Managing Thyroid Disorders in Children

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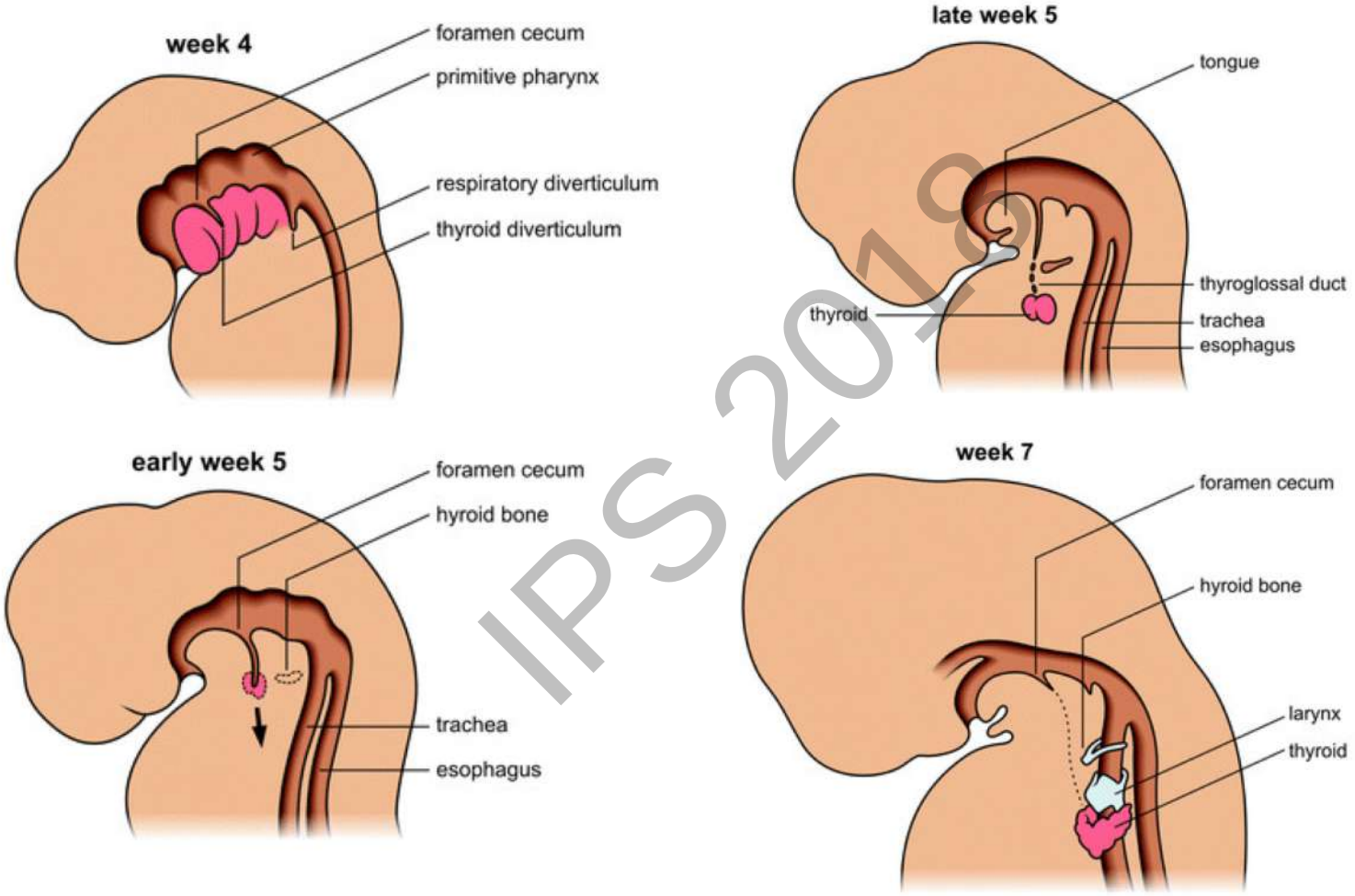
Content

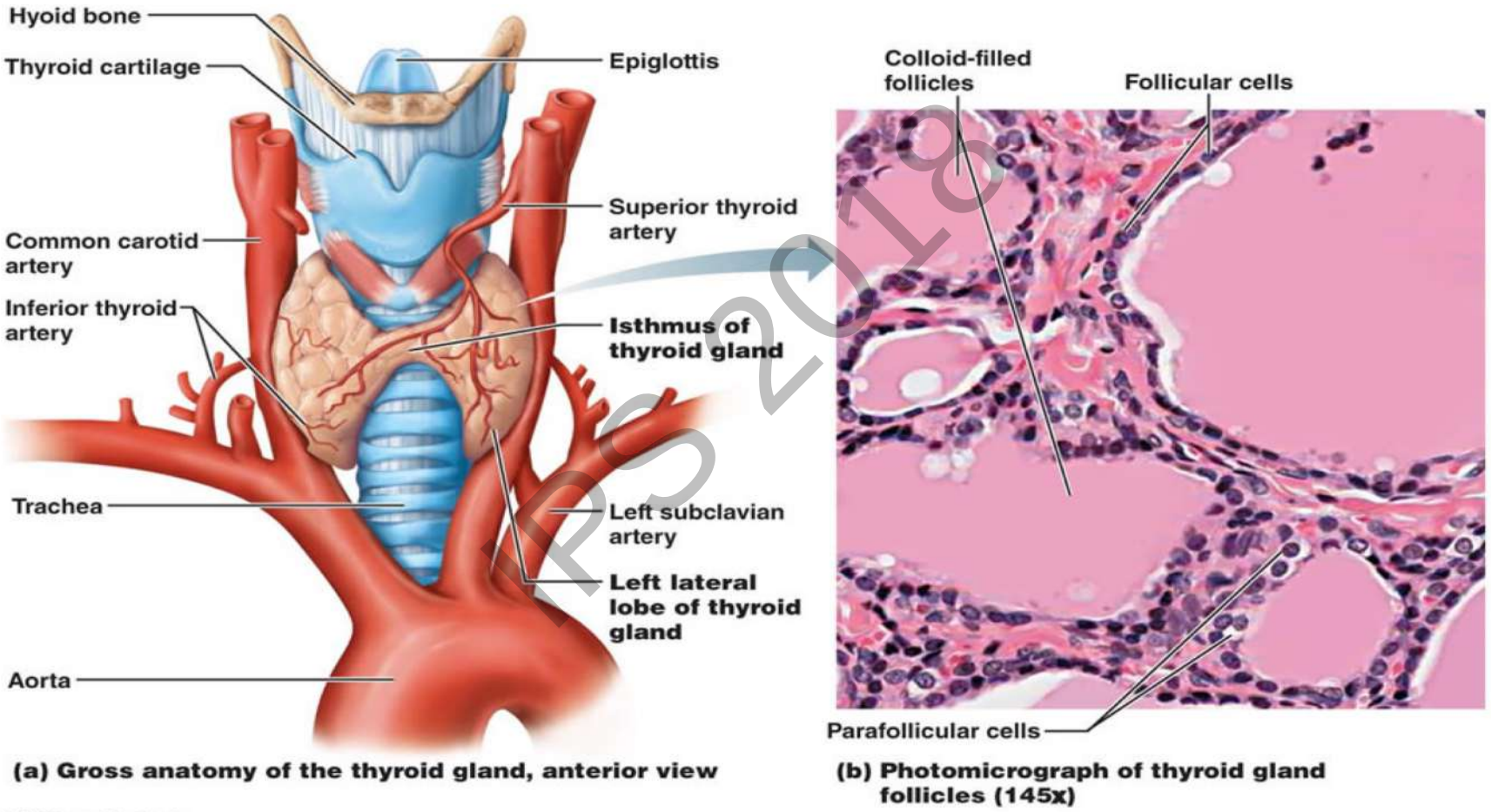
- Thyroid Structure & Hormone synthesis
- Congenital
  - Hypo
  - Hyper
- Acquired
  - Hypo
    - Secondary, Tertiary
  - Hyper
- Cancer
  - Multiple Endocrine Neoplasia

Embryology

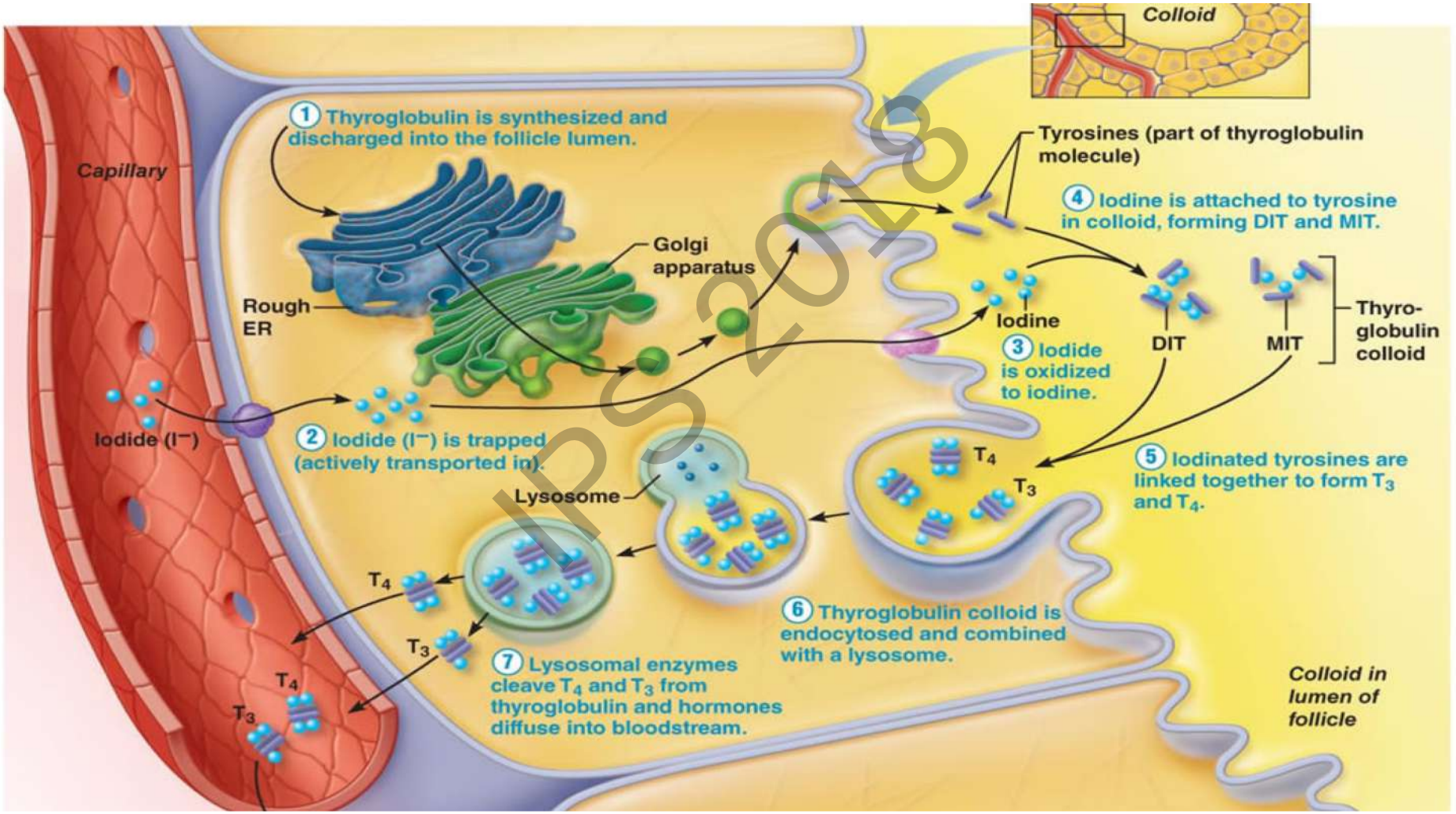


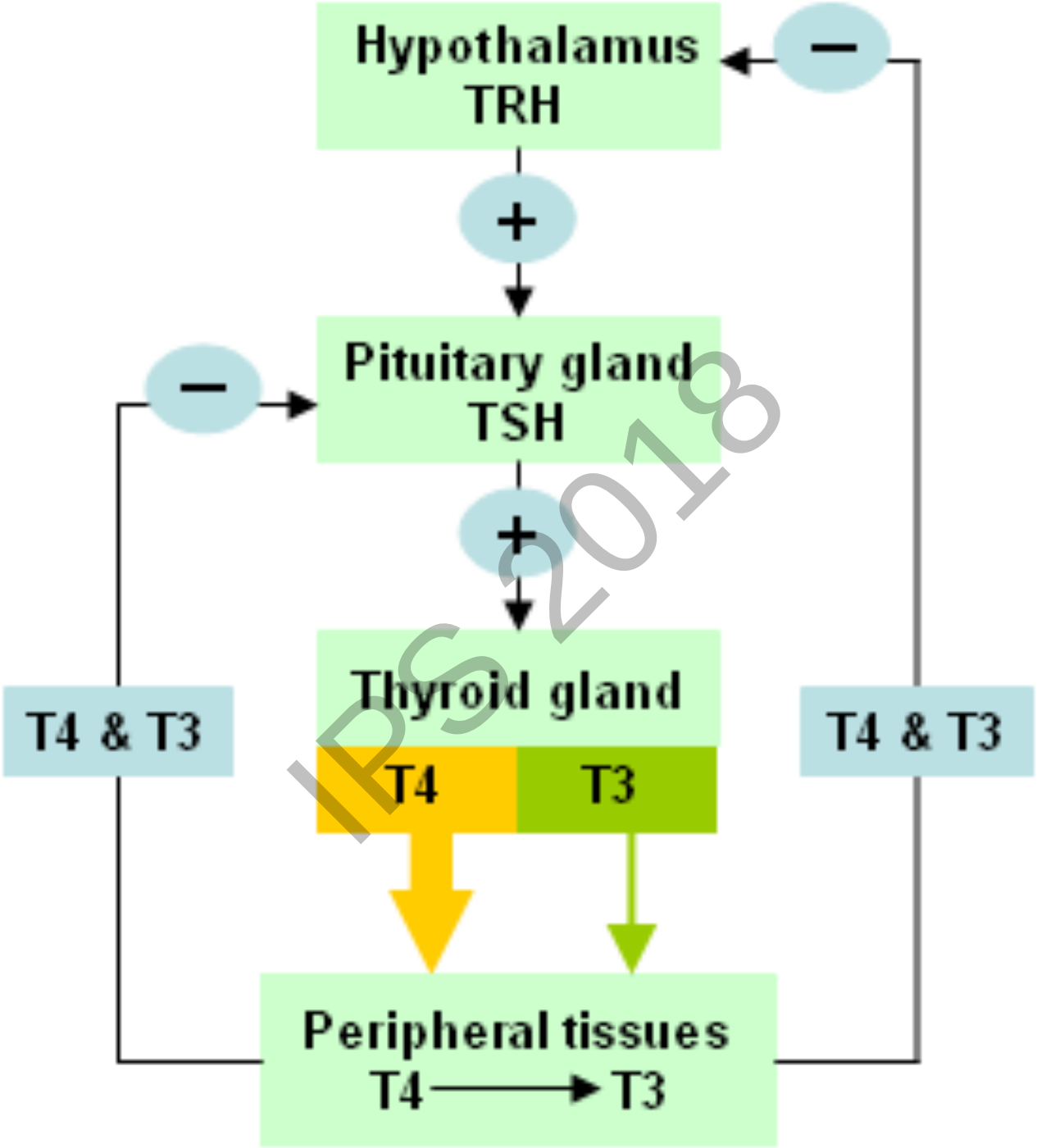
Genes controlling thyroid descent – NKX2, FOXE1 and PAX8

Anatomy



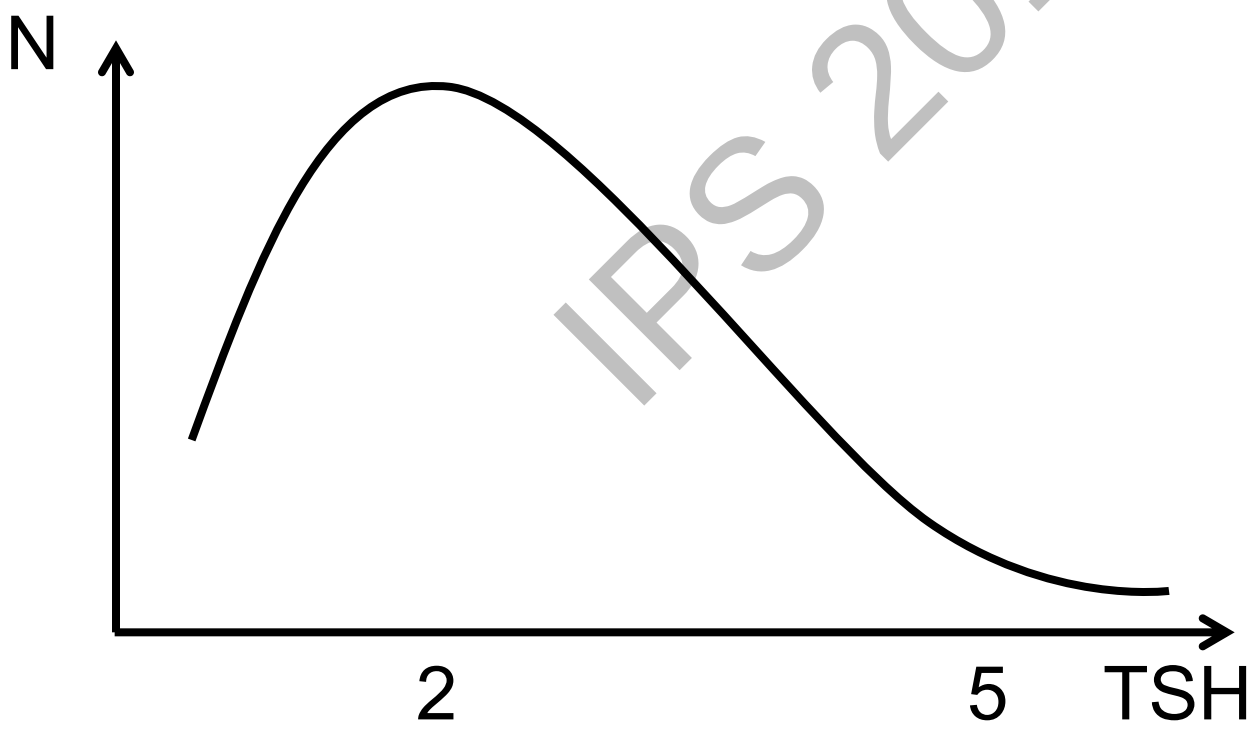
Thyroid Hormone Synthesis




Hypothalamus
TRH
−
+
Pituitary gland
TSH
−
+
Thyroid gland
T4
T3
T4 & T3
T4 & T3
Peripheral tissues
T4 ⟶ T3

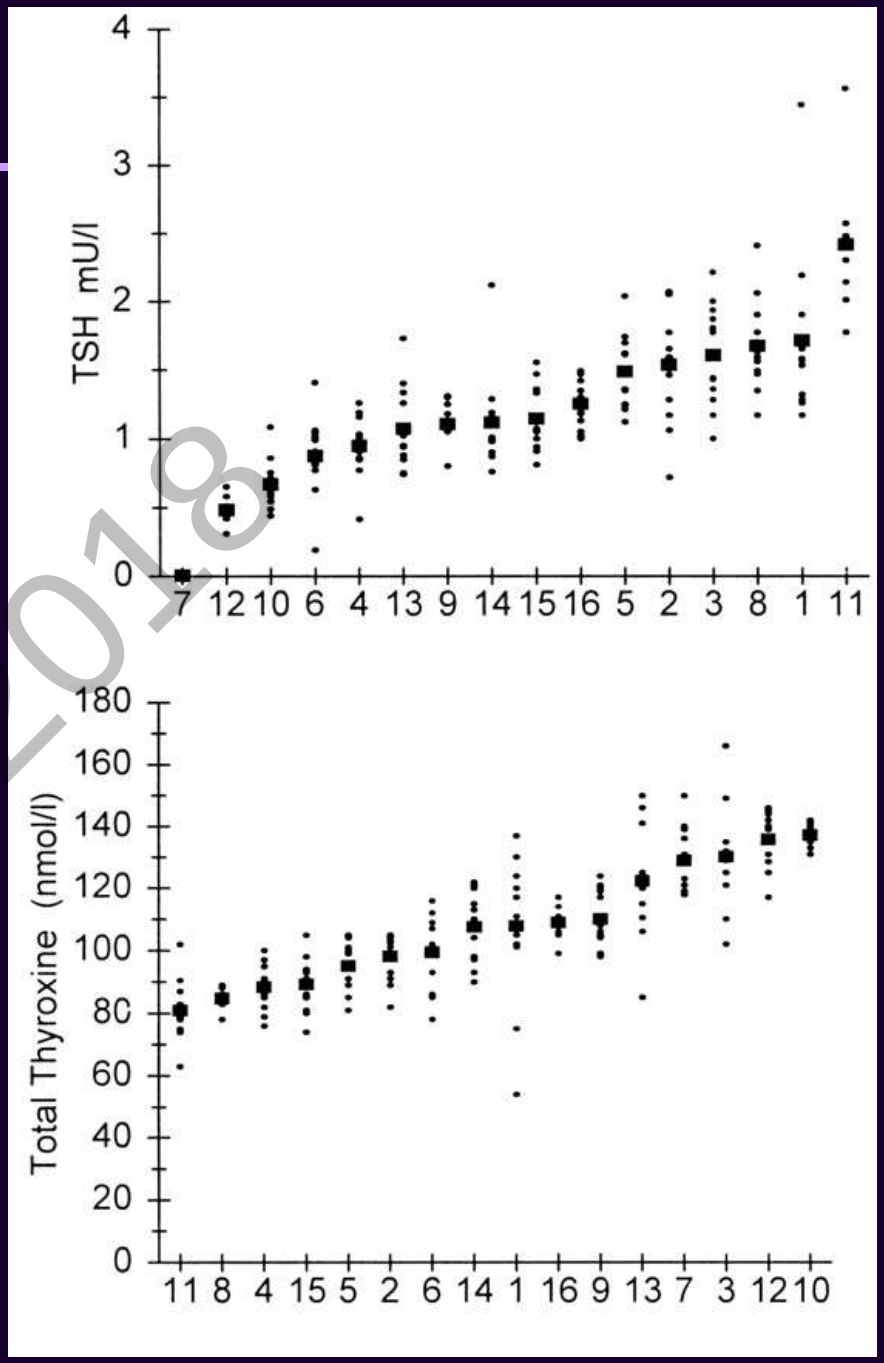
Normal values

- Free Thyroxine (fT4) : 9-24 pmol/l
- TSH 0.3 – 5.0 mU/l



Narrow individual range

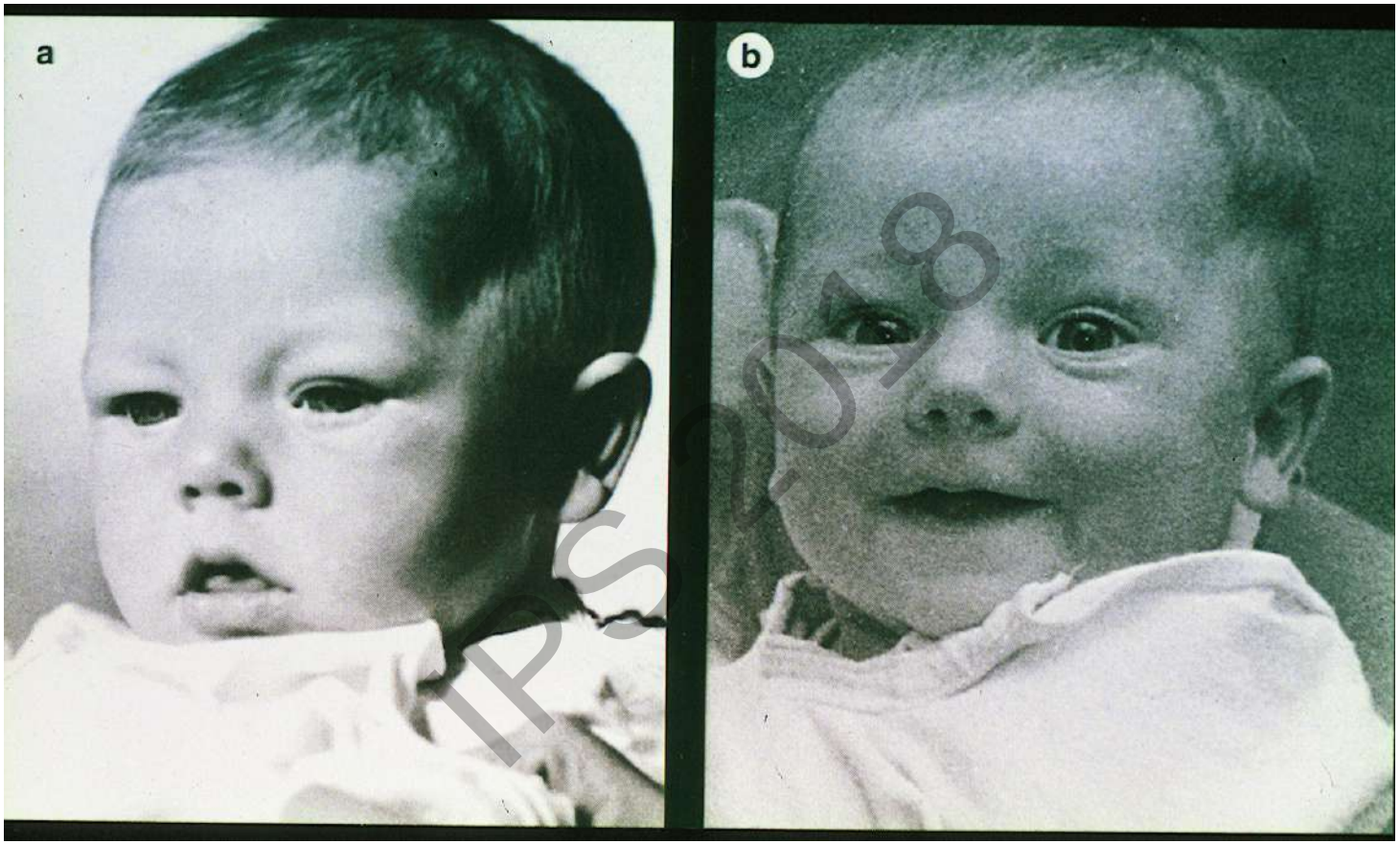
Serum TSH and total T4
in 16 normal subjects
taken monthly for 12 months.



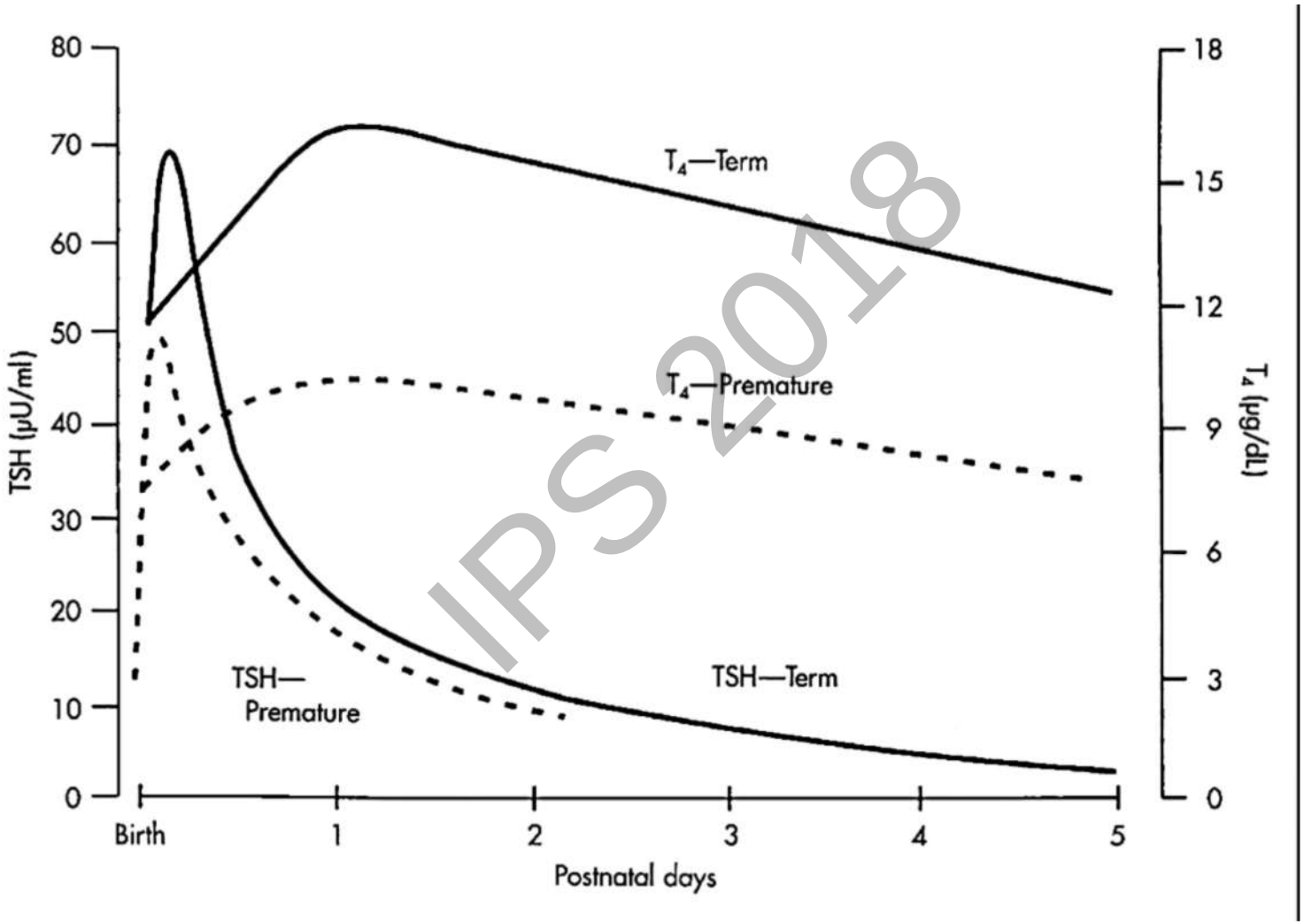
Andersen S et al. JCEM 2002; 87: 1068-72

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Congenital Hypothyroidism



Neonatal Changes



Congenital Hypothyroidism

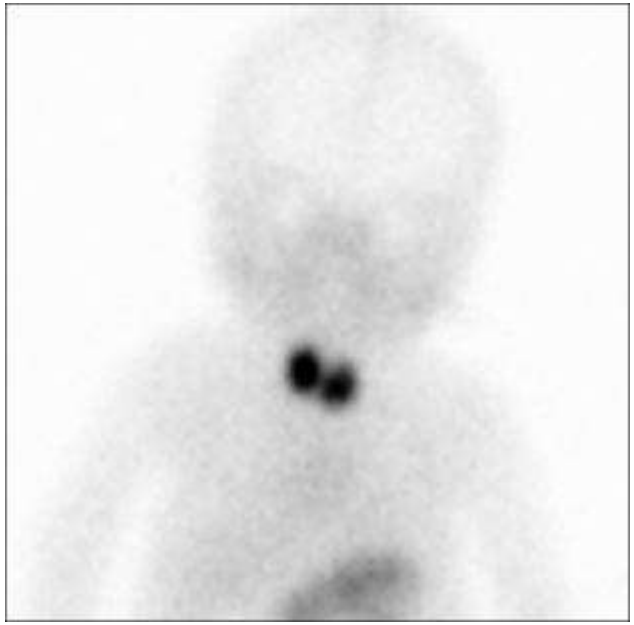
- Primary or Secondary
- Incidence 1:2500
- Permanent forms of Congenital Hypothyroidism
  - 85% thyroid dysgenesis – agenesis, hypoplasia, ectopy
  - 15% dyshormonogenesis
- Transient hypothyrodism
- Screening – two techniques both equivalent for picking up
  - TSH based screening – used in UK, Europe, Japan – picks up subclinical hypothyroidism but misses central hypothyroidism
  - T4/backup TSH – USA, Netherlands – picks up central hypothyroidism, hyperthyroxinaemia but misses some cases subclinical/compensated hypothyroidism

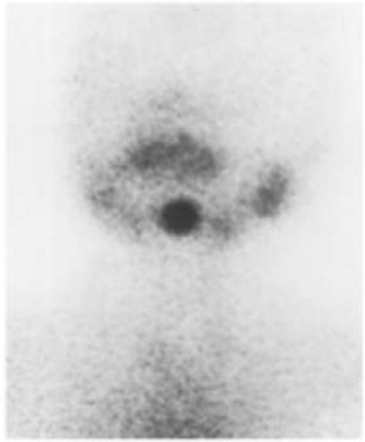
Screening/Investigation

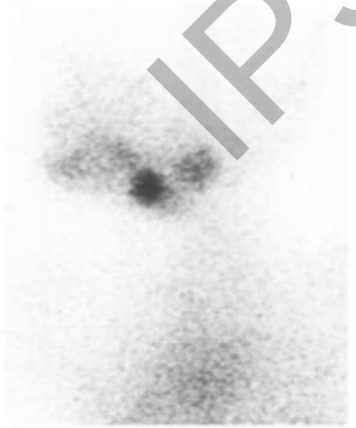
- Initial blood spot TSH (original cut offs)
  - >50 mU/L – immediate evaluation
  - 20-50 mU/L repeat blood spot requested, still >20 mU/L then for evaluation
  - <20 mU/l clear (trend to reduce this level)
- Evaluation
  - Mother and Baby TFT and anti-TPO antibodies
  - Thyroid isotope scan
- Management – 10 -15 mcg/kg levothyroxine but
  - In general don't use < 25 micrograms in term baby
  - Doses of 50 mcg or more often produce clinical/biochemical thyrotoxicosis

Venous TFTs and whether to start treatment – ESPE guideline

- fT4 low – start treatment
- TSH > 20 mU/L – start treatment
- TSH < 6 treatment not required
- TSH 6 – 20 with normal free T4 – await imaging, start treatment if TSH still high in 3-4 weeks

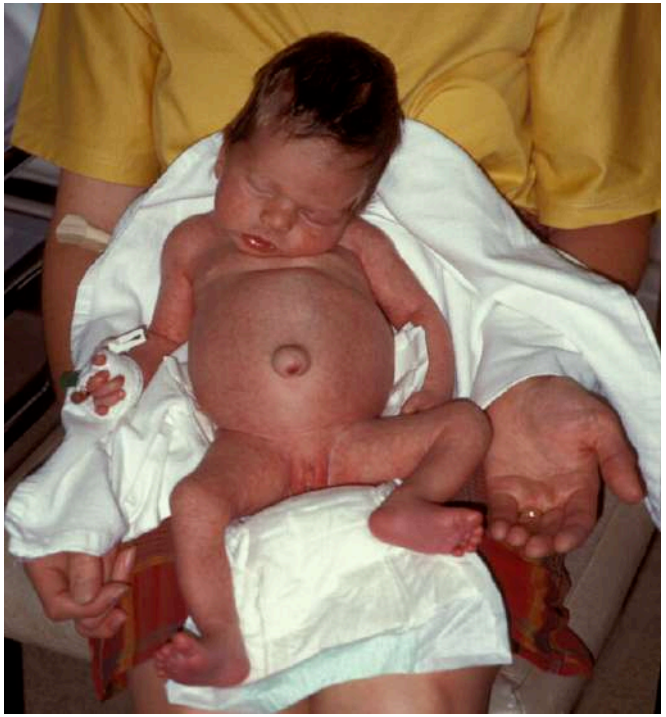






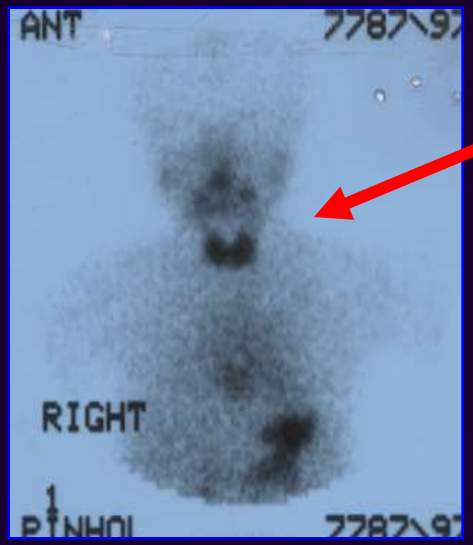
Anterior view

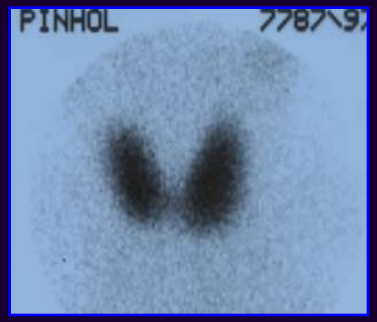
Lateral view



Clinical examination, US and Tc-99m scan

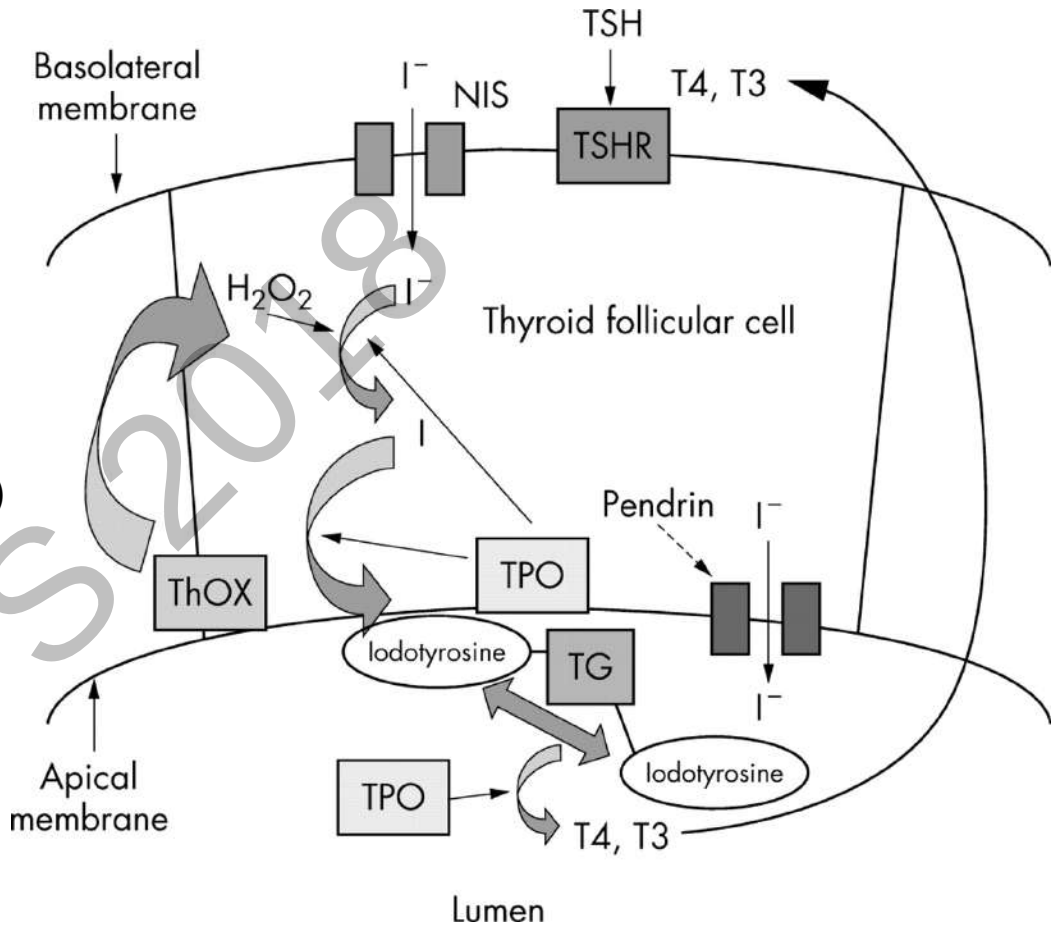
No goitre	Goitre or normal size Eutopic
85-90%	10-15%
Thyroid dysgenesis: 1.Agenesis 20-40% 2.Hypoplasia 25-35% 3. Ectopic 35-40% Females>males 2% familial TSH receptor Transcription factors: *TITF1/NKX2-1, FOXE1, PAX8*	Dyshormonogenesis: 1. Iodide transport (*NIS, Pendrin*) 2. Iodide oxidation (*DUOX2*) organification & coupling (*TPO*) 3. Iodine recycling (*deiodinase*) *Tg* synthesis Nondyshormonogenesis Iodine deficiency 'Endemic cretinism'





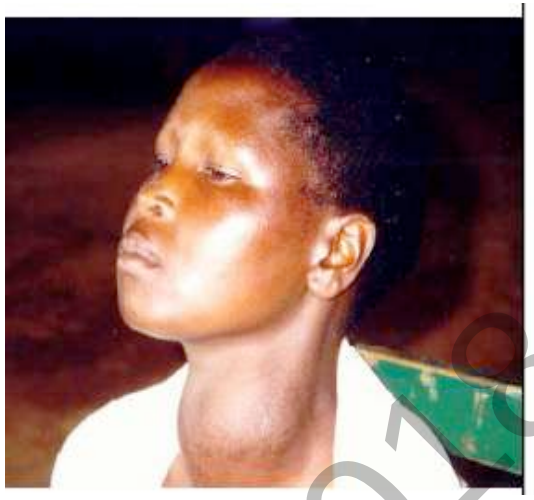
Congenital Hypothyroidism

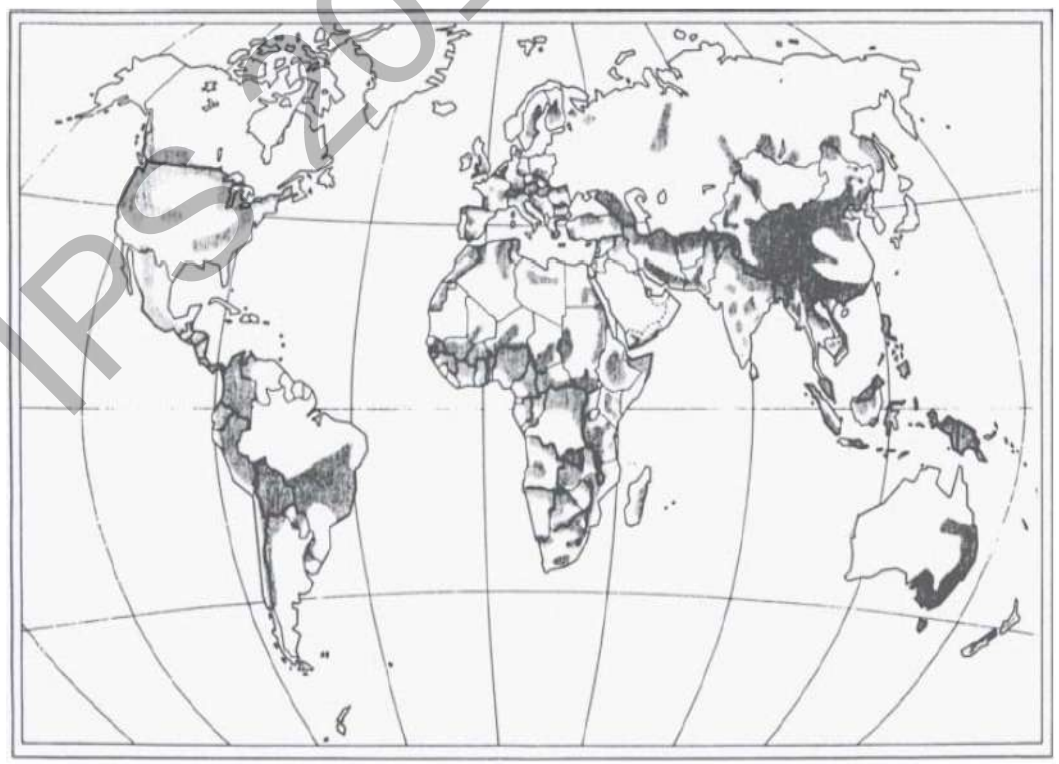
- Thyroid dysgenesis
  - Agenesis
  - Hypoplasia
  - Ectopy
  - Hemithyroid
- Dyshormonogenesis
  - Na/I transporter
  - TPO
  - Pendrin
  - Thyroid oxidase (THOX2)
  - Thyroglobulin
  - Halogenase
- Transient
  - Iodine contamination
  - Maternal antibodies
  - Antithyroid drugs
- Central hypothyroidism
  - Hpa defects
  - Isolated TSH deficiency
- Genetic defects ± other features



Parks et al J Med Genet 2005

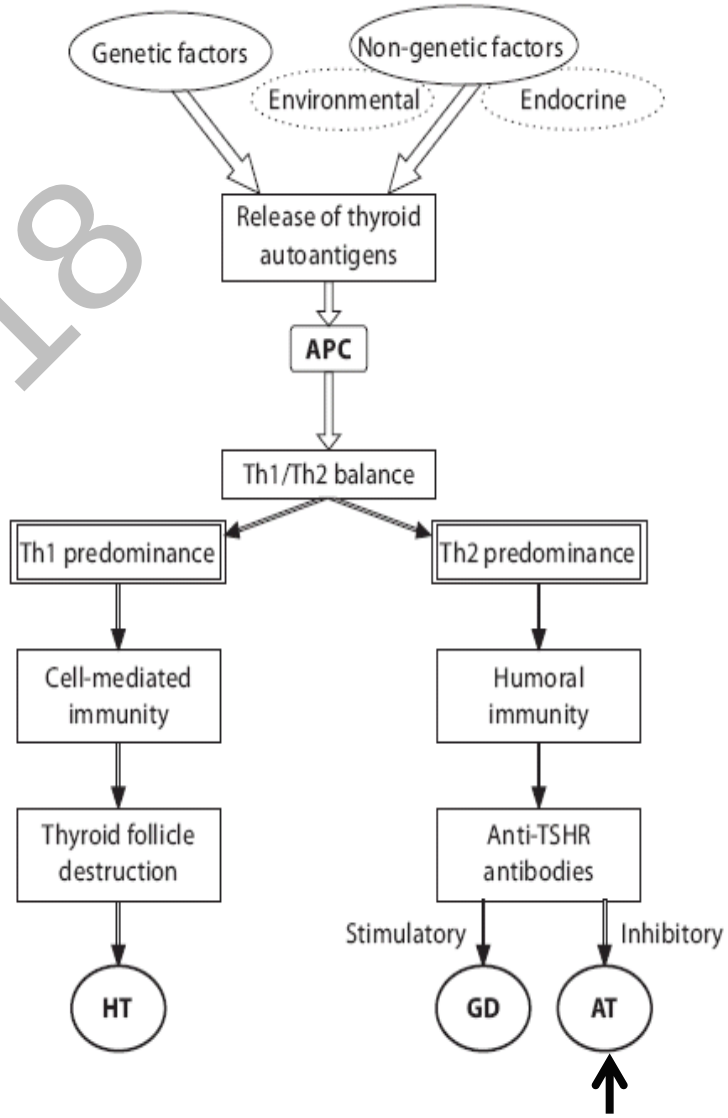
Iodine Deficiency: Congenital & Acquired Hypothyroidism





Autoimmune Thyroid Disorders

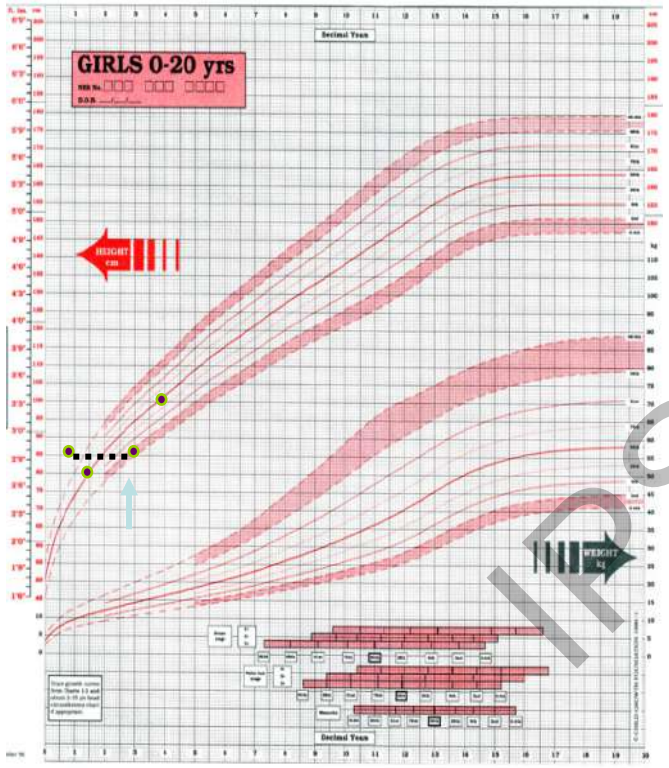
- Hashimoto's
  - Firm, diffuse goitre
  - Usually hypothyroid
  - Autoantibody +
  - Diffuse lymphoid infiltration
- Graves
  - Neonatal
  - Childhood

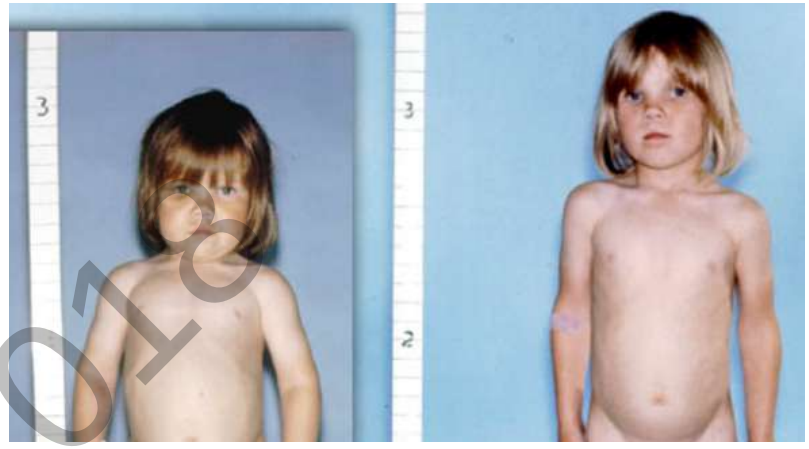


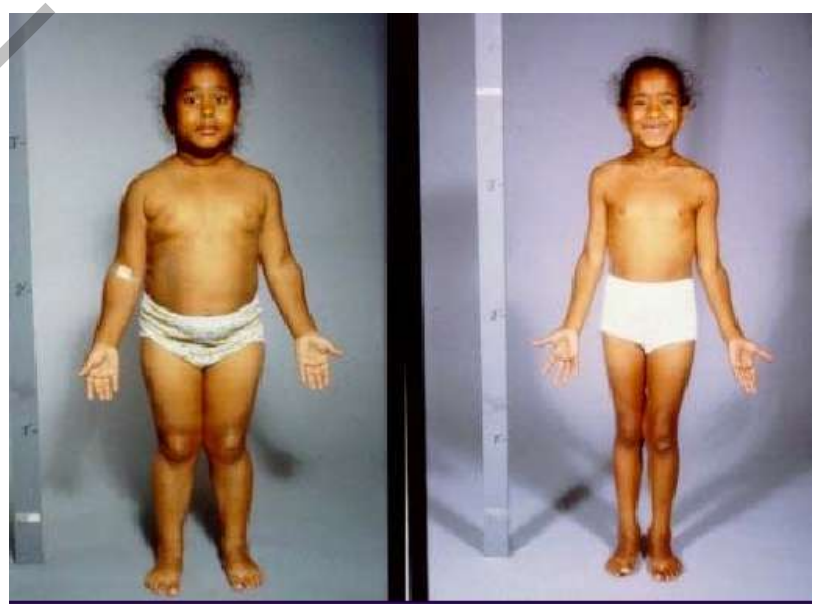
Clinical Features

- HT (hypo)
  - Slow growth
  - Weight gain
  - Cool, dry skin
  - Bradycardia
  - Lethargy
  - School performance variable
- GD (hyper)
  - Weight loss
  - Anxiety
  - Fidgety
  - Tremor
  - Tachycardia
  - Myopathy
  - School performance usually poor

Hashimoto's Autoimmune Hypothyroidism

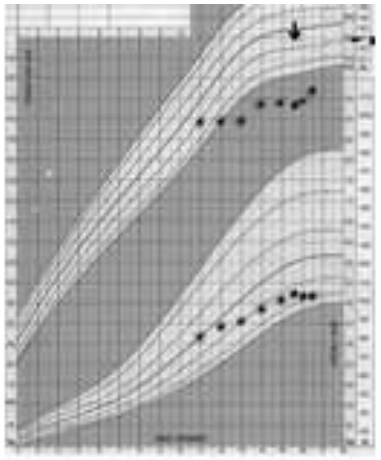






Slow development of Clinical Features



Presentation

13 yr old girl

Constipation since age 2-3 yrs

Short stature and virtually no growth for past 6 years - age 7yrs she was on 50th centile

Tired and poor stamina

Menarche age 11yrs – now irregular heavy periods

- Family History – Mother's side
  - Mum DMD carrier
  - Grandmother – motor neurone disease
  - 3 maternal uncles died in adolescence from DMD
- Family History – Father's side
  - Brothers and sisters short – one described as "dwarf"
- Brother aged 16 yrs with ADHD

Clinical Examination

- Weight 32.9kg (below 2nd centile)
- Height 128cm (well below 0.4th centile)
- Pubertal staging: Breast 2-3; Pubic hair 3, Axillary hair not present

- HR 68/min, feeble pulse
- “Sallow” complexion
- Rough dry skin
- Delayed relaxation time for ankle reflexes
- No goitre

- No neck folds
- Clinodactyly both hands

Differential Diagnosis of Short stature, Growth stasis and Tiredness in an adolescent girl

- Endocrine
  - Hypothyroidism
    - primary (autoimmune): isolated or with Turner syndrome
    - secondary and associated with GH deficiency (craniopharyngioma)
- Nonendocrine
  - Coeliac disease
  - Inflammatory bowel disease

Investigations

- Hb 10.4 g/dL
- MCV 96.9 fl (78 – 95)
- MCH 31.8 pg (25 - 32)

- ALT 100 u/L (raised)
- CK 2192 u/L (raised)

- Free T_4 1.1 pmol/L (9 - 24)
- TSH >100 Mu/L (0.2 - 5)
- TPO Ab 116 IU/ml (0 - 59)

- Normal results:
  - Coeliac Screen,
  - Orosomucoid
  - Ferritin
  - Renal function
  - Serum folate, B12

Impression

- Longstanding severe autoimmune hypothyroidism
- High CK - ? DMD carrier or hypothyroidism
- High ALT - ? hypothyroidism
- Started Levothyroxine tablet 25 mcg daily for 2 weeks

	Initial	2 weeks	7 weeks	5 months	1 year
TSH mU/L (0-10)	>100				3
Free T_4 pmol/l (15-34)	1.1				cient
LevoT4	25 mcg/d				nue
Comments					
Weight	32.9 kg (<2nd C)				C
Height	128 cm (<<0.4th C)		129.5 cm (<<0.4th C)		140.5 cm (<0.4th C)
Ht velocity			9.8 cm/y		8.9 cm/y
Puberty stage	B2-3, P3			B2-3, P3	
Treatment				GnRHa	

Pelvic Ultrasound

- Normal post pubertal anteverted uterus with endometrial echo
- Both ovaries clearly visible, contain multiple small follicles, maximum diameter 10mm

Oestadiol 55 pmol/L (45 - 607)

LHRH - prepubertal response

- LH 0.2 → peak 1.4 iu/l at 60 mins
- FSH 3.2 → peak 3.7 iu/l at 60 mins

Causes of primary acquired hypothyroidism

Autoimmune

Chronic lymphocytic thyroiditis

Females>males

FH of autoimmune thyroid disease in 30%

Goitre from lymphocytic infiltration & compensatory ↑ TSH

Background predisposition
Environmental factors
Hormonal factors

Syndromes: Down. Turner, Klinefelter, Noonan

T1 diabetes

Autoimmune polyglandular syndrome

- APS1 – APECED AIRE (autoimmune regulator) mutation
- APS2 – CLT, T1D, AI

Iodine deficiency – endemic goitre

Radiotherapy for lymphoma, brain tumours

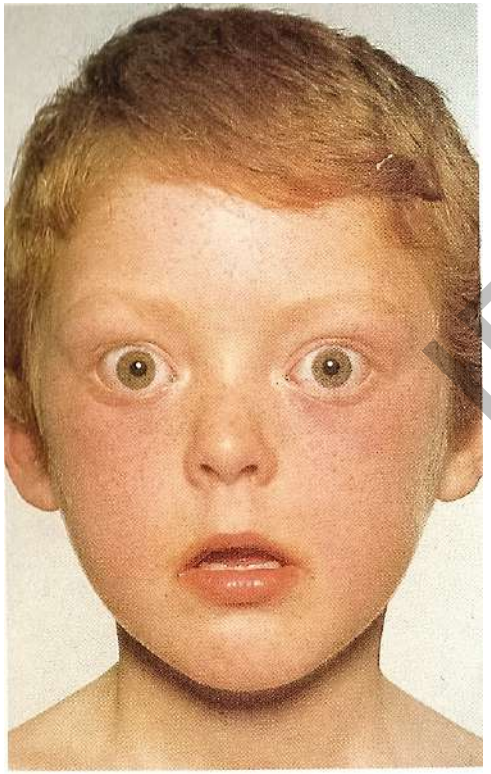
Neonatal GD: Transplacental maternal TSH-R(s) Abs

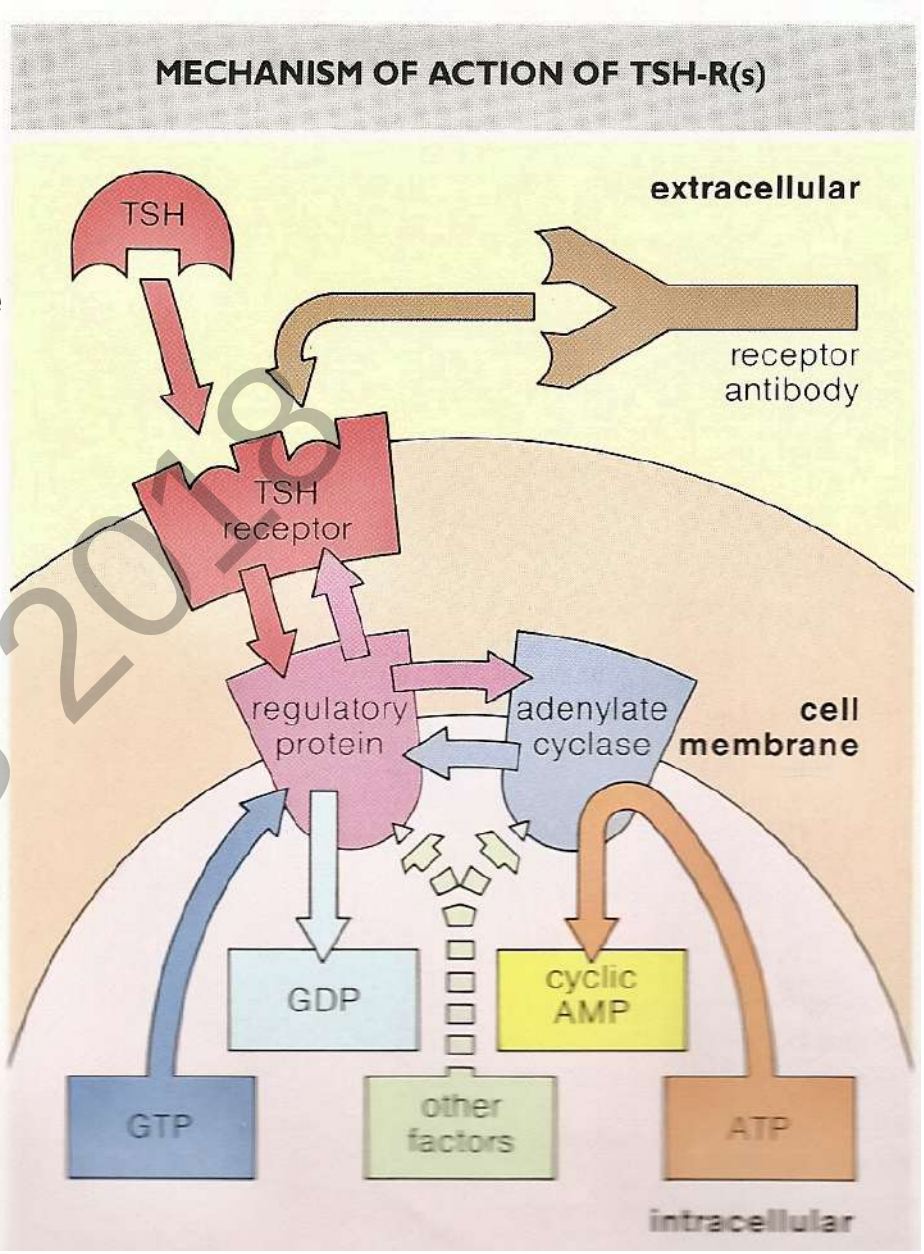
(Onset can be delayed if mother has a mix of TSH-R(s) & (b) Abs)

Childhood GD: Female preponderance

TSH-R(s) Abs

Goitre ± bruit





Neonatal Graves disease (GD) (autoimmune hyperthyroidism)

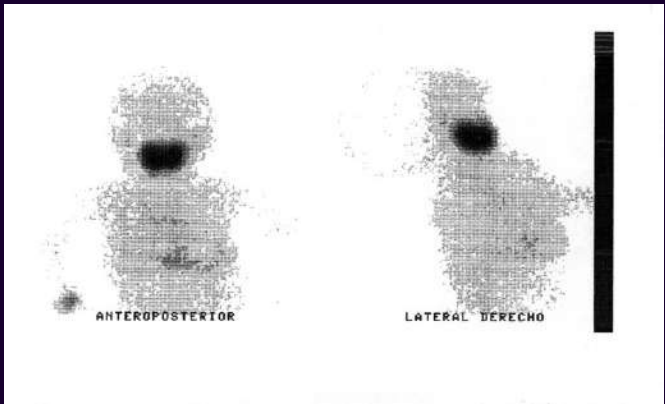
Occurs in ≈ 2% of offspring of mothers with GD

Usually transient, resolves by age 3m

Major risks to affected infants

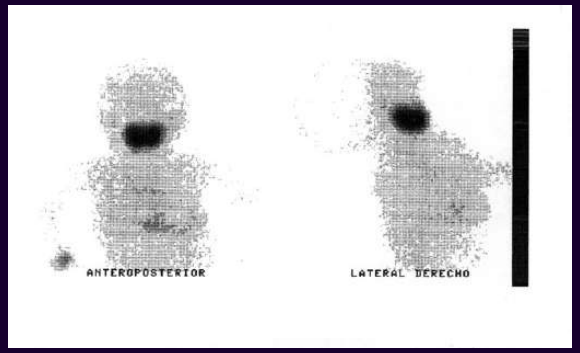
- Cardiac insufficiency
- Foetal death
- IUGR
- Prematurity
- Craniosynostosis
- Microcephaly
- Psychomotor disabilities

NB: Foetal TSH receptors become physiologically responsive to TSH (& TRAb) in 2nd half of gestation, around 20wk



Monitoring foetus

- US foetal thyroid from 20wk and every 4wk
  - enlarged thyroid = dysfunction



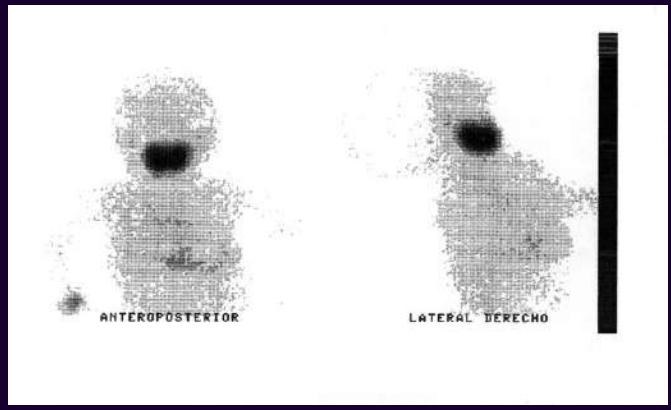
- Distal femoral epiphyses
  - Normally absent <28wk, dot-like at 32 wk, visible at 35wk
  - Not visible at 32 wk ➔ hypothyroidism
  - Visible before 32 wk ➔ hyperthyroidism

- Foetal heart rate
  - >160/min ➔ hyperthyroidism

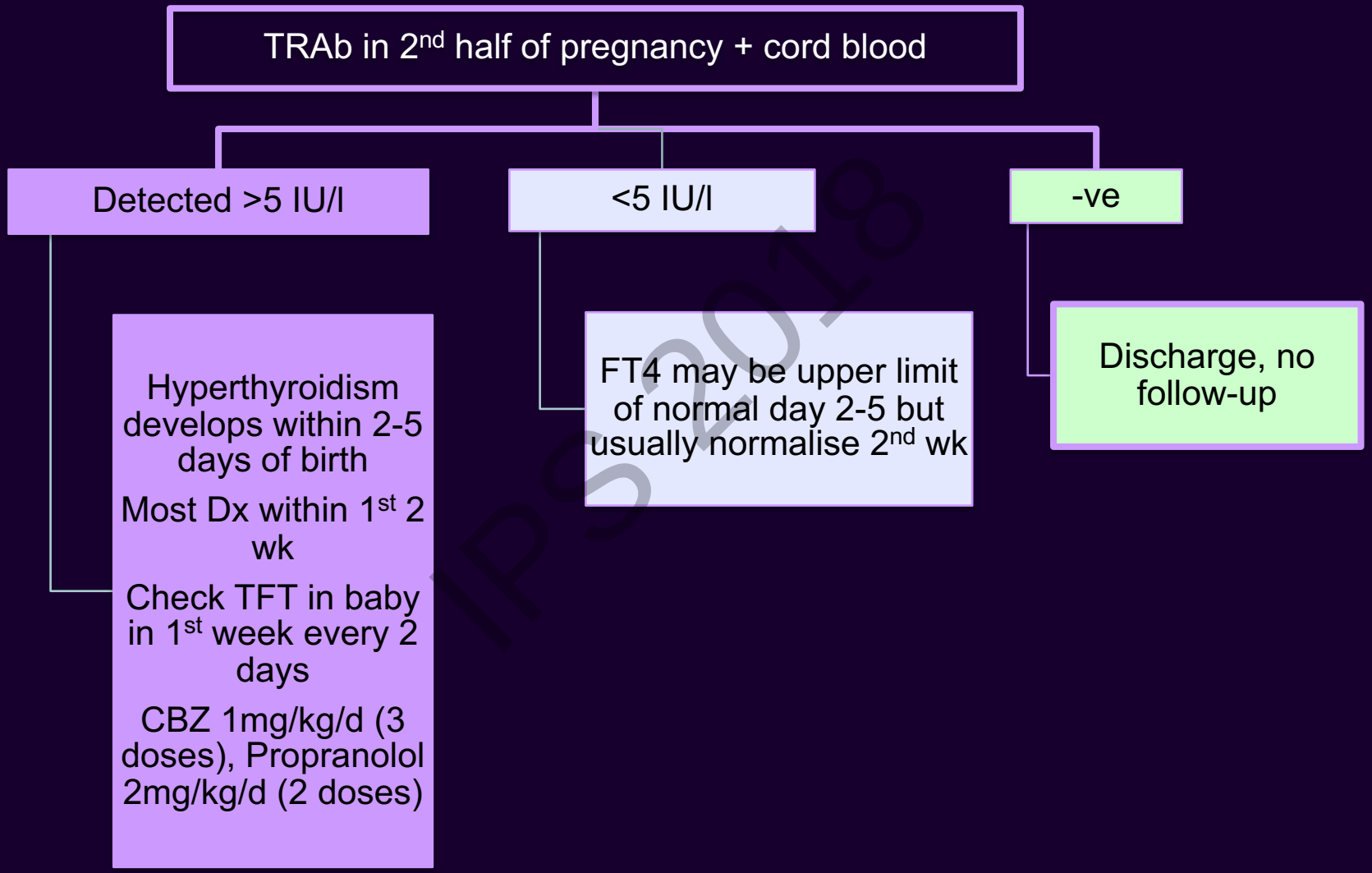
Foetal hyperthyroidism ➔ neonatal disease

Clinical features

- Tachycardia
- Hyperexcitability
- Poor wt gain despite feeding well
- Goitre
- Staring, eyelid retraction, exophthalmia
- Small ant fontanelle
- Craniosynostosis
- Microcephaly
- Advanced BA
- Hepatomegaly, splenomegaly
- Psychomotor disabilities



Newborn of mother with thyroid disease



Action of Anti-Thyroid Drugs

Carbimazole: converted to the active form, methimazole, which prevents thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones T3 and T4

Like methimazole, PTU inhibits the enzyme thyroid peroxidase, and also acts by inhibiting the enzyme 5'-deiodinase, which converts T4 to the more active form T3

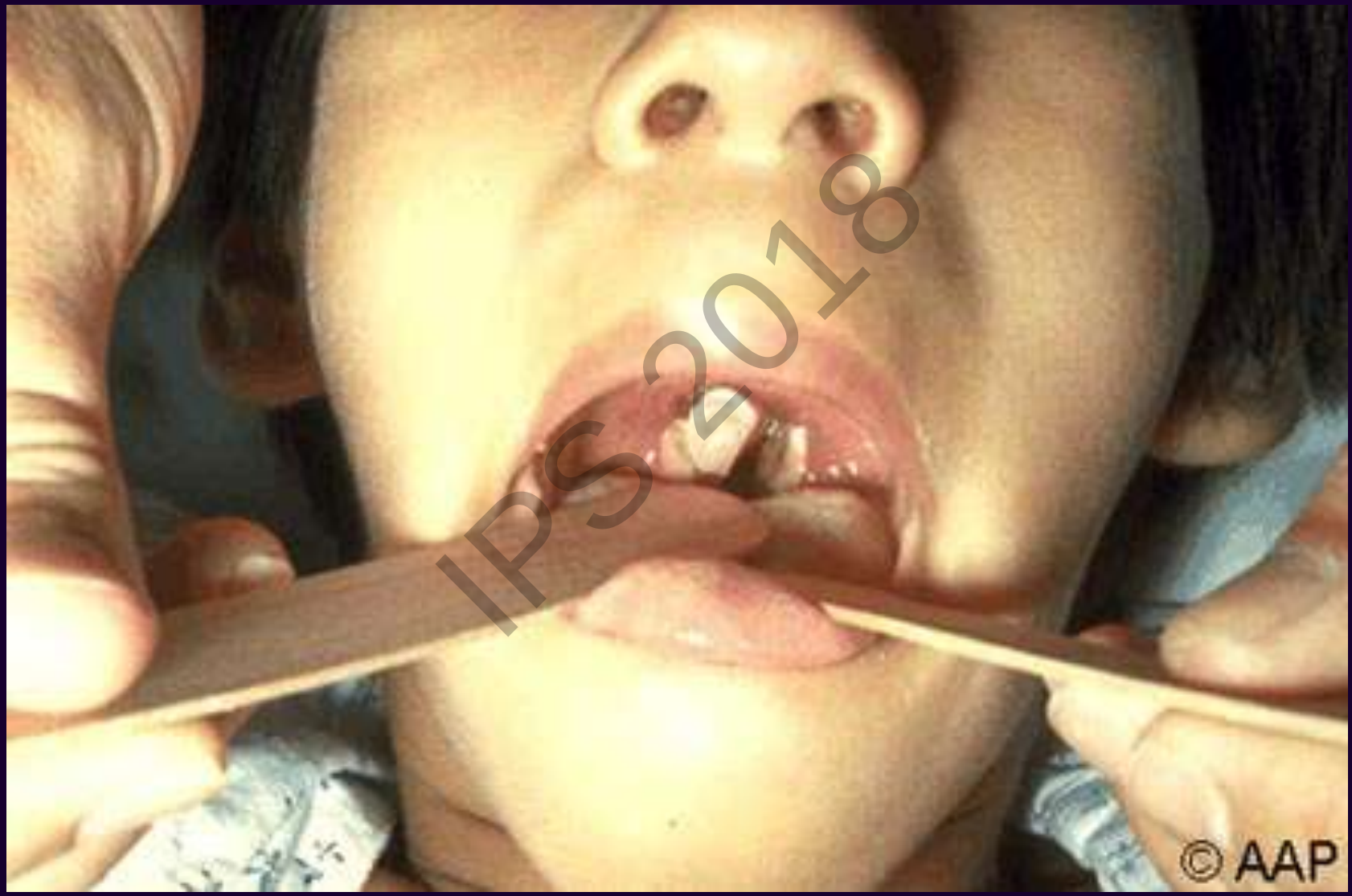
Carbimazole – first line therapy

Initial dose 20-30 mg/day

Regimens

- Dose titration – lowest possible dose
- Block and replace – block with Carbimazole + add supplemental Thyroxine

Carbimazole side effects



Initial presentation

- **KE** 15 yr
- **Hx** 6 months Increased appetite, wt loss, diarrhoea
  Feeling hot, craving sweets, flare up of eczema,
  easily tired, feeling sweaty
- **O/E** large diffuse goitre, no nodularity
  mild resting tremor, no eye signs, no menstrual problems
- **Ix** TSH < 0.1 MU/L(0.2- 5) , FT4 >100 pmol/L
  TPO Abs 85 IU/ML (<10)
  USS heterogeneous echo texture diffusely and
  symmetrically enlarged
- **Dx** **Thyrotoxicosis**
- **Tx** Carbimazole 5mg TDS

Referral to Endocrine

- **April 09** Carbimazole stopped after 2 months due to alopecia
  Changed to Propylthioracil **PTU 100** mg TDS
- **June 09** OPD: tired, headache,
  TFT - hyperthyroid
  Admitted to hospital for monitoring
- **July 09** Endocrine assessment: mum said "she has frog's eyes"
  Bald patchy alopecia, no tremor
  Mild proptosis, large goitre, no bruit.
  Warm peripheries, bounding pulses, HR 85
  Admitted poor compliance

Clinical Course

- **Jan 10** Well, good energy levels, regular periods, no proptosis, goitre, claimed good compliance
  However biochemical evidence of **relapse**

- **Feb 10** Clinical and biochemical Thyrotoxicosis

- **May 2010** Clinically euthyroid but still has goitre: **Definitive treatment** discussed

- Seen by surgeon and adult endocrine services for discussions about advantages and disadvantages of surgery versus radioiodine therapy

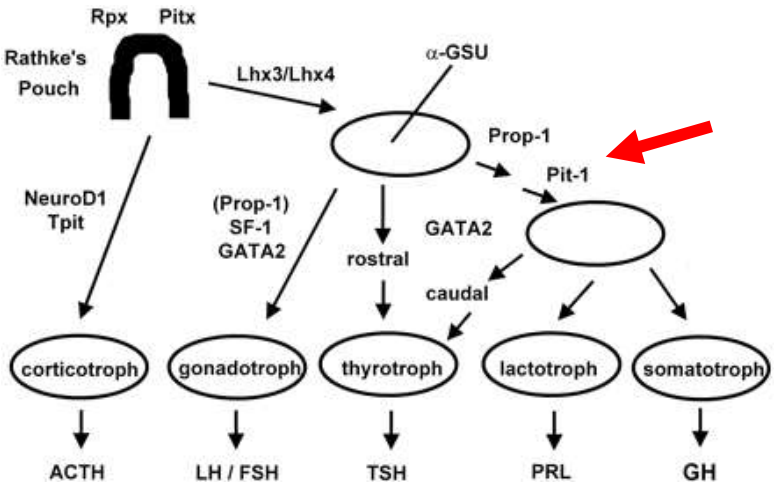
	TSH (0.3-5.0 mU/l)	FT4 (9-24 pmol/l)	T3 (1.3-3.0) nmol/l	TX
19/01/09	**<0.1**	**>100**		Carbimazole 5 mg TDS
10/03/09	**<0.02**	**67**	**30.8**	10mg TDS
1/4/09	**<0.02**	**55**	**26.4**	PTU 100mg TDS
29/04/09	**<0.02**	**>100**	**37.6**	PTU 150,100,150
04/06/09	**<0.02**	**76**	**37.4**	PTU 150 TDS
July 09	**0.02**	**37**	**15**	PTU 200 TDS
4/8/09	**<0.01**	**21**		PTU 200,150,200
18/8/09	**<0.01**	**18**		PTU 150 TDS
6/10/09	**<0.02**	**28**		PTU 200,150,200
4/1/10	**<0.01**	**56.6**	**6**	PTU **200,150,200**
29/1/10	**<0.01**	**76.8**	**5.2**	PTU **200 TDs**
22/2/10	**<0.01**	**39.7**		? compliance
May 10	**<0.01**	**9.8**		PTU 150 TDS
20/1/2011	**1.7**	**56.4**		PTU 100 BD
29/3/11	**1.6**	**41.7**	**1.6**	PTU 100 OD

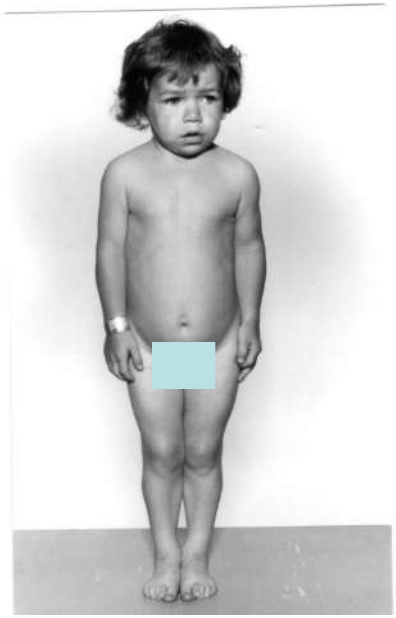
Post Operation

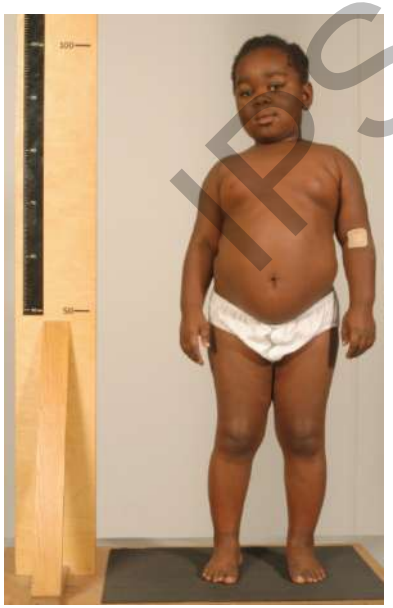
- **9/8/11** Thyroidectomy after having iodine for 8 Days .
- **Post op** problematic hypocalcaemia due to transient hypoparathyroidism
- Discharged 12/08/11
- Remained hypocalcaemic with pins and needles needing high doses of Calcium and One Alfa Calcidol
- **Sep 10 well**, husky voice, but no symptoms of hypocalcaemia
- **Jan 12** : 4/12 post op well, euthyroid , no pins and needles , voice returned to normal

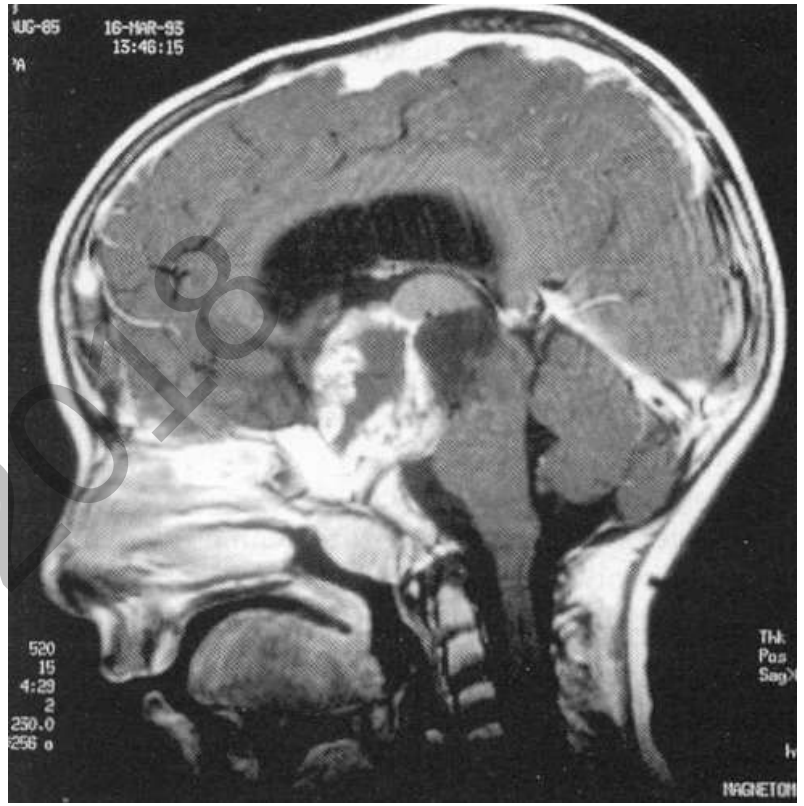
Secondary & Tertiary Hypothyroidism

Congenital









Acquired

Papillary carcinoma

Commonest

Usual presentation: asymptomatic thyroid mass in teenager

Often metastatic at presentation but prognosis excellent

Anti-thyroid antibodies may be present

Thyroglobulin levels

- Marker of the disease process

Multiple Endocrine Neoplasia

- Type 1
  - Parathyroid hyperplasia
  - Pituitary adenoma (prolactinoma)
  - Insulinoma, gastrinoma
- MEN1 gene

- Type 2a
  - Medullary Thyroid Cancer
  - Parathyroid hyperplasia
  - Phaeochromocytoma
- Type 2b
  - MTC, Phaeo + Marfanoid body habitus & mucosal neuromata
- FMTC
- RET oncogene

Medullary carcinoma

Tumours of parafollicular C-cells derived from neural crest

Pre-invasive C-cell hyperplasia stage ➔ carcinoma

Histology: nests of small cells in amyloid stroma

Produce calcitonin and levels high in serum (normally undetectable)

- valuable tumour marker in follow-up

5HT or prostaglandin may be produced by tumour cells

- diarrhoea

LN involved in 50-60% cases

Blood-borne metastases common

Almost always component of MEN 2a or 2b