	5.85–18.68	19.53–266.26	19.53–358.70	19.17–44.7
1 wk	0.96–4.08	0.58–5.58*	5.90–18.58	20.83–265.61	19.53–338.52	19.16–44.68
1 mo	1.00–3.44	0.58–5.57*	6.06–18.27	25.39–264.31	19.53–283.84	19.12–44.59
3 mo	1.04–2.86	0.58–5.57*	6.39–17.66	36.46–259.75	19.53–197.90	19.02–44.35
6 mo	1.07–2.44	0.58–5.56*	6.75–17.04	51.43–252.59	19.53–137.36	18.87–44
1 yr	1.10–2.19	0.57–5.54	7.10–16.16	74.87–240.87	18.23–85.93	18.56–43.28
2 yr	1.11–2.05	0.57–5.51	7.16–14.98	103.51–228.50	16.93–55.99	17.94–41.82
5 yr	1.08–1.93	0.56–5.41	6.39–12.94	131.50–212.23	13.02–35.81	16–37.3
8 yr	1.04–1.87	0.55–5.31	5.72–11.71	130.85–202.46	11.72–30.60	14.2–33.09
12 yr	0.99–1.81	0.53–5.16	5.08–10.58	119.78–192.70	11.07–27.99	12.54–29.24
15 yr	1.03–1.77	0.52–5.05	4.84–10.13	110.02–184.88	10.42–27.34	11.96–27.89
18 yr	0.93–1.73	0.51–4.93		101.56–179.03	10.42–26.04	

Lem AJ, et al. Serum thyroid hormone levels in healthy children from birth to adulthood and in short children born small for gestational age. *J Clin Endocrinol Metab*. 2012;97:3170-3178.

How is hypothyroidism classified?

HYPOTHYROIDISM

CONGENITAL

Hypothyroidism present since birth

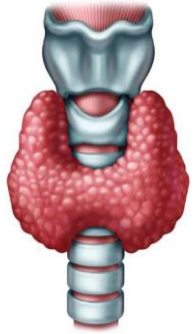
ACQUIRED

Hypothyroidism develops during childhood

Congenital hypothyroidism (CH)

First things first!!!

Congenital hypothyroidism (CH)



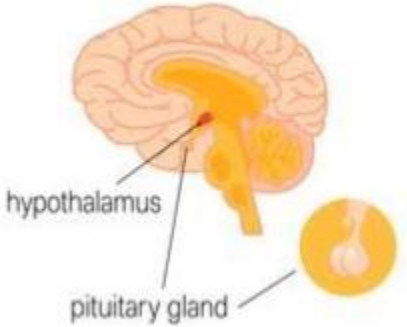
Thyroidal (Primary)

At the level of thyroid

Central (Secondary, Tertiary)

At the level of pituitary or hypothalamus

*Isolated TSH deficiency, *MPHD



THYROID DYSGENESIS

(80-90%) Most common

Ectopic

Aplasia

Hypoplasia

THYROID DYSHORMONOGENESIS

(10-20%)

Defect at any step of thyroid hormone synthesis

TRANSIENT

Maternal iodine deficiency (Most common)

Maternal TSHR blocking antibodies

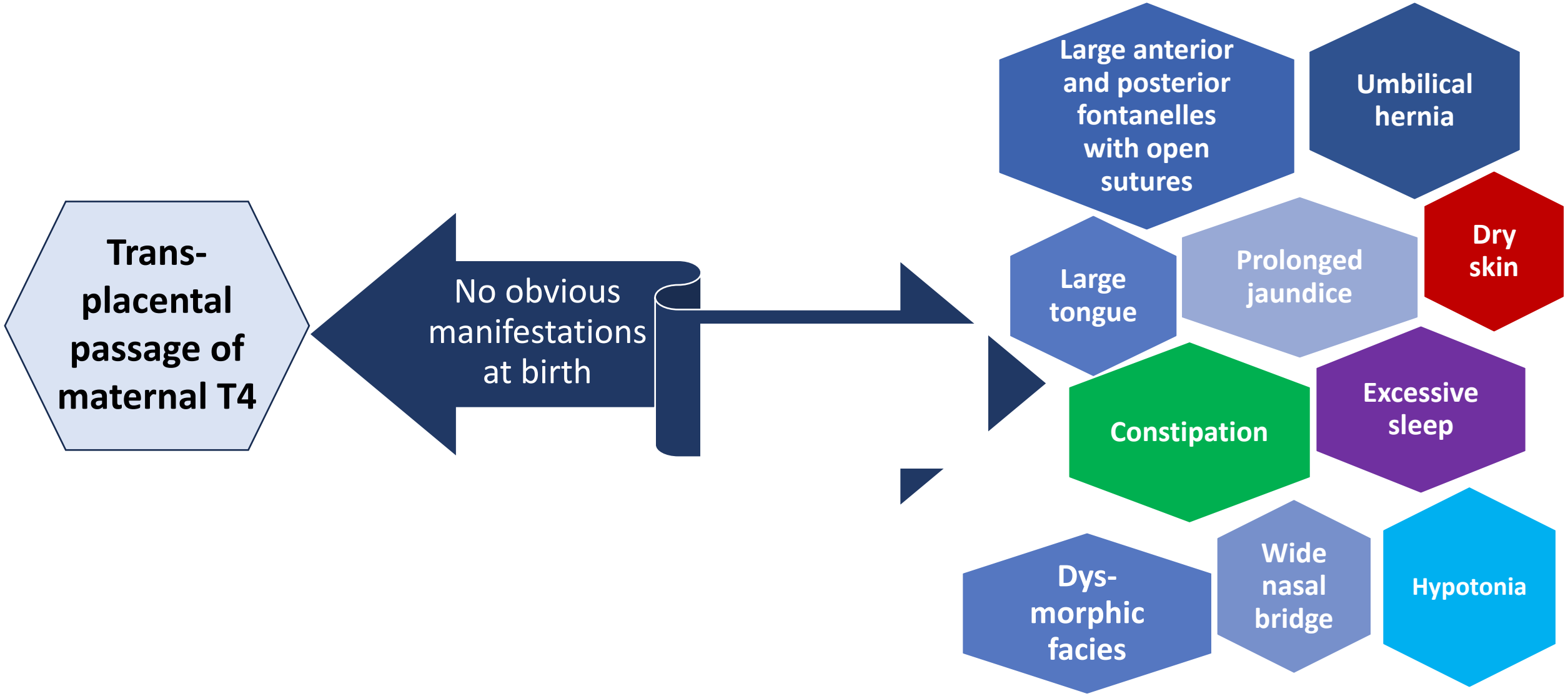
Maternal antithyroid drugs

OTHERS

Thyroid hormone resistance

Large hemangiomas (Consumptive hypothyroidism)

How does CH present?



Presentation of CH, if untreated by 3-6 months of age

- **Delayed developmental milestones progressing to disability**
- **Short stature (short extremities)**
- **Delayed dentition**
- **Hypotonia**
- **Myxedema facies (dysmorphic facies):**
  - **Narrow palpebral fissures with swollen eyelids**
  - **Dry and coarse skin**
  - **Coarse hair**
- **Infant Hercules; Kocher-Debre-Semelaigne (KDS) syndrome**

CH missed at birth, presenting later

Why is early detection of CH important?

Most common preventable cause of intellectual disability
Prevalence of CH : In World- 1 : 3,000 to 1 : 4,000
In India - 1 : 800 to 1 : 1,500

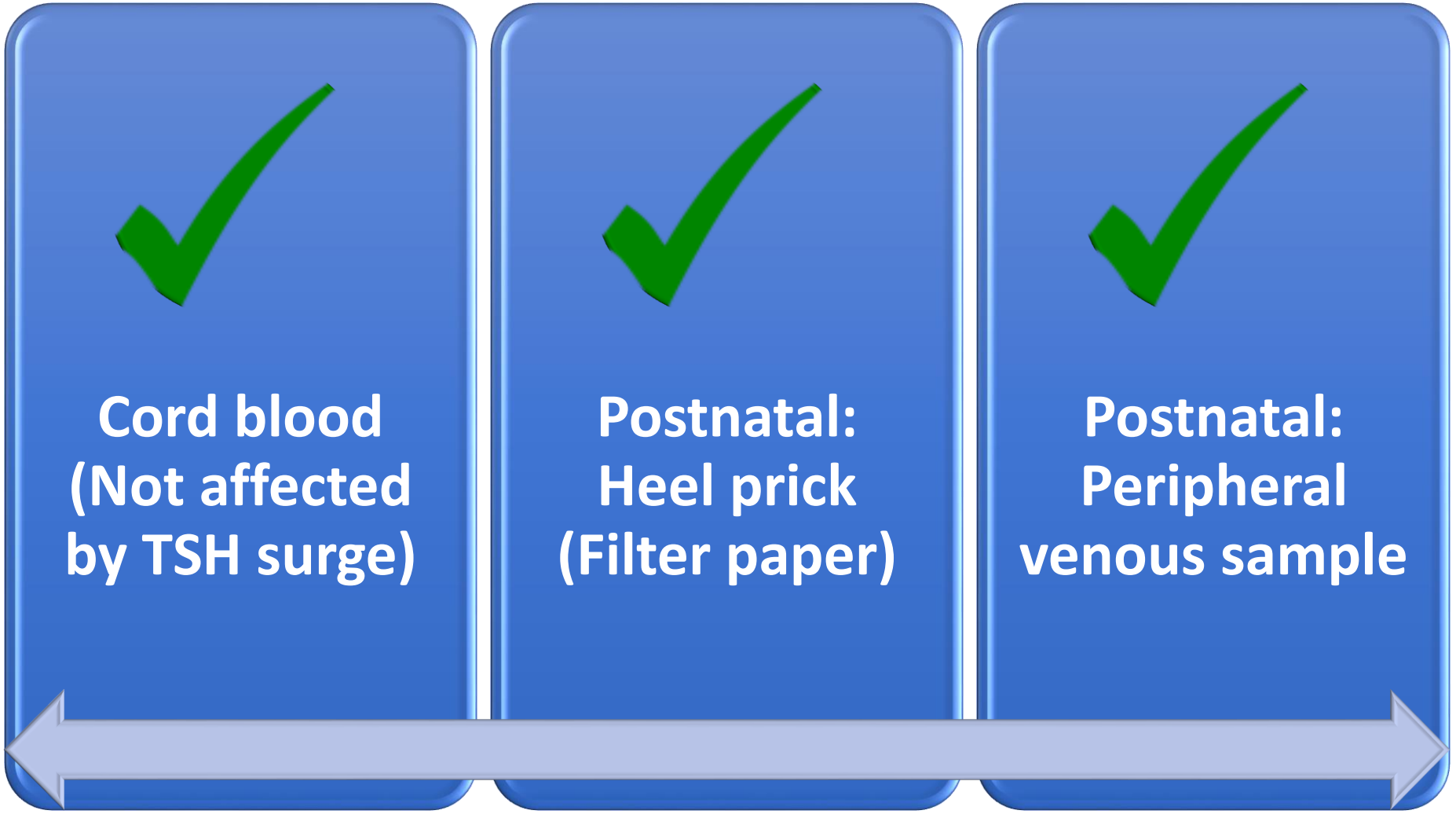
Near normal outcomes are seen, if CH diagnosed and treated before 2 weeks of age

Early detection is recommended to prevent neurodevelopmental disability and to optimize the developmental outcomes

Less than 5% newborns and only up to 10% may show symptoms in the first month of life

A day's delay in the diagnosis = a percent decrease in the neurodevelopment (DQ/IQ)

Newborn screening (NBS) - which sample?



NBS: Which sample?

Cord blood

Advantages:
TSH surge is spared *
Useful in early hospital discharge
No prick for newborn

Disadvantages:
Requirement of round the clock personnel

Caution
Blood collection: Placental end of cord from umbilical vein
Cord blood TSH <25 µIU/mL

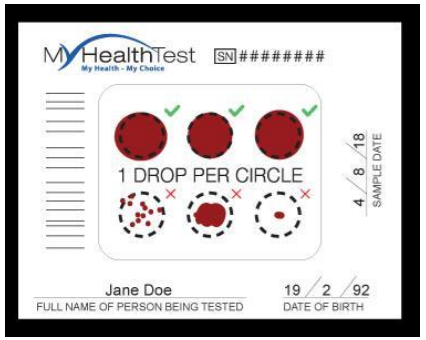
Postnatal sample (Heel prick)

Advantages:
Screening of other conditions
Home delivered babies

Disadvantages:
Postnatal TSH surge
Requirement of special reagents and equipment and trained personnel

Caution:
Error free blood spots

* TSH surge is not spared always– to be interpreted appropriately for deciding normal range



Site for Heel prick

NBS: When to test?

- **Routine screening at 48-72 hours, NOT later than 5 days after birth**
- **High-risk neonates such as Preterm/LBW/VLBW/Down syndrome/ Sick neonates admitted in NICU - second screening may be needed at 4 weeks of age**

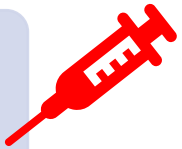
All newborns, including those treated in the NICU should be uniformly screened for CH without fail

NBS – When to test?

Preterm/ SGA	• **48-72 hrs after birth (as for term neonates)**
Sick newborn	• **Before 7 days of life OR at discharge – whichever is earlier**

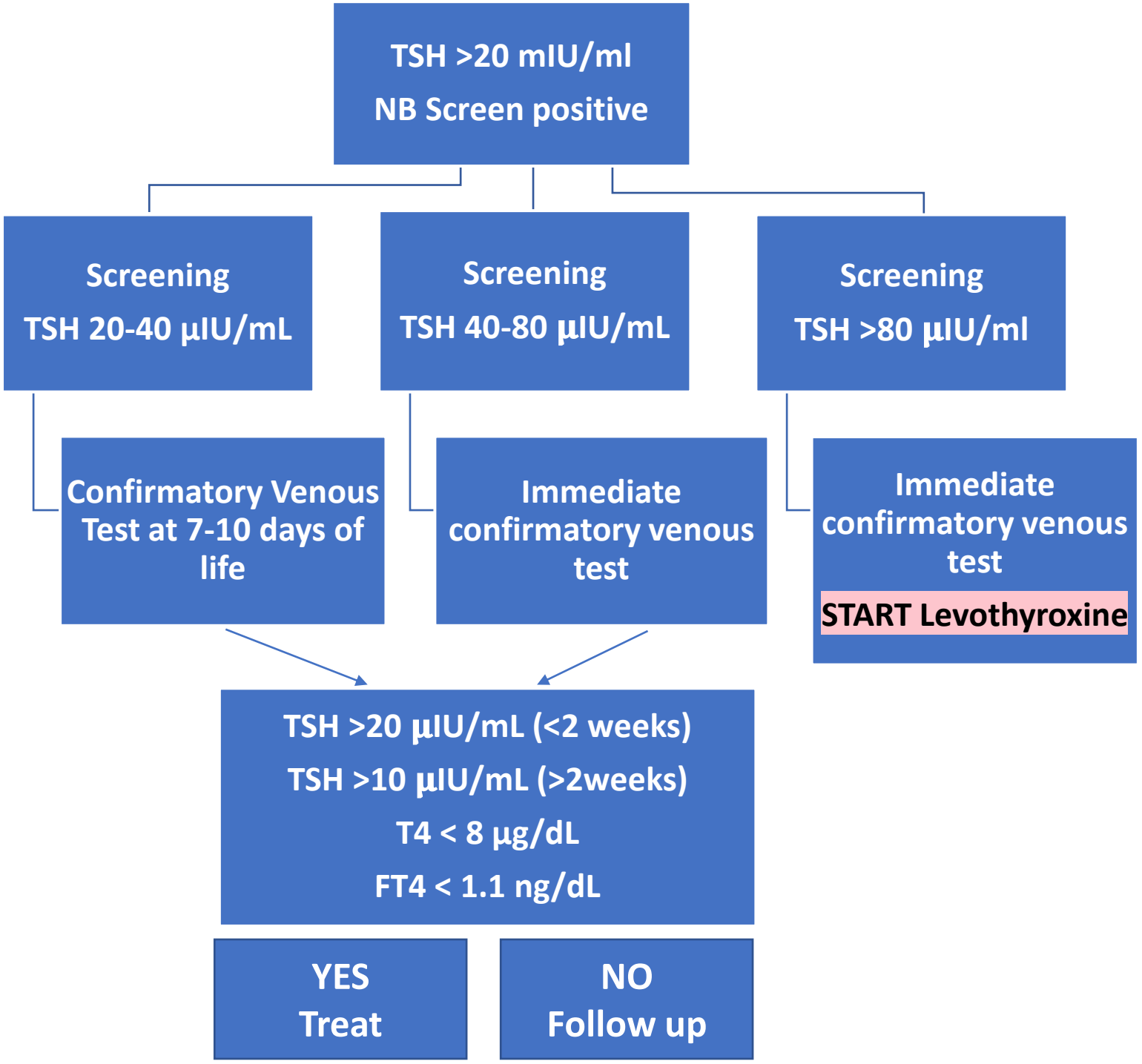
CH screen: Which test?

T4 based	TSH based
Identifies primary and central hypothyroidism	More sensitive and specific
Higher false positivity	Preferred screening test
May miss subclinical hypothyroidism	May miss central hypothyroidism



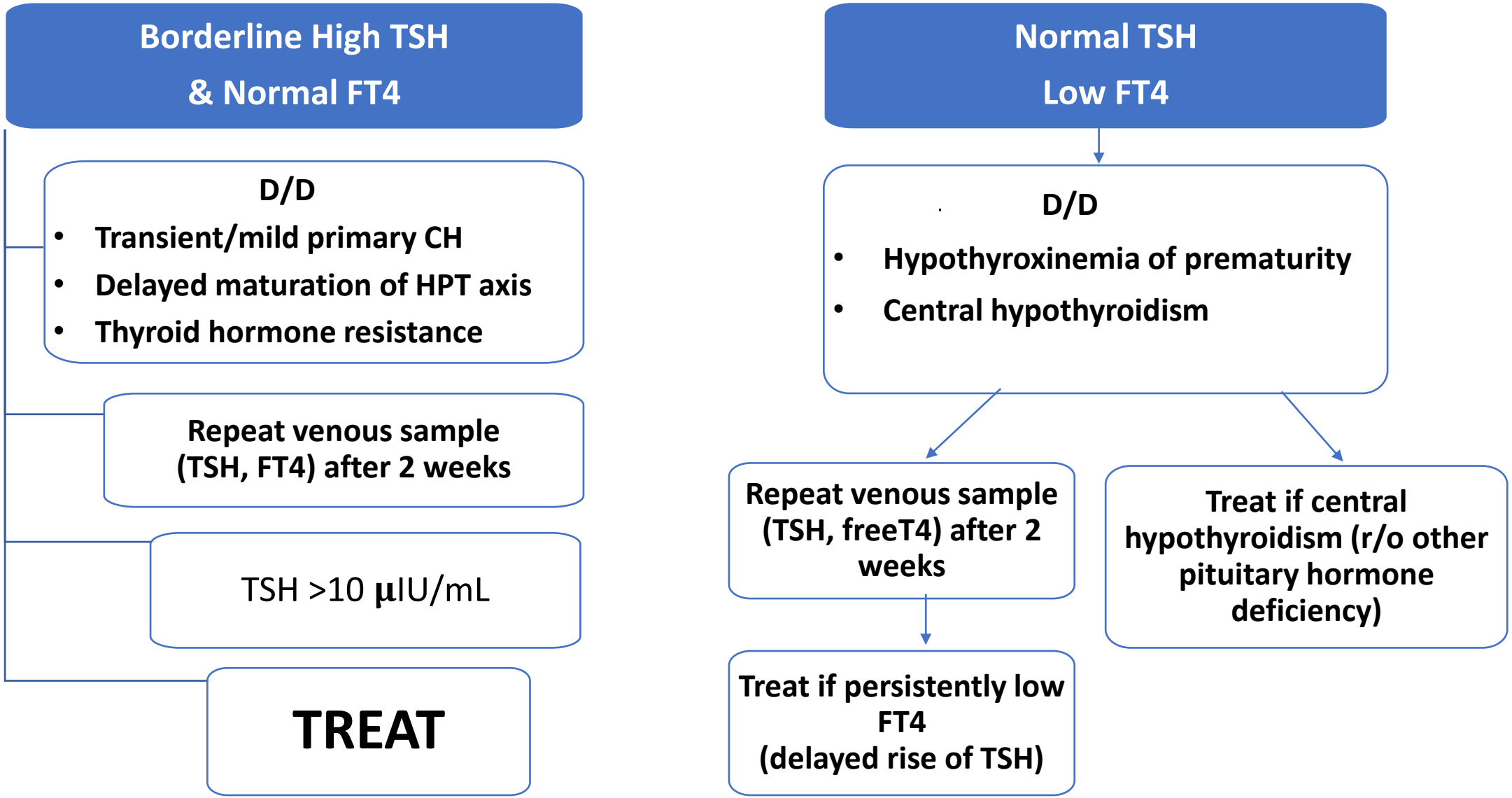
TSH based screening is recommended in India

ISPAE Guidelines on Congenital Hypothyroidism screening (2018)



Borderline Thyroid Function Tests*

*Take help from pediatric endocrinologist



Sick euthyroid syndrome

- **It refers to changes in thyroid function tests in an inpatient or ICU during critical illness**
- **Occurs due to transient alterations in the HPT axis**
- **Presents as:**
  - **low total T3 and FT3 levels**
  - **low or normal T4 and TSH levels**
- **So, when serum TSH is not elevated, the euthyroid sick syndrome should be considered even in patients with known thyroid disease and low serum FT3 or T4 levels**
- **Most of the times treatment is not required (self-limiting)**

Indications for second screening

- **Preterm neonates (<37 weeks)**
- **LBW and VLBW**
- **Neonates admitted to NICU**
- **Borderline high TSH & normal T4 during NBS**
- **Multiple births**
- **Down syndrome**

WHEN?

After 2 weeks of age

OR

2 weeks after the first screening

NBS in preterm neonates

Attenuated TSH surge

- Immature HPT axis

Low T4 & T3

- Loss of maternal T4, immature gland, high type 3 deiodinase activity

Drugs down-regulating TSH secretion

- Steroids, dopamine, topical iodine

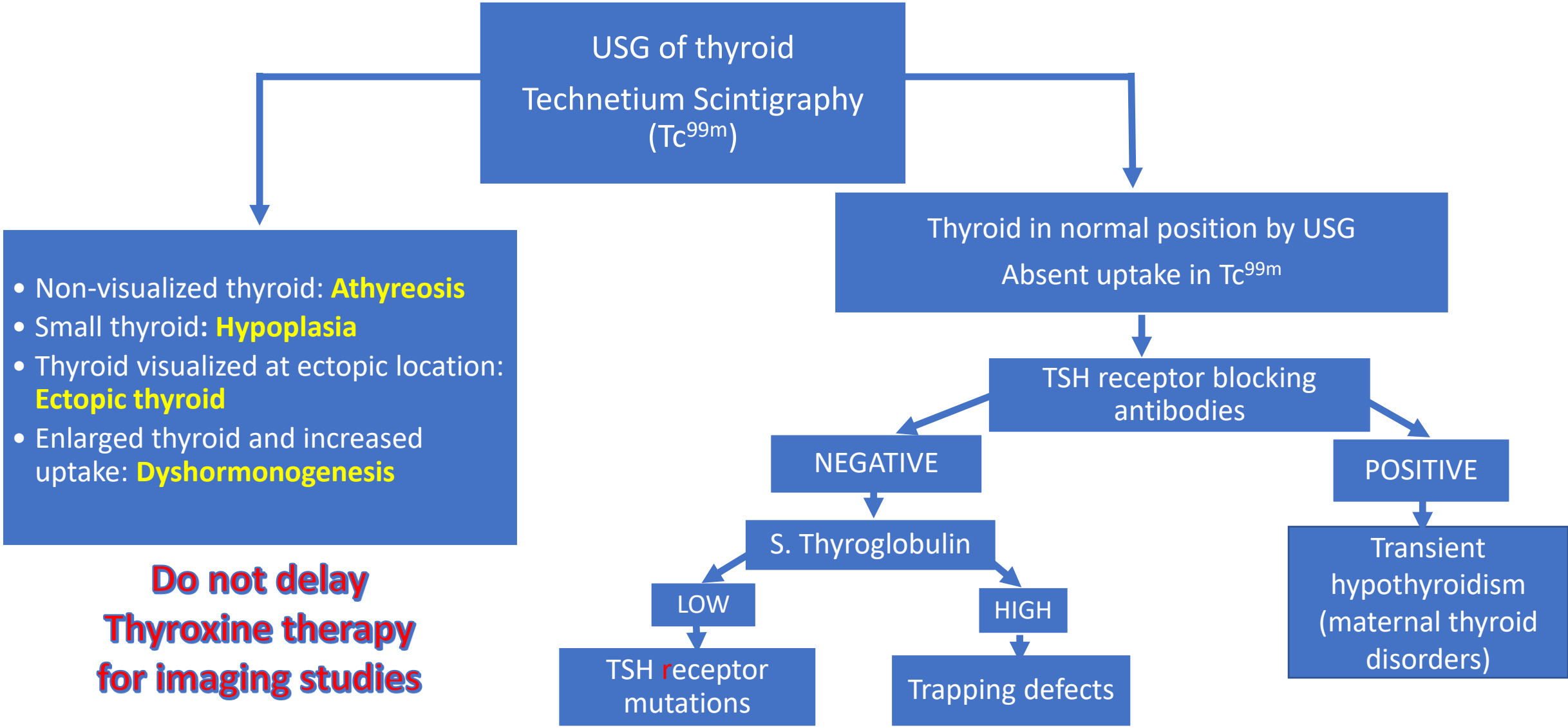
Sick euthyroid syndrome

- False negative or positive screen

History & Physical examination

- **Consanguinity, maternal autoimmune thyroid disease, iodine exposure**
- **Gestational age, birth weight, neonatal events**
- **Dysmorphism**
- **Other anomalies (cleft palate, congenital heart disease) & hypotonia**

Role of imaging in CH



Do not delay Thyroxine therapy for imaging studies

- Identification of etiology of CH
  (Absent thyroid gland needs: full dose of thyroxine)
- Helps in counselling family regarding lifelong replacement
- If permanent etiology confirmed initially, it can avoid re-evaluation by interrupting treatment at 3 years of age

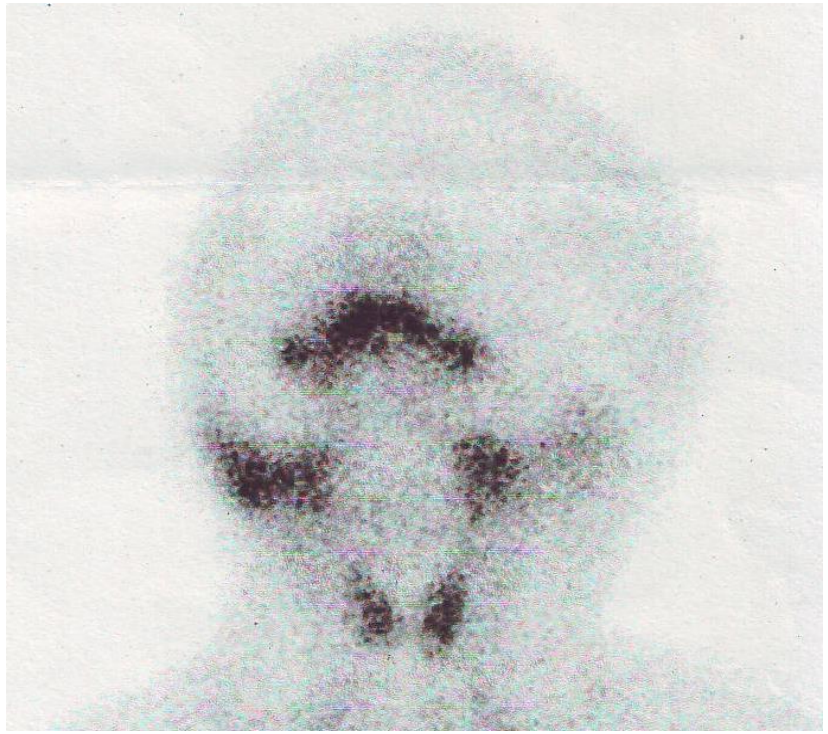
WHY?

- USG can be done anytime before or after starting treatment (requires expertise)

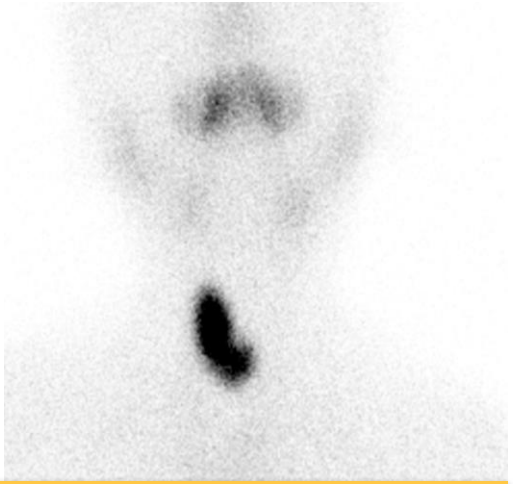
- Tc^{99m} scan should be done before starting treatment or within 7 days

WHEN?

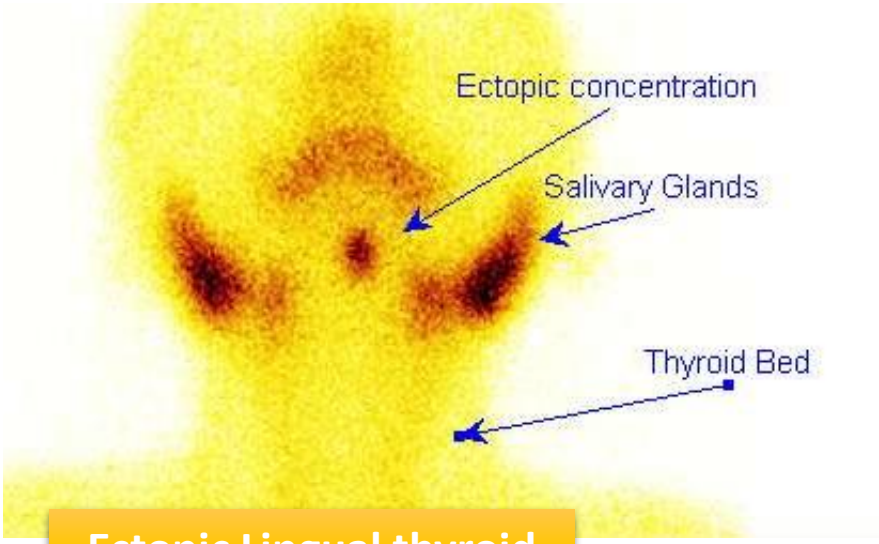
Role of Imaging (Tc^{99m}) – Cong. Hypothyroidism



Normal Thyroid gland uptake

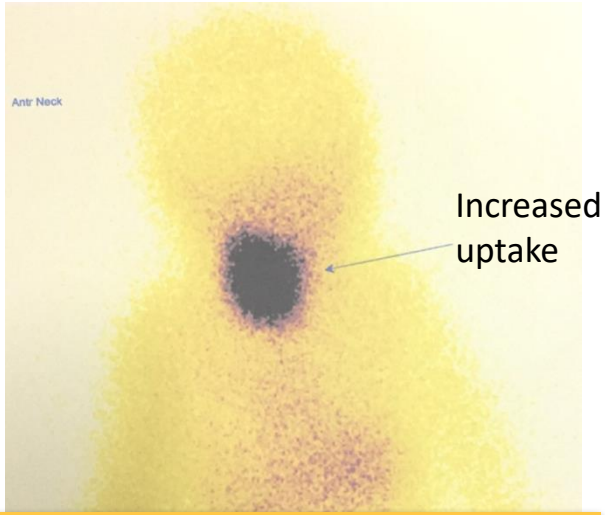


Hemiagenesis



Ectopic Lingual thyroid

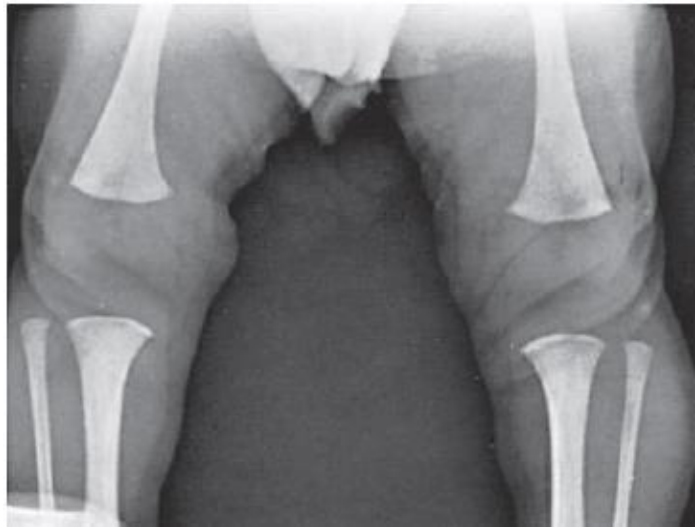
Complete Agenesis



Thyroid Dyshormonogenesis

Other investigations

- **Hearing screen (SNHL, Pendred syndrome)**
- **AP radiograph of knee: Absent lower femoral epiphysis + upper tibial epiphysis (suggests CH)**
- **S. cortisol (in central hypothyroidism to rule out hypopituitarism**



If serum cortisol levels are low

↓

Start hydrocortisone prior to thyroxine to prevent adrenal crisis

Treatment of CH

- **Replacement with Levothyroxine (LT4)**
  - **Dosage: 10-15 µg/kg/day**
  - **Administration: Early in the morning on an empty stomach**
- **Crush tablet, mix in small quantity of breastmilk/water**
- **Do not add tablet to formula feeds**
- **Avoid iron/calcium/vitamins within 3-4 hours of thyroxine**

Counsel the family –
NEVER to stop thyroxine

Rechecking for permanency of CH

Re-evaluation not required in cases of Permanent CH (e.g. ectopic thyroid, agenesis)

- ***Indications***

Suspected transient hypothyroidism

Etiological evaluation (imaging studies) not done at diagnosis

When only low dose of thyroxine is required

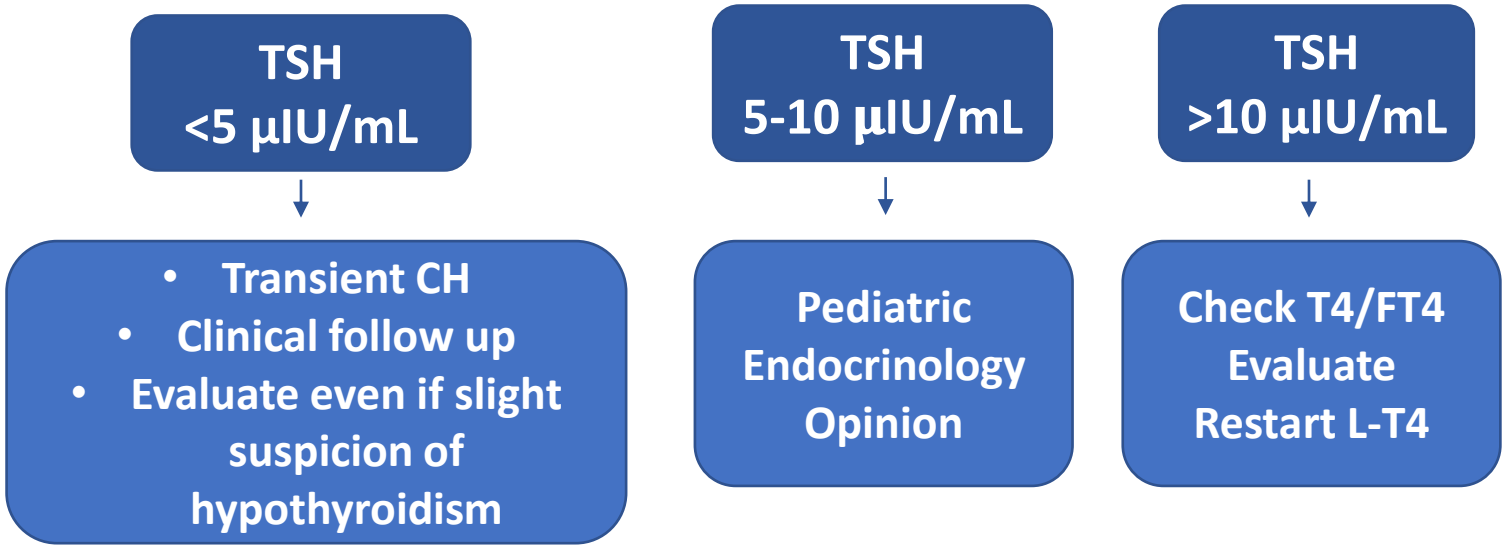
- ***When?***

At 3 years of age

- ***How?***

Stop thyroxine for 4 weeks

Recheck TSH and FT4



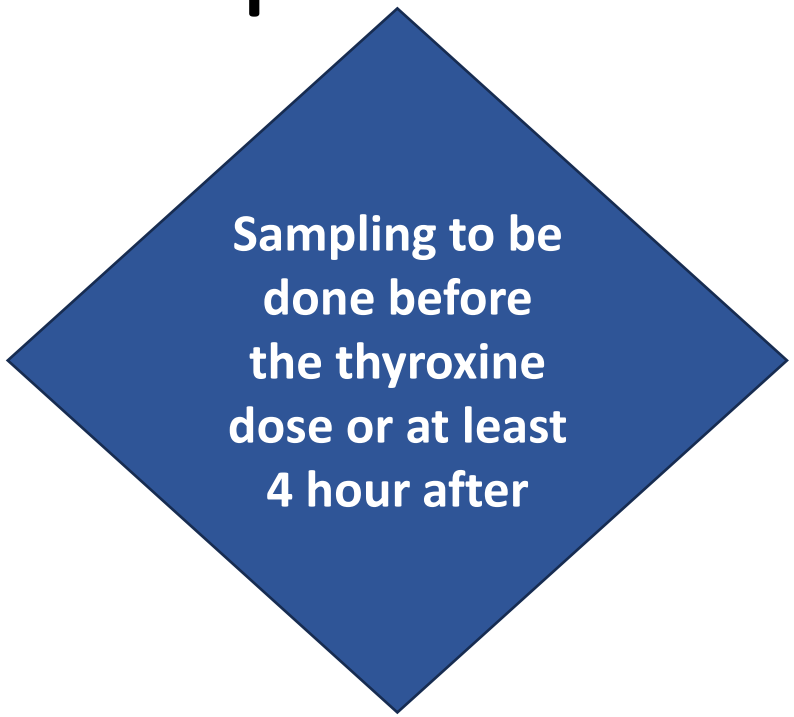
Monitoring and follow up

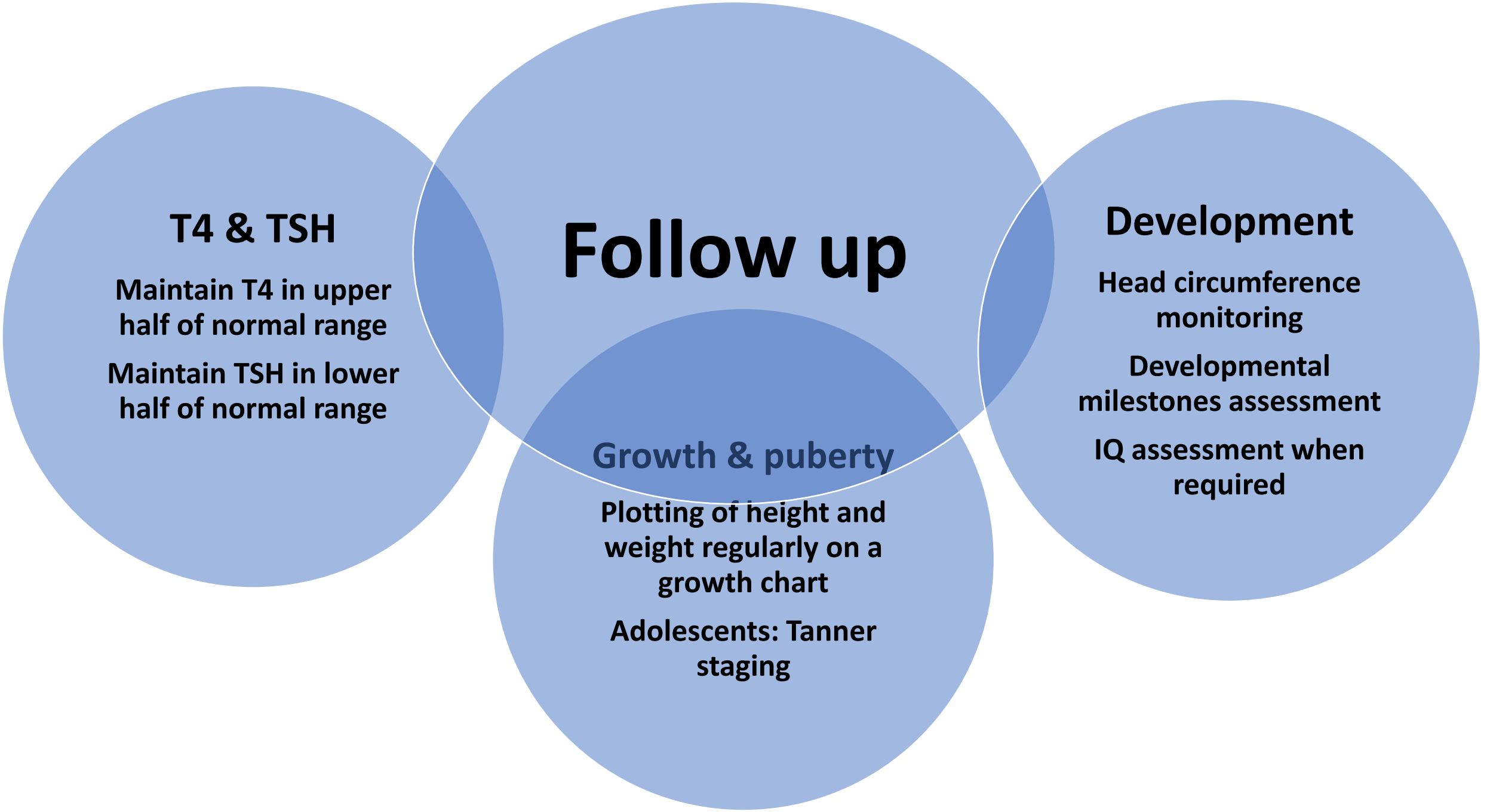
- **Investigations: Serum TSH and T4/FT4**

- **After 2 weeks of starting therapy**
- **At 1 month**

- **Subsequent follow up**
  - **Every 2 months till 6 months of age**
  - **Every 3 months from 6 months to 3 years**
  - **Every 3-4 months thereafter till completion of growth and puberty**

- **4 weeks after changing thyroxine dose**
  - **Target FT4 – Upper half of reference range by 2 weeks**
  - **Target TSH – Lower half of normal range by 4 weeks**




Follow up
T4 & TSH
Maintain T4 in upper half of normal range
Maintain TSH in lower half of normal range
Growth & puberty
Plotting of height and weight regularly on a growth chart
Adolescents: Tanner staging
Development
Head circumference monitoring
Developmental milestones assessment
IQ assessment when required

Prognosis

- **Early diagnosis and adequate treatment from the 1st week of life results in normal linear growth and development, normal scoring in psychometric testing**

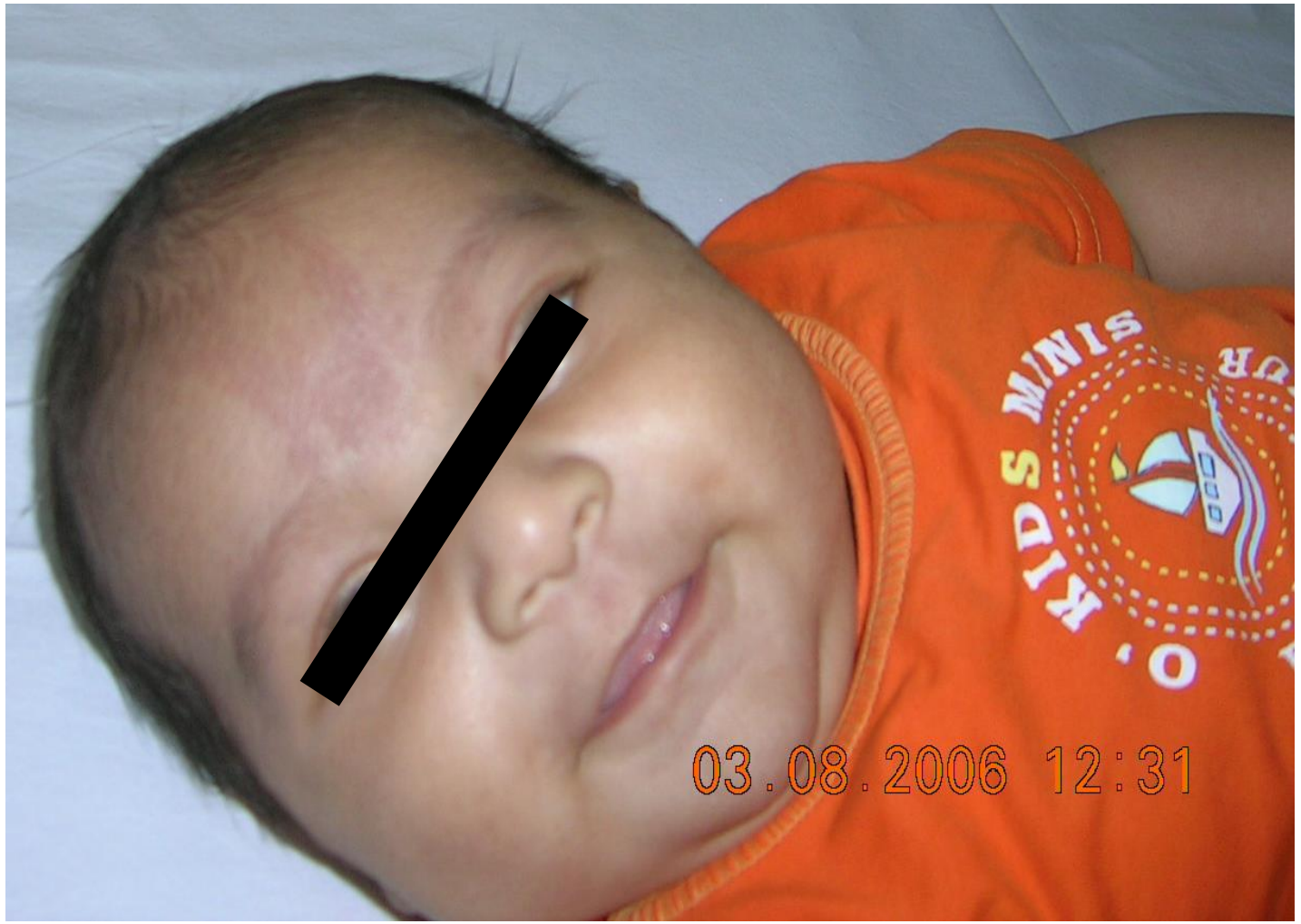
- **Delay in diagnosis, inadequate treatment & poor compliance results in variable degrees of brain damage**

Case scenario

Q. Tanuj, 3-month old boy
Exclusively breastfed infant
C/o Constipation –

- **bowel movement once in 4 days, only after Dulcolax suppository**
- **H/o constipation from 6 weeks of age, passing stools once in 2-3 days**

Earlier, 3-4 stools per day
No treatment sought – grandmother said “no worries”
No newborn thyroid screening was done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Tc99m scan
Sublingual
(ectopic)
thyroid

- Had social smile, no head control, anicteric
- AF wide open, PF open
- Sagittal suture wide, metopic suture open
- Hypothyroid facies; Large tongue, no umbilical hernia
- Tracheal rings easily felt, thyroid not palpable

- S. Total T_4 1.31 µg/dL (6.0-17.6), S. TSH 351.8 µIU/mL (0.58–5.57),
- Tc^{99m} scan – Sublingual (ectopic) thyroid

- Advised L-thyroxine 37.5 µg OD
- Parents counselled; advised lifelong replacement therapy

Learning points

1. **Importance of NBS for CH**
2. **Symptom of constipation when exclusively breastfed, ignored**
3. **Wide open fontanelles, suture lines not examined**
4. **Delayed motor development not recognized**

Take home message

NBS should be routinely undertaken in ALL live newborns to rule out CH

Most common preventable cause of intellectual disability is CH

Acquired Hypothyroidism (AH)

Common causes of AH

- **Autoimmune thyroid disease-**

  Female (5–15%) : Male (1–5%)*

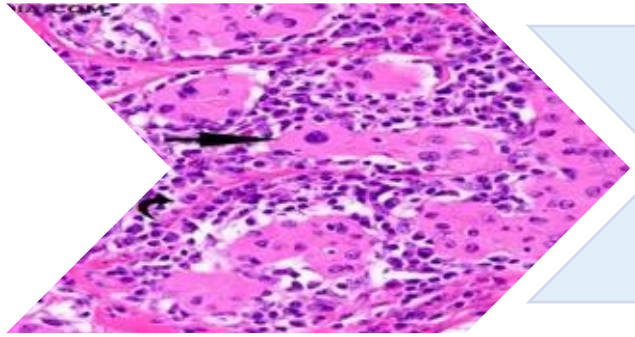
  Hashimoto's thyroiditis (juvenile AH)

  Autoimmune polyglandular syndromes type 1 and 2
- **Iodine deficiency**
- **Central hypothyroidism: Trauma, tumour, and tuberculosis**
- **Infectious thyroiditis**

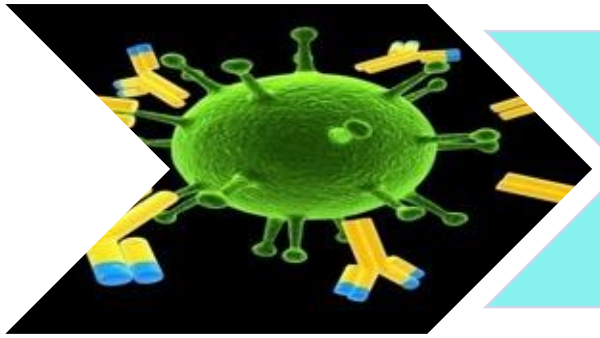
  Suppurative thyroiditis
- **Drugs: Anticonvulsants, amiodarone, lithium, chemotherapy, and radiotherapy**
- **Miscellaneous: Post-ablative, post-thyroidectomy, etc.**

*Franco JS, et al. Thyroid disease and autoimmune diseases. In: Anaya JM, et al., editors. Autoimmunity: From Bench to Bedside [Internet]. Bogota (Colombia): El Rosario University Press; 2013 Jul 18. Chapter 30.

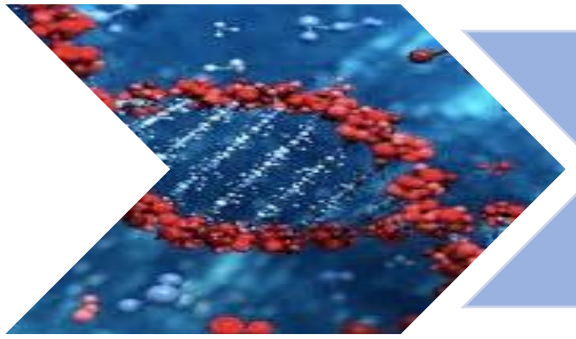
Etiology



Cellular immune responses



Humoral immunity

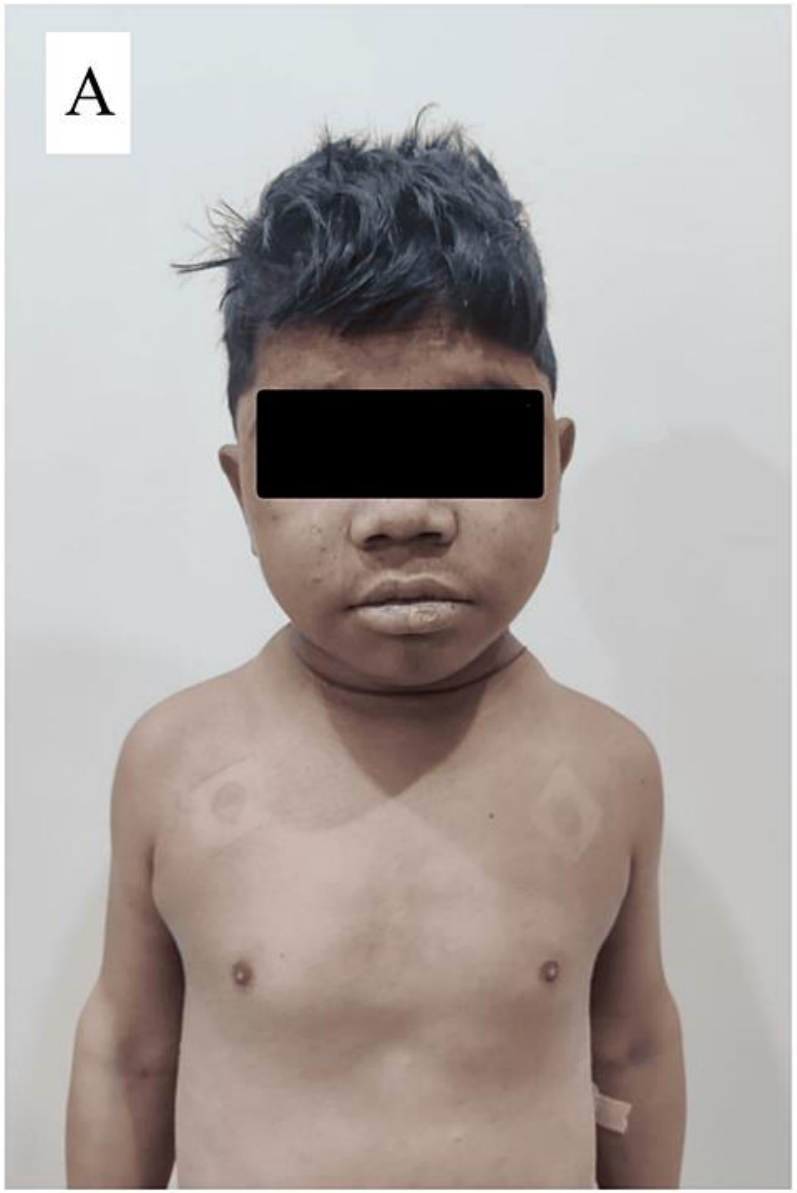


Immune-susceptible genes

J Clin Res Pediatr Endocrinol 2013;5(Suppl 1):45-49A

Clinical features that suggest the possibility of AH

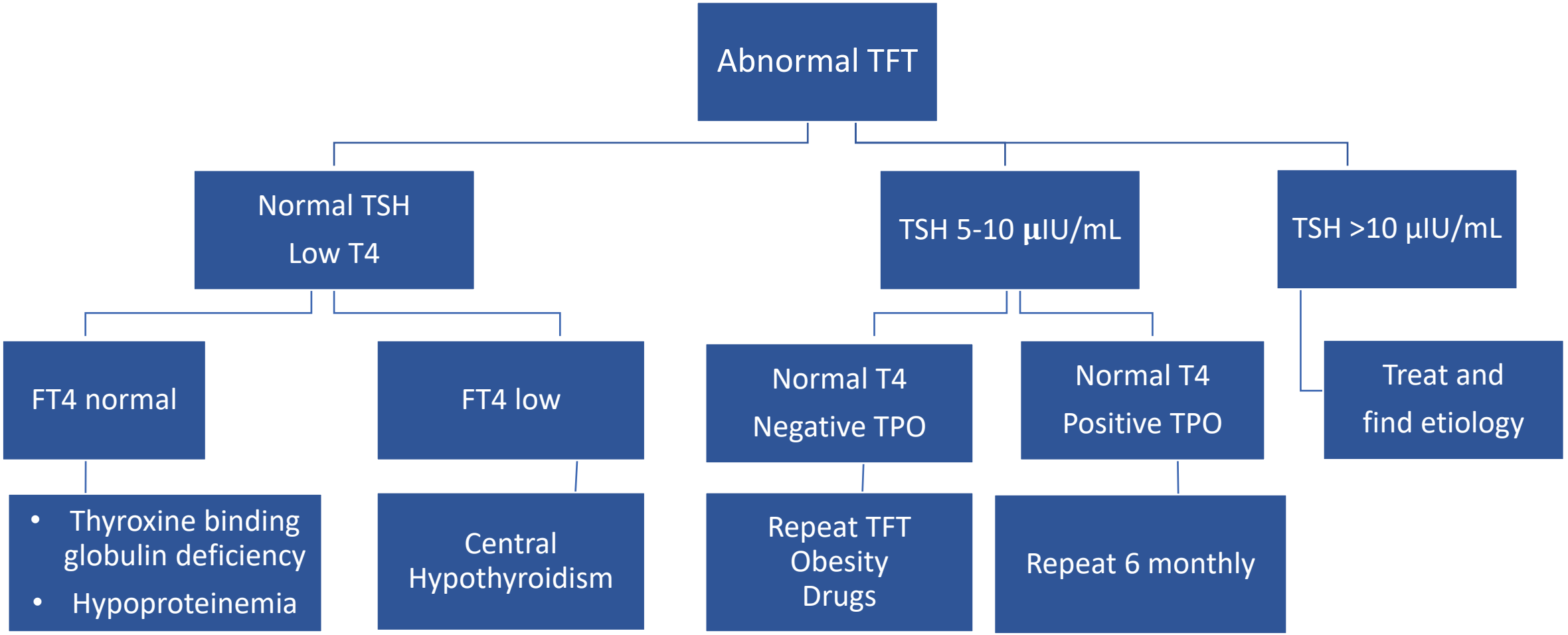
- Sluggishness
- Constipation
- Hoarseness of voice
- Dry rough skin
- Cold intolerance
- Hypothyroid facies
- Weight gain / obesity
- Short stature
- Delayed DTR
- Cardiomyopathy / Effusion
- Calf muscle hypertrophy
- Pubertal disorders: puberty delay or precocious puberty / irregular menses



Clinical picture
Myxoedematous facies.

- **With enlarged testicular volume**
- **Absence of pubic hair.**

Approach to AH



*T3 remains normal in initial stages, as levels do not decline until T4 is very low; Anti-TPO titers= <9.0 IU/ml

Van Wyk Grumbach Syndrome

- **Long-standing untreated or poorly controlled hypothyroidism – congenital or acquired**
- **High levels of TSH**
- **Isosexual precocity**
- **Lack of pubic and axillary hair growth**
- **Delayed bone age / Short stature despite precocity**
- **Improves rapidly with thyroxine replacement – only treatment required**

<u>Boys</u>: Macro-orchidism (Sertoli cell hyperplasia)
<u>Girls</u>: Thelarche (Occasional galactorrhea), vaginal bleeding, ovarian hyperstimulation with large follicles on USG.
May present as a surgical abdomen due to twisted ovarian cyst

Ref: Boddu S. et al. Van Wyk Grumbach Syndrome and Ovarian Hyperstimulation in Juvenile Primary Hypothyroidism: Lessons From a 30-Case Cohort. J Endocr Soc. 2023 May 15;7(6):bvad042. doi: 10.1210/jendso/bvad042. PMID: 37197410; PMCID: PMC10184442.

Other investigations

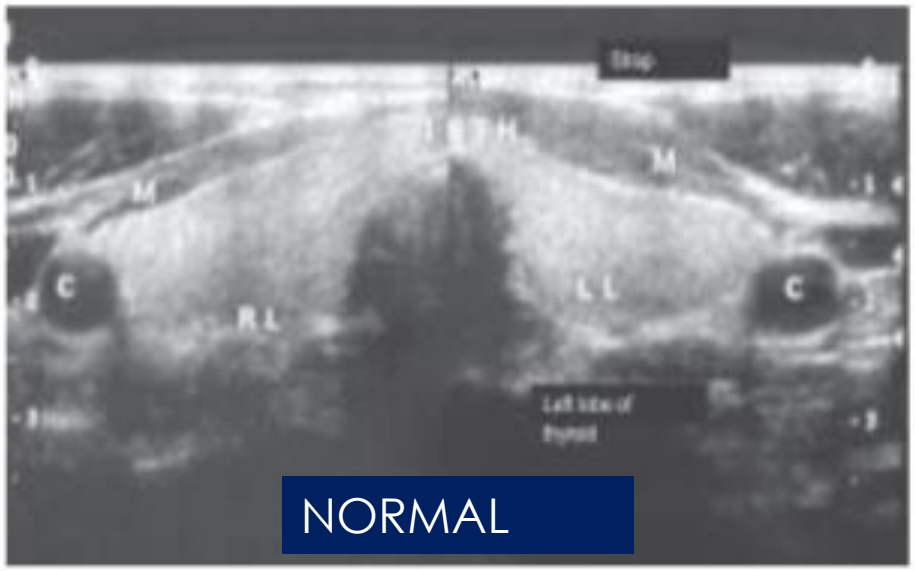
- **X-ray for bone age:**
  - **Delayed skeletal maturation in severe/untreated cases**
  - **Stippling of epiphysis may be seen**

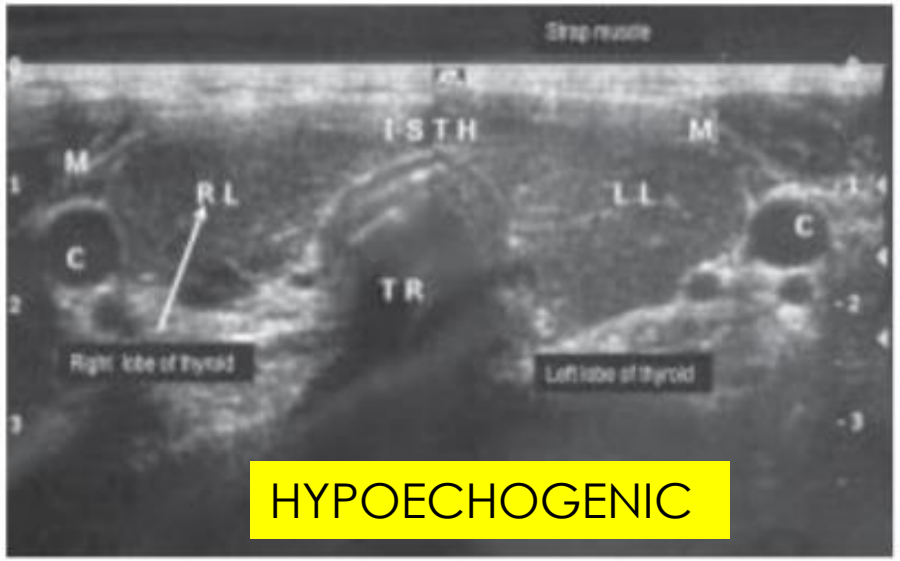
- **Thyroid imaging:**
  - **Ultrasonography: Thyroid morphology**
  - **Scintigraphy: Dyshormonogenesis**

- **Screening for associated autoimmune disorders like celiac disease, autoimmune hepatitis, adrenal insufficiency, type 1 diabetes and pernicious anemia**

Role of thyroid ultrasound

Evaluation of the Role of Ultrasonography in Diagnosis of Autoimmune Thyroiditis in Goitrous Children
RK Marwaha, N Tandon, M Ashraf Gani, et al. Indian Pediatr 2008;45; 279





At the same time
Do ultrasound thyroid gland, and if need be FNAC if one suspects a nodule

Thyroid USG has a useful, though limited, role in excluding thyroid disease in children.
The sensitivity of echogenicity for the diagnosis of autoimmune thyroiditis in children is less than that reported in adults.

Treatment of AH

- **Oral Levothyroxine therapy started based on weight or body surface area**
- **Early morning, empty stomach, almost the same time every day**

100 µg/m²/day: as a single dose

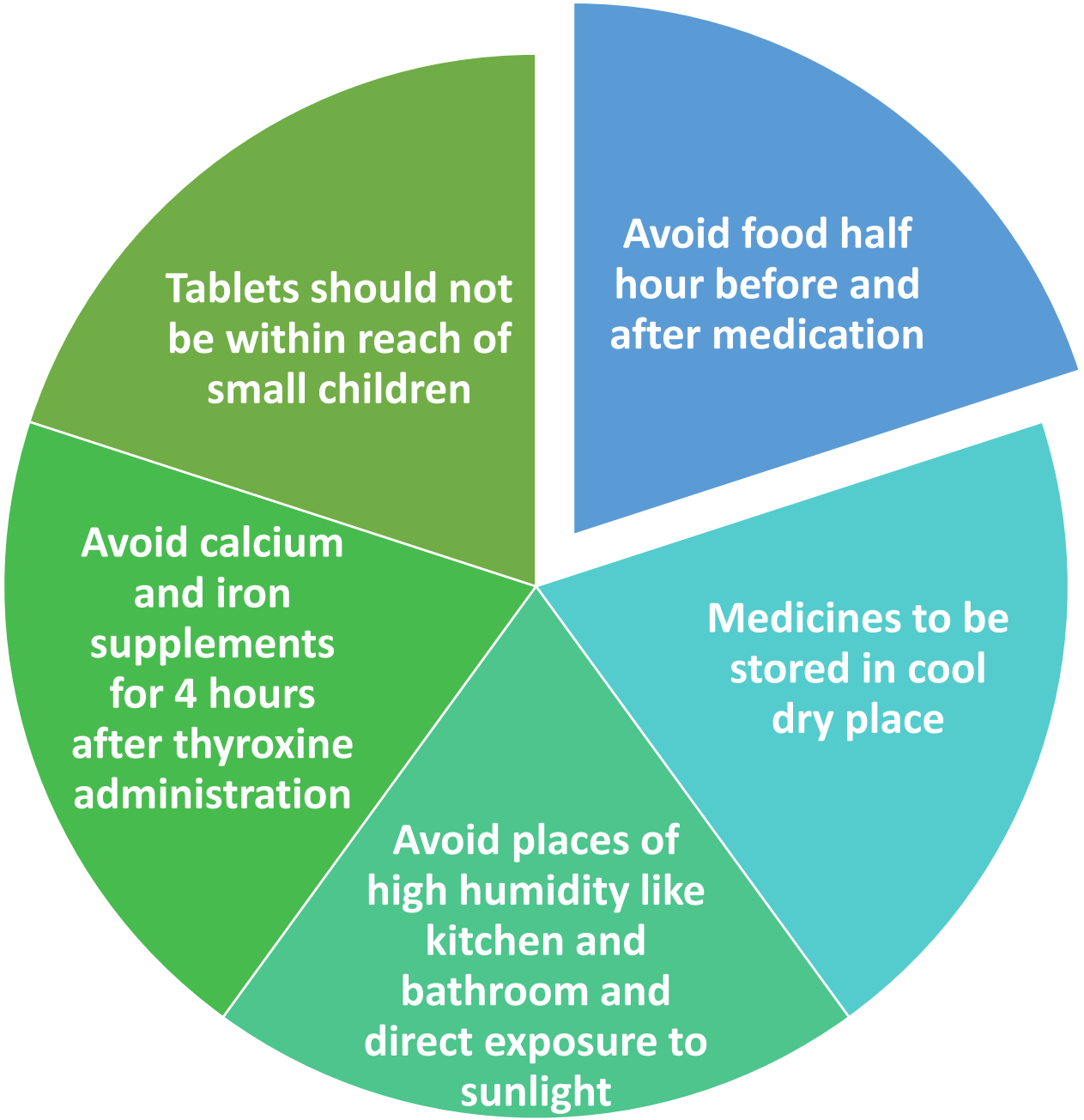
OR

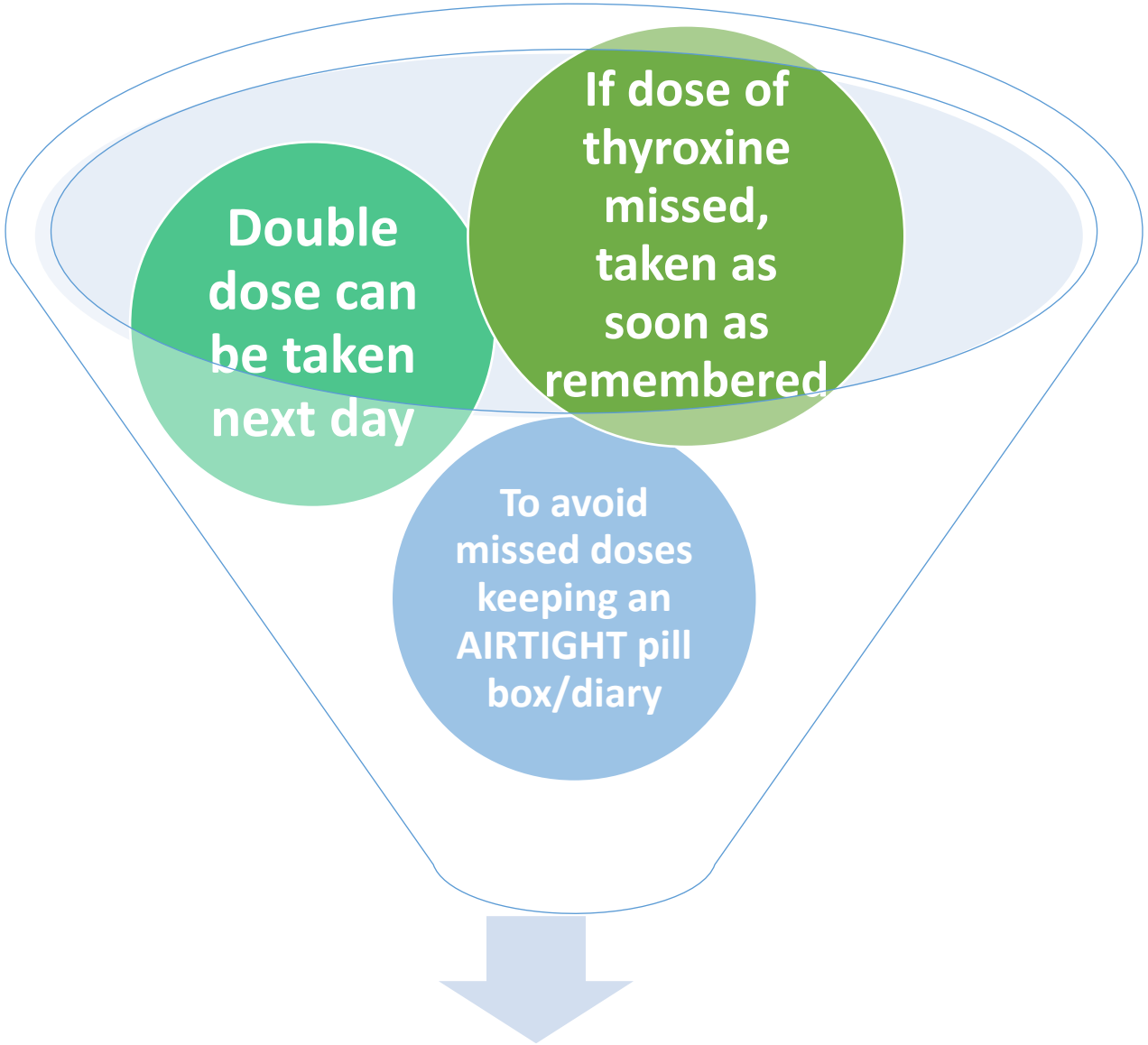
Age-dependent dosing

- ✓**1-3 years: 4-6 µg/kg**
- ✓**3-10 years: 3-5 µg/kg**
- ✓**10-16 years: 2-4 µg/kg**

Goal of treatment:
Euthyroidism
+
Normal growth, development and puberty

- **Further dose adjustments with age to maintain TSH and T4/FT4 in range**
- **For long-standing untreated hypothyroidism, thyroxine should be started at lower dose and gradually stepped up over several weeks to reach full dosing**
- **Children with central hypothyroidism require lower doses as compared to those with primary hypothyroidism**


Avoid food half hour before and after medication
Medicines to be stored in cool dry place
Avoid places of high humidity like kitchen and bathroom and direct exposure to sunlight
Avoid calcium and iron supplements for 4 hours after thyroxine administration
Tablets should not be within reach of small children



DOSE NOT TO BE MISSED, EVEN ON SICK DAYS

Blood sampling for monitoring

- **Blood sample for thyroid function (TSH, Total T4, FT4) should be taken before the morning dose**
- **TSH result is not impacted by the morning thyroxine dose**

Follow-up

- **Clinical monitoring: height, weight, BMI, SMR**
- **Laboratory monitoring:**

FT4 (in upper range of normal), TSH (0.1-5 µIU/mL)

  - **6 weeks after initiation of thyroxine**
  - **6 weeks after dose adjustment**
  - **Thereafter every 4 monthly**

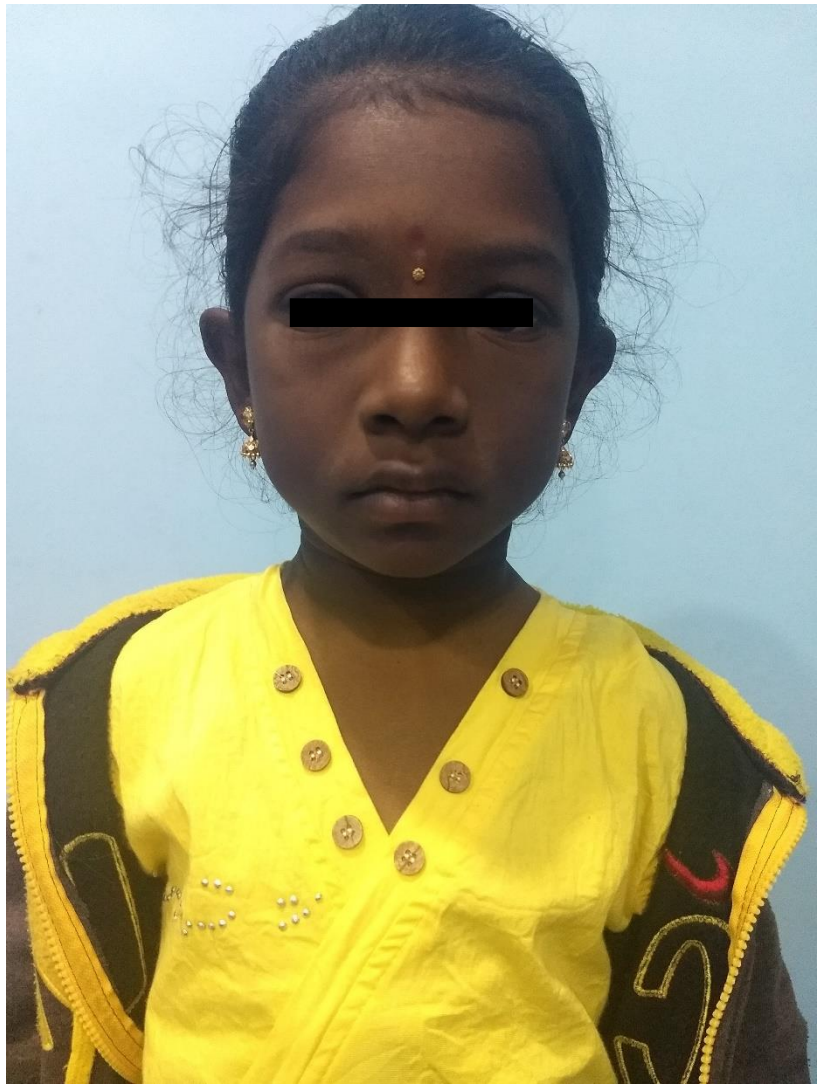
A. 9y 6m child

TFT -

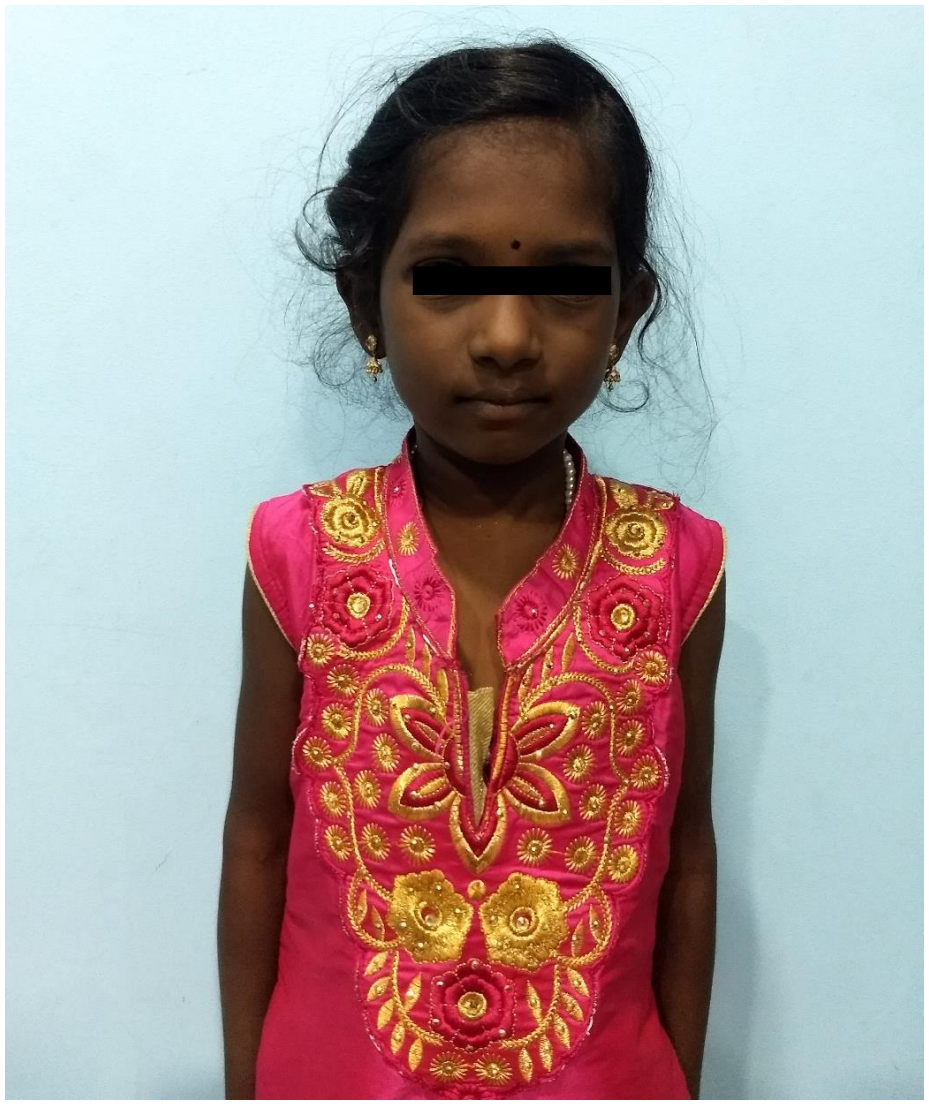
S. Total thyroxine (TT4)	**0.68 µg/dL**
S. Free thyroxine (FT4)	**0.23 ng/mL**
S. Total T3	**0.27 ng/mL**
S. TSH	**> 100 µIU/mL**

Repeat TSH with double dilution technique - 498.55 µIU/mL

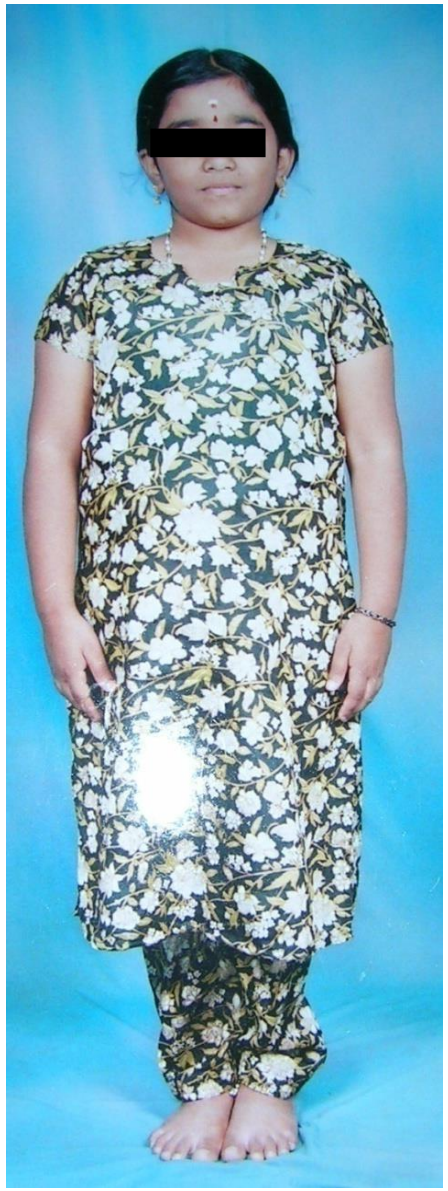
S. Anti-TPO antibody	**512 IU/mL**
S. Anti-TG antibody	**115 IU/mL**

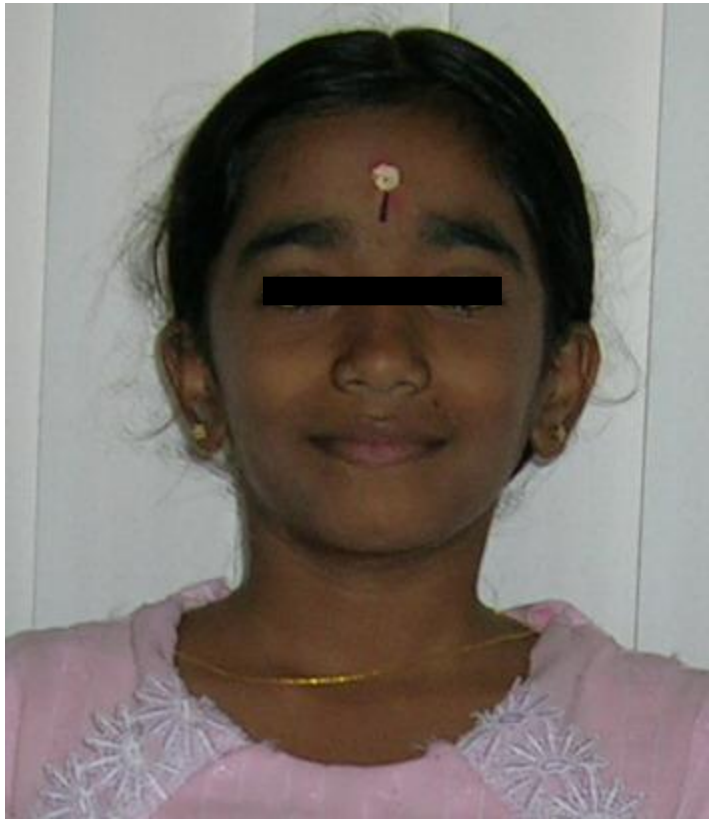


Pre-treatment



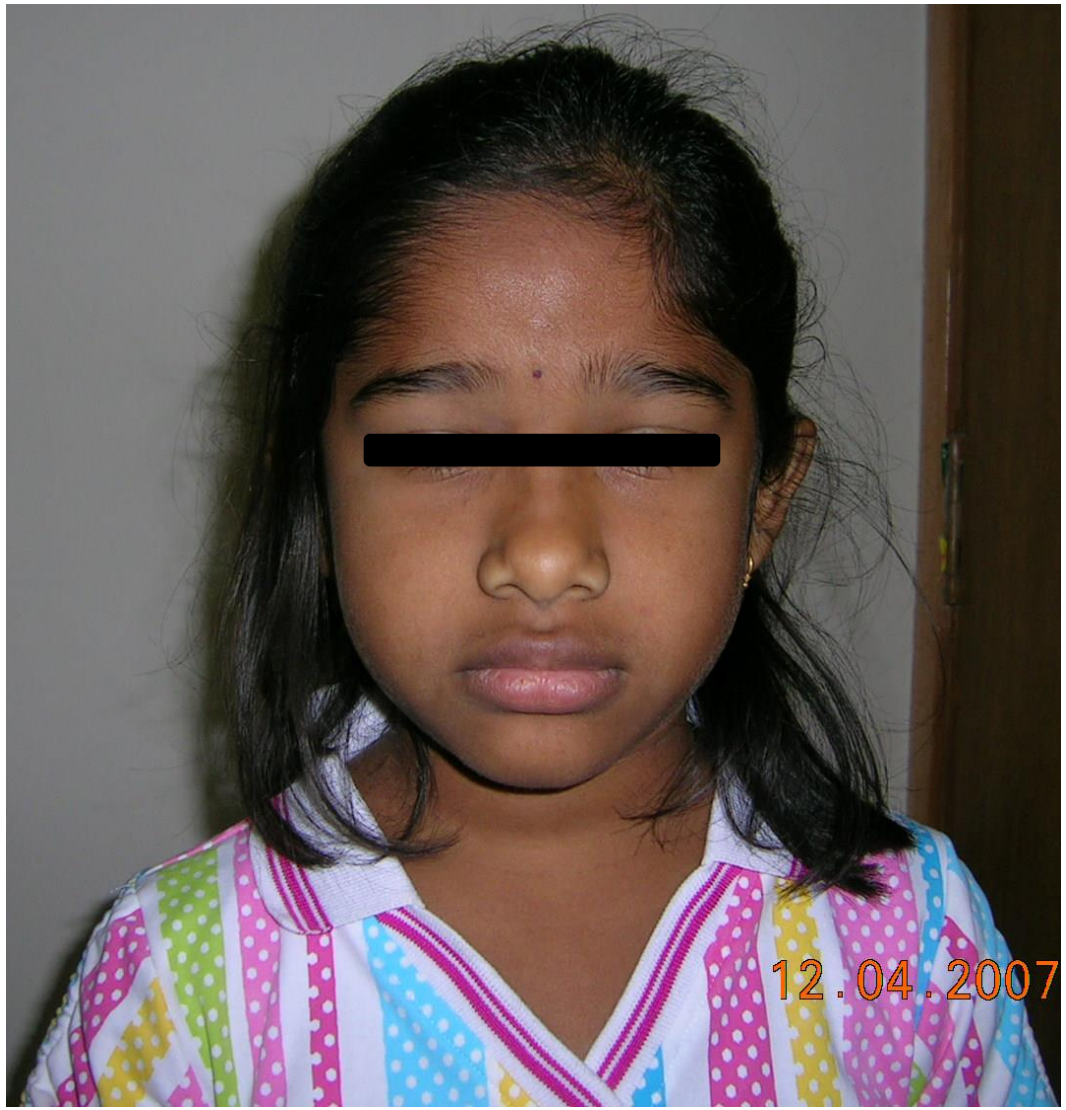
Post Treatment



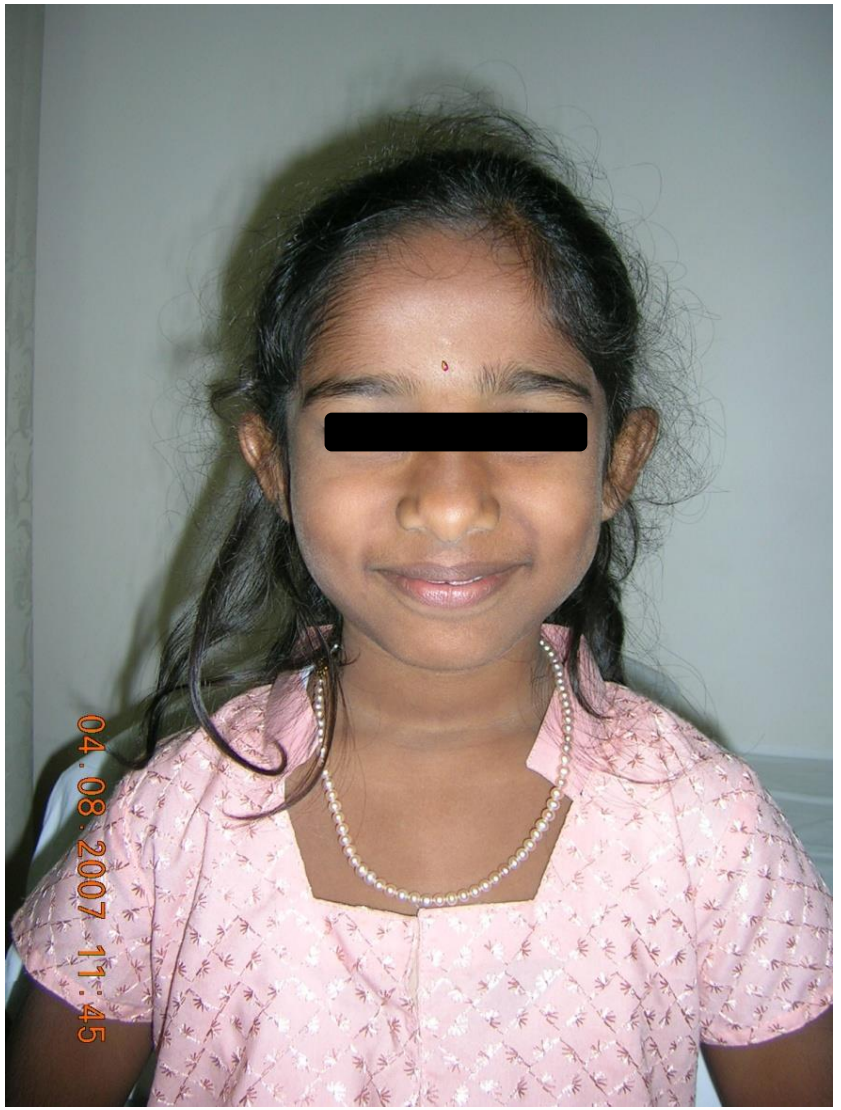


Pre-treatment

Post Treatment

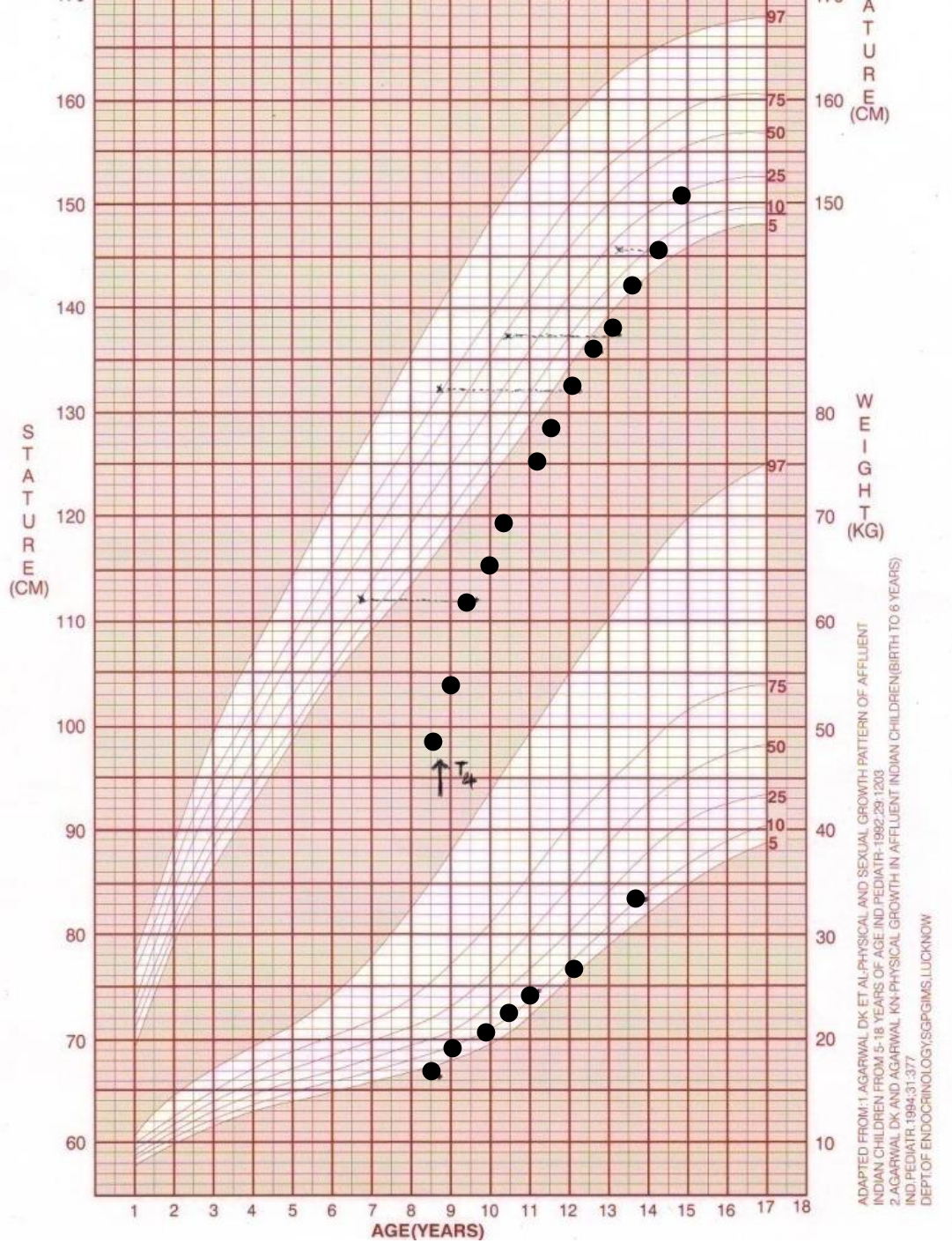


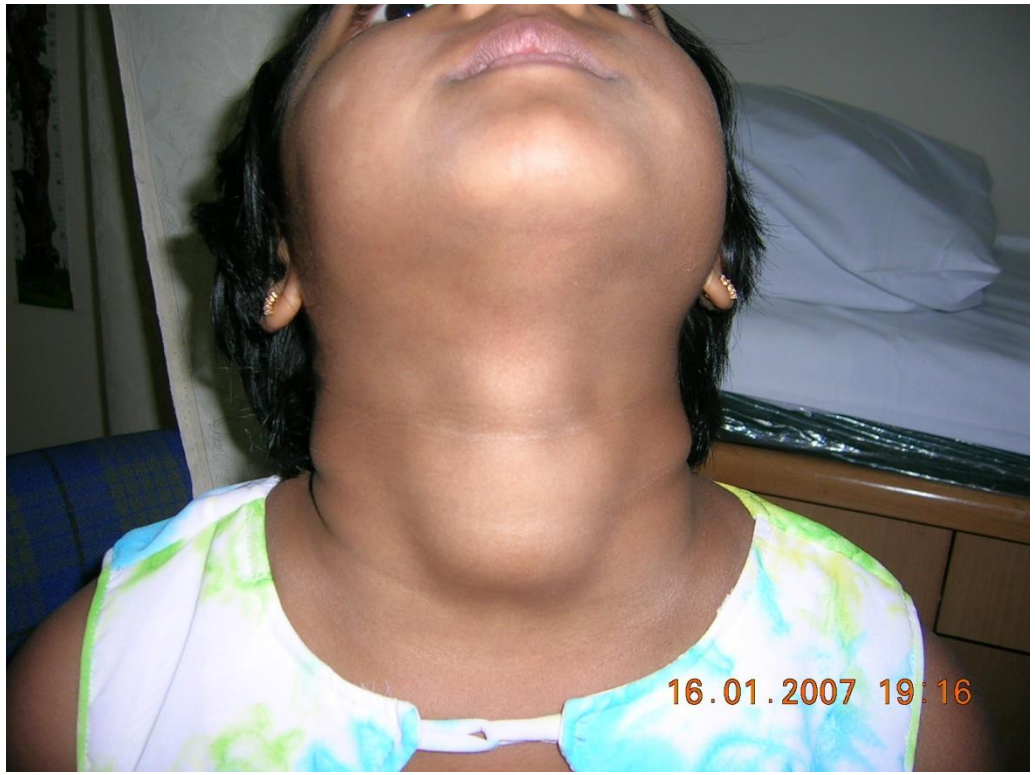
Pre-treatment



Post Treatment

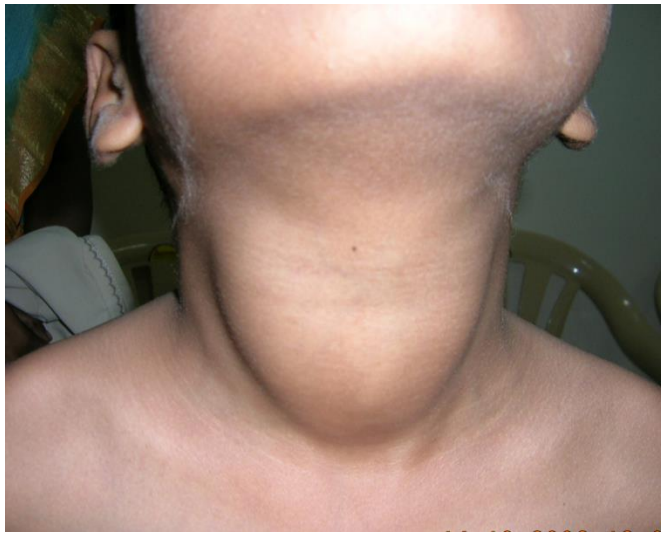
Growth after initiation of thyroxine therapy (Catch-up growth)

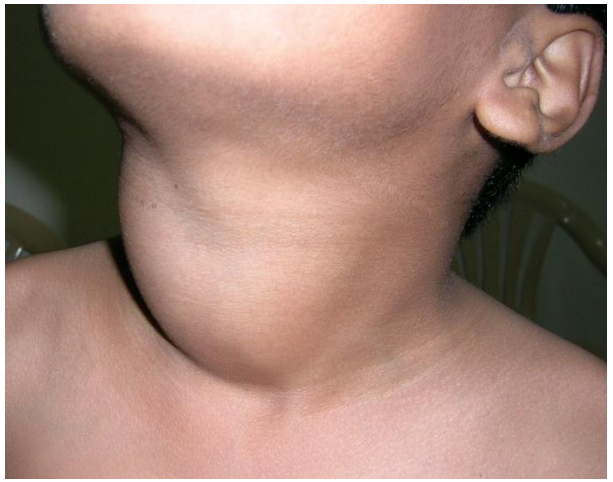




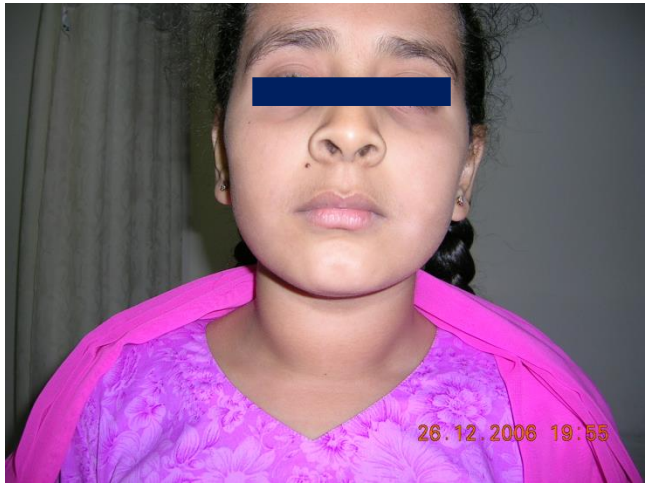
Goitre

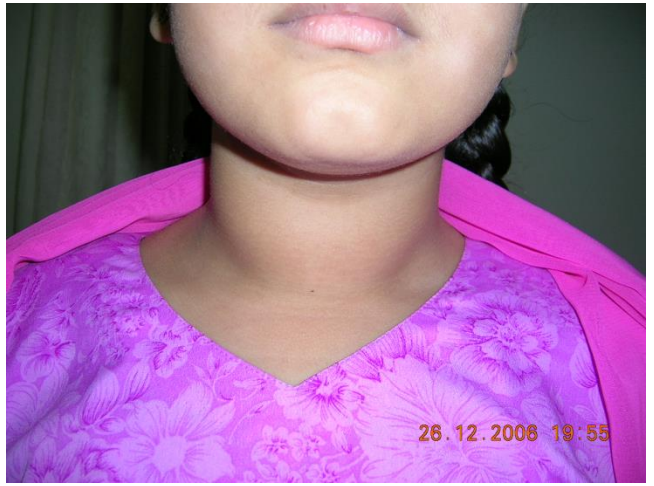
1. Goitre: Acquired Hypothyroidism





2. Goitre: Autoimmune Thyroiditis





Take-Home Messages

- Presenting features - Not a goitre always
- Easy and inexpensive treatment
- Precaution: Thyroxine to be taken on an empty stomach
- Gradual increasing of doses – In long-standing hypothyroidism
- Monitor growth and scholastic performance and pubertal status in adolescents at every visit
- Follow up every 3 monthly to catch early growth faltering
- Screen for other autoimmune diseases, if symptomatic

Thank you