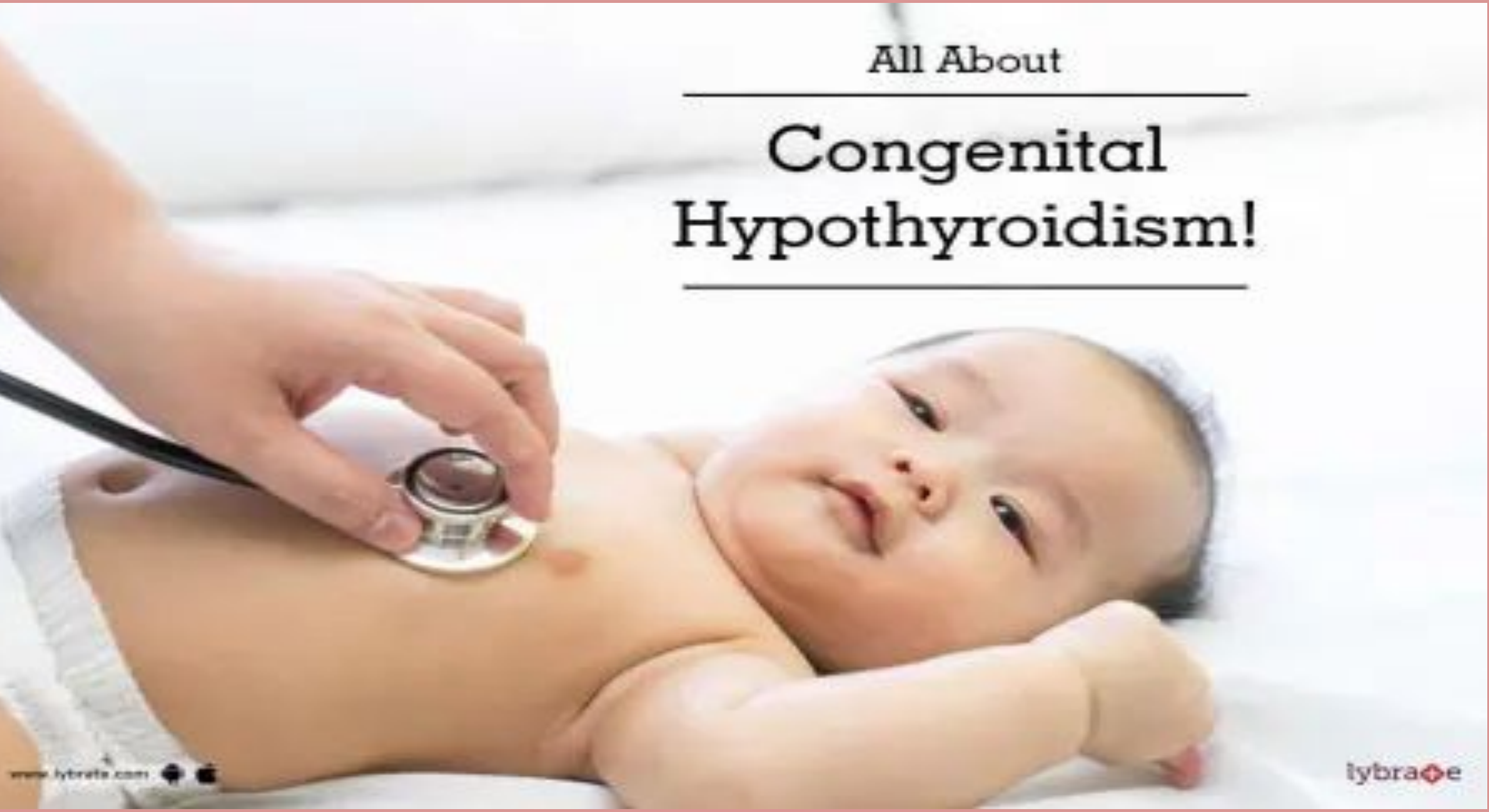
All About
Congenital Hypothyroidism!
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CONGENITAL HYPOTHYROIDISM

GOOD MORNING

CONGENITAL HYPOTHYROIDISM

It is a common & serious disease, its prevalence is about 1/2000

Causes

- Primary (most common) due to defects in the thyroid gland or thyroid hormone

- Thyroid Dysgenesis; Female>Male . It is the most common cause of cong hypothyroidism (80-85%), it include: aplasia, hypoplasia, or ectopic

- • **Defective Thyroxine synthesis (Dyshormonogenesis**

- It is AR with Goiter is always present. When the defect is incomplete

- **Defect of Iodide Transport;**
- Rare, due to mutations in the sodiumiodide symporter & involve both thyroid and salivary glands. Dx by ↓ uptake of radioiodine, but can be treated by large doses of potassium iodide or better by thyroxine. Pendred syndrome is an AR synd which is caused by a mutation in the
- chloride–iodide transport protein pendrin that is expressed in both
- thyroid gland and cochlea, thus patient has goiter and sensorineural deafness.

- • **Defect of Iodide Organification**;
- It is the most common of thyroid hormone synthetic defects; it is due to defects in its organification and coupling with iodine. Dx by marked decrease in thyroid radioactivity when perchlorate is taken 2 hr after administration of test dose of radioiodine, perchlorate discharges 40–90% of radioiodine compared with < 10% in normal.
- • Defects of Thyroglobulin Synthesis;
- It causes absent or low levels of thyroglobulin (TG) → ↓ T4, ↑ TSH

- • **Defects in Deiodination**;
- It is due to deiodinase deficiency → severe iodine loss due to constant urinary excretion of non-deiodinated tyrosines → hormone deficiency and goiter.

- • **Defects in Thyroid Hormone Transport into cells;**
- It is due to mutation in transporter gene → hypothyroidism with severe neurologic manifestations.

- • **Maternal TRBAb**; It is due to transplacental passage of maternal thyrotropin receptor–blocking antibody (TRBAb) which inhibits binding of TSH to its receptor in the neonatal thyroid. It an unusual cause of transitory cong hypothyroidism, but should be suspected whenever there is hx of maternal autoimmune thyroid disease or recurrent cong hypothyroidism of transient nature in subsequent siblings. Dx by measuring TRBAb level in the mother & infant. Thyroid scans may fail to detect thyroid tissue (mimicking Agenesis). Remission of hypothyroidism occurs 3-6 mo once the TRBAb are cleared from the infant circulation during which Rx with thyroxine is required.

- • Maternal administration of Radioiodine or Antithyroid drug
- propylthiouracil, methimazole, or amiodarone (antiarrhythmic) → cong hypothyroidism & goiter.

- • Iodine Exposure; Perinatal exposure, especially premature or LBW to iodine antiseptic. Iodine is also present in some asthma preparations & amiodarone. Iodine-induced hypothyroidism is transient once the exposure is discontinued.

- Iodine-Deficiency (Endemic Goiter);
- It is due to insufficient intake of iodine by the pregnant woman. It is the most common cause of cong hypothyroidism worldwide, especially in preterm infants.

- • **Thyrotropin (TSH) Deficiency**
- It is due to defects of pituitary or hypothalamus; many have other pituitary hormones deficiencies. It should be suspected in any newborn with midline facial anomalies.

Thyroid Function in Preterm Infants

- It is qualitatively similar but quantitatively reduced compared with that of term infants due to immaturity of the hypothalamic-pituitary-thyroid axis with loss of maternal contribution of thyroid hormone. TSH & T4 surge is reduced (although serum free T4 is normal) which may remain ↓ when there is neonatal Cxs e.g. RDS.

clinical picture

- Most infants with congenital hypothyroidism are asymptomatic at birth (may be due to transplacental passage of maternal T4), thus

Hx + Ex

- Hx. Lethargy, sleepy, poor hoarse cry, poor appetite & feeding, apnea, noisy respiration, constipation, &

- Other features include: birth weight & length are normal, head size is normal or slightly increased, hypothermia (temp < 35°C), bradycardia +/_ heart murmurs, abdominal distention, umbilical hernia, cold mottled skin which is yellow in color (due to carotenemia in addition to jaundice), myxedema, & later on, delayed dentition. The muscles are usually hypotonic, but in rare instances generalized muscular pseudohypertrophy occurs. Cong hypothyroidism may be associated with

Complication

- f untreated [illegible] i/ mo of life, it will severely affect physical and mental developm ent → delayed milestone

Investigation

- • Neonatal Screening is mandatory. It depend on measuring serum T4

- (N.R. 6-22 μg/dl), if low, measure

- Note: Be careful during screening of identical twins who share 1 placenta because T4 may transfer from the euthyroid

- • X-ray of knees show absent of distal femoral epiphysis in ≈ 60% of cases, which normally should be present at birth.

- • Skull X-ray show large fontanels, wide sutures, wormian skull, and enlarged sella turcica.

- • CXR may show cardiomegaly +/_ pericardial effusion.

- Thyroid scan with radioiodine will reveal its uptake if there is any normal thyroid tissue, whereas failure of radioiodine uptake suggest either thyroid aplasia, iodide-trapping defect, or neonates with TRBAb.

- • Thyroglobulin level; it ↓ in thyroid aplasia or defects in its synthesis, but ↑ in ectopic glands and goiter.

- • Genetic study is available for most

Treatment

- Levo-thyroxine (T4) is given orally; initial dose 10–15 µg/kg/day for neonates & infants. Oral thyroxine should not be mixed

- The goal of replacement Rx is to bring levels of T4 & TSH to normal range which require frequent monitoring at

prognosis

- Thyroid hormones are very essential for brain development in the early postnatal months, thus early Dx & Rx is critical to prevent progressive neuropsychological sequelae.
- If the onset of hypothyroidism occur after 2 yr of life, there may be normal neurological development

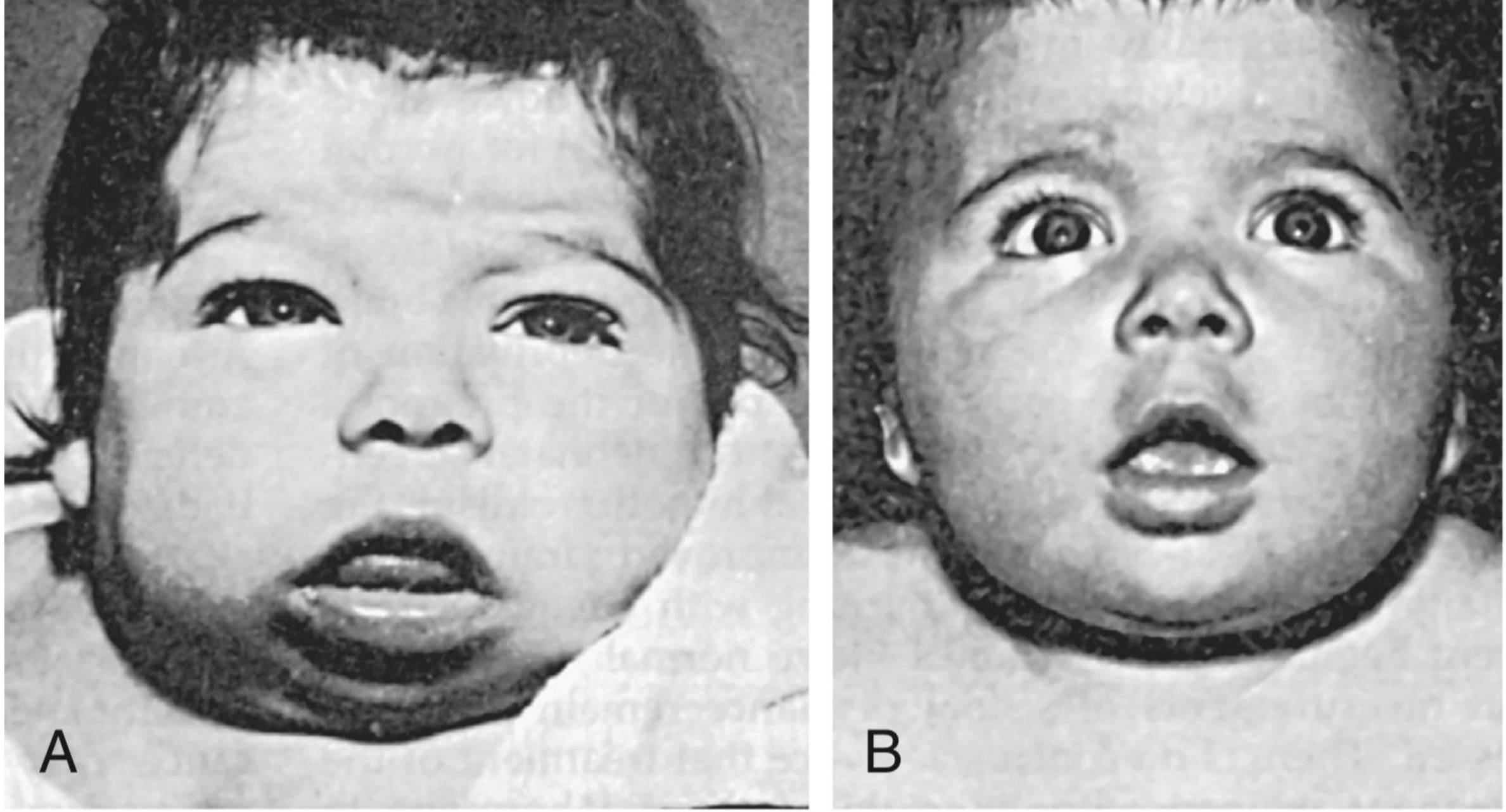


Fig. 581.1 Congenital hypothyroidism in an infant 6 mo of age. The

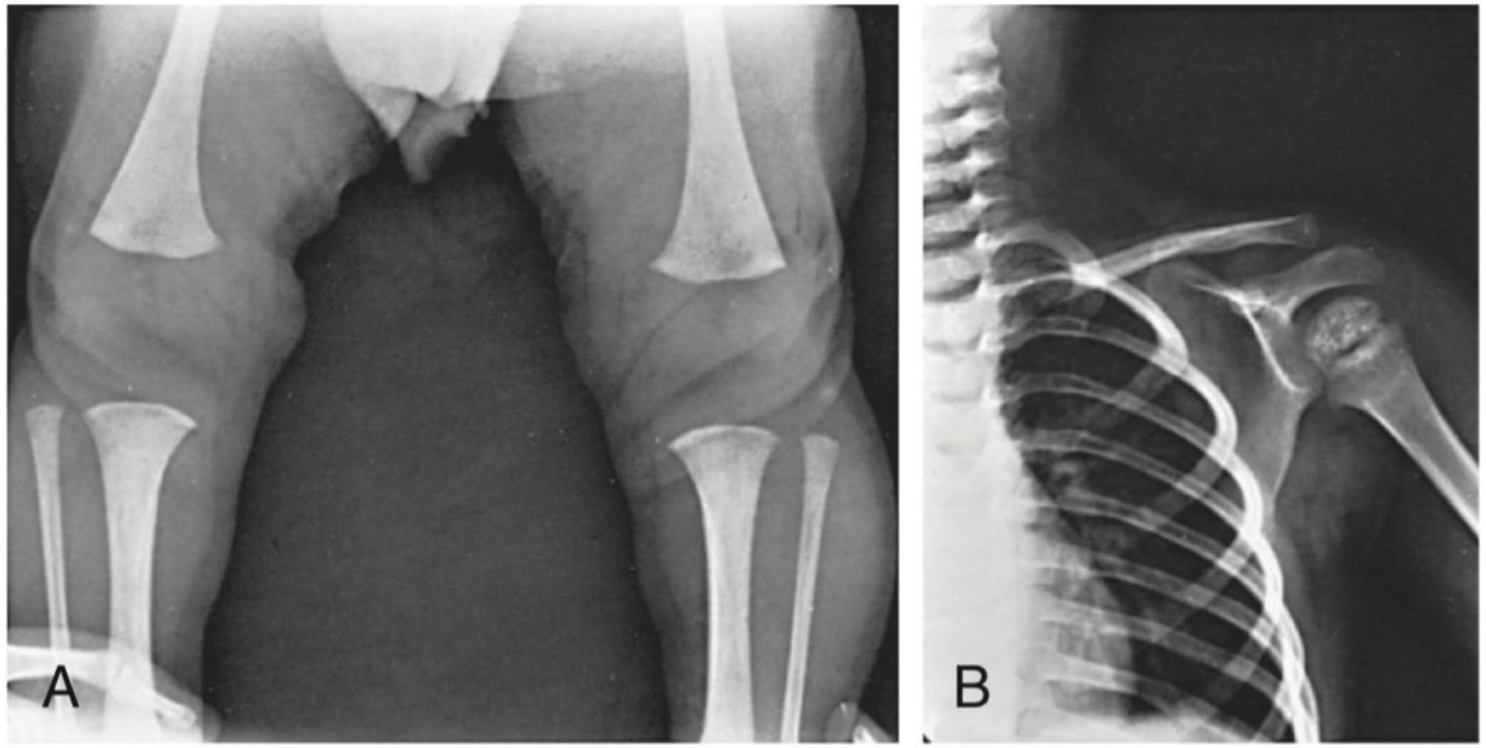


Fig. 581.2 Congenital hypothyroidism. **(A)** Absence of distal femoral epiphyses in a 3 mo old infant who was born at term. This is evidence for onset of the hypothyroid state during fetal life. **(B)** Epiphyseal dysgenesis in the head of the humerus in a 9 yr old girl who had been inadequately treated with thyroid hormone.

Table 581.3 Thyroid Function Tests

AGE	U.S. REFERENCE VALUE	CONVERSION FACTOR	SI REFERENCE VALUE
THYROID THYROGLOBULIN, SERUM			
Cord blood	14.7-101.1 ng/mL	×1	14.7-101.1 µg/L
Birth to 35 mo	10.6-92.0 ng/mL	×1	10.6-92.0 µg/L
3-11 yr	5.6-41.9 ng/mL	×1	5.6-41.9 µg/L
12-17 yr	2.7-21.9 ng/mL	×1	2.7-21.9 µg/L
THYROID-STIMULATING HORMONE, SERUM			
Premature Infants (28-36 wk)			
1st wk of life	0.7-27.0 mIU/L	×1	0.7-27.0 mIU/L
Term Infants			
Birth to 4 days	1.0-17.6 mIU/L	×1	1.0-17.6 mIU/L
2-20 wk	0.6-5.6 mIU/L	×1	0.6-5.6 mIU/L
5 mo-20 yr	0.5-5.5 mIU/L	×1	0.5-5.5 mIU/L
THYROXINE-BINDING GLOBULIN, SERUM			
Cord blood	1.4-9.4 mg/dL	×10	14-94 mg/L
1-4 wk	1.0-9.0 mg/dL	×10	10-90 mg/L
1-12 mo	2.0-7.6 mg/dL	×10	20-76 mg/L
1-5 yr	2.9-5.4 mg/dL	×10	29-54 mg/L
5-10 yr	2.5-5.0 mg/dL	×10	25-50 mg/L
10-15 yr	2.1-4.6 mg/dL	×10	21-46 mg/L
Adult	1.5-3.4 mg/dL	×10	15-34 mg/L
THYROXINE, TOTAL, SERUM			
Full-Term Infants			
1-3 days	8.2-19.9 µg/dL	×12.9	106-256 nmol/L
1 wk	6.0-15.9 µg/dL	×12.9	77-205 nmol/L
1-12 mo	6.1-14.9 µg/dL	×12.9	79-192 nmol/L
Prepubertal Children			
1-3 yr	6.8-13.5 µg/dL	×12.9	88-174 nmol/L
3-10 yr	5.5-12.8 µg/dL	×12.9	71-165 nmol/L
Pubertal Children and Adults			
>10 yr	4.2-13.0 µg/dL	×12.9	54-167 nmol/L
THYROXINE, FREE, SERUM			
Full term (3 days)	2.0-4.9 ng/dL	×12.9	26-63.1 pmol/L
Infants	0.9-2.6 ng/dL	×12.9	12-33 pmol/L
Prepubertal children	0.8-2.2 ng/dL	×12.9	10-28 pmol/L
Pubertal children and adults	0.8-2.3 ng/dL	×12.9	10-30 pmol/L
THYROXINE, TOTAL, WHOLE BLOOD			
Newborn screen (filter paper)	6.2-22 µg/dL	×12.9	80-283 nmol/L
TRIIODOTHYRONINE, FREE, SERUM			
Cord blood	20-240 pg/dL	×0.01536	0.3-0.7 pmol/L
1-3 days	180-760 pg/dL	×0.01536	2.8-11.7 pmol/L
1-5 yr	185-770 pg/dL	×0.01536	2.8-11.8 pmol/L
5-10 yr	215-700 pg/dL	×0.01536	3.3-10.7 pmol/L
10-15 yr	230-650 pg/dL	×0.01536	3.5-10.0 pmol/L
>15 yr	210-440 pg/dL	×0.01536	3.2-6.8 pmol/L
TRIIODOTHYRONINE RESIN UPTAKE TEST (RT_3U), SERUM			
Newborn	26–36%	×0.01	0.26-0.36 fractional uptake
Thereafter	26–35%	×0.01	0.26-0.35 fractional uptake
TRIIODOTHYRONINE, TOTAL, SERUM			
Cord blood	30-70 ng/dL	×0.0154	0.46-1.08 nmol/L
1-3 days	75-260 ng/dL	×0.0154	1.16-4.00 nmol/L
1-5 yr	100-260 ng/dL	×0.0154	1.54-4.00 nmol/L
5-10 yr	90-240 ng/dL	×0.0154	1.39-3.70 nmol/L
10-15 yr	80-210 ng/dL	×0.0154	1.23-3.23 nmol/L
>15 yr	115-190 ng/dL	×0.0154	1.77-2.93 nmol/L

Adapted from Nicholson JF, Pesce MA: Reference ranges for laboratory tests and procedures. In Behrman RE, Kliegman RM, Jenson HB, editors: *Nelson textbook of pediatrics*, ed 17, Philadelphia, 2004, WB Saunders, pp 2412–2413; TSH from Lem AJ, de Rijke YB, van toor H, 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* 97:3170–3178, 2012; free T_3 from Elmlinger MW, Kuhnel W, Lambrecht H-G, et al: Reference intervals from birth to adulthood for serum thyroxine (T_4), triiodothyronine (T_3), free T_3, free T_4, thyroxine binding globulin (TBG), and thyrotropin (TSH), *Clin Chem Lab Med* 39:973–979, 2001.

Table 581.1	Etiologic Classification of Congenital Hypothyroidism

PRIMARY HYPOTHYROIDISM

Defect of thyroid development (dysgenesis)
- Agenesis
- Hypoplasia
- Ectopia

Defects in Thyrotropin (TSH) responsiveness
- TSH receptor-blocking antibodies
- Mutation in TSH receptor (TSHR)
- Defects in Gsα (GNAS)—pseudohypoparathyroidism

Defect in thyroid hormone synthesis (dyshormonogenesis)
- Defective iodide uptake into follicular cell: sodium–iodide symporter (NIS)
- Defective iodide transport from follicular cell into colloid: Pendred syndrome (SLC26A4)
- Iodide organification defects: thyroperoxidase (TPO), dual oxidase 2 (DUOX2), dual oxidase maturation factor 2 (DUOXA2)
- Thyroglobulin synthesis defect: thyroglobulin (TG)
- Deiodination defect: iodotyrosine deiodinase (IYD)
- Thyroid hormone transport defect: monocarboxylate transporter 8 (SLC16A2)—X-linked

Iodine deficiency (endemic goiter)

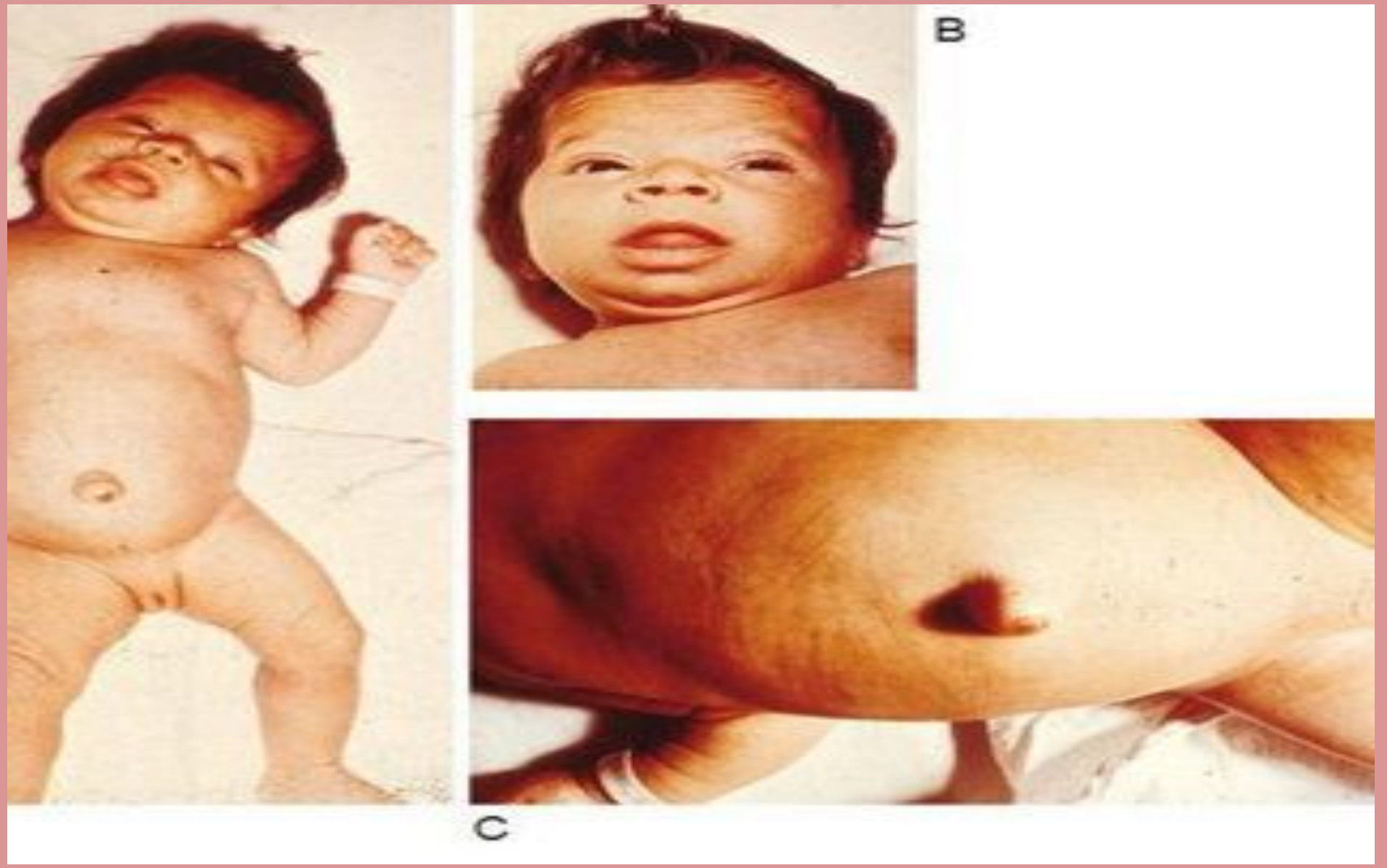
Iodine excess

Maternal medications
- Iodides, amiodarone
- Methimazole, propylthiouracil
- Radioactive iodine (131I)

CENTRAL (SECONDARY) HYPOTHYROIDISM

Isolated TSH deficiency
- Mutation in TSH β-subunit (TSHβ)—depending on mutation measured TSH level may be low, normal, or elevated
- Mutation in TRH receptor (TRHR)
- Mutation in IGFS1—X-linked central hypothyroidism and macroorchidism (prolactin deficiency and variable GH deficiency)

Multiple pituitary hormone deficiencies
- Mutation in POU1F1—deficiency of TSH, GH, and prolactin
- Mutation in PROP1—deficiency of TSH, GH, LH, FSH, prolactin, and variably ACTH
- Mutation in HESX1—variable deficiencies of TSH, GH, LH, FSH, prolactin, and ACTH
- Mutations in other genes: OTX2, LHX3, LHX4, SOX3, FGF8, FGFR1, GLI2, LEPR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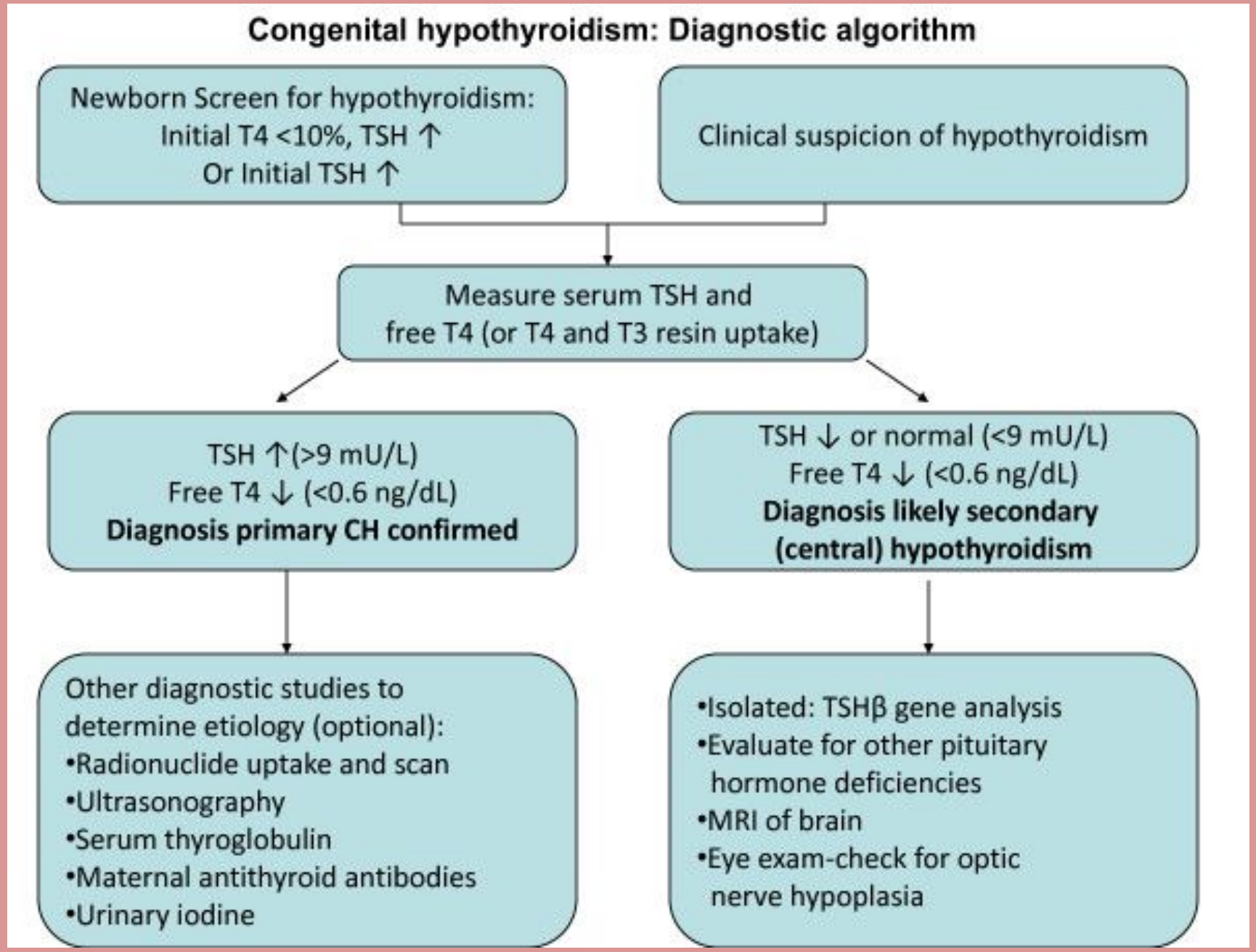
Congenital hypothyroidism: Diagnostic algorithm
Newborn Screen for hypothyroidism:
Initial T4 <10%, TSH ↑
Or Initial TSH ↑
Clinical suspicion of hypothyroidism
Measure serum TSH and
free T4 (or T4 and T3 resin uptake)
TSH ↑(>9 mU/L)
Free T4 ↓ (<0.6 ng/dL)
Diagnosis primary CH confirmed
TSH ↓ or normal (<9 mU/L)
Free T4 ↓ (<0.6 ng/dL)
Diagnosis likely secondary
(central) hypothyroidism
Other diagnostic studies to
determine etiology (optional):
•Radionuclide uptake and scan
•Ultrasonography
•Serum thyroglobulin
•Maternal antithyroid antibodies
•Urinary iodine
•Isolated: TSHβ gene analysis
•Evaluate for other pituitary
hormone deficiencies
•MRI of brain
•Eye exam-check for optic
nerve hypoplasia


THANK
YOU