Thyroid physiology and dysfunction

Georg Griesinger
UK-SH, Campus Lübeck

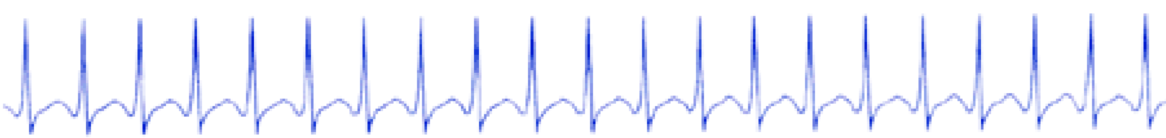
History

Robert James Graves
1796-1853

Carl Adolph von Basedow
1799 -1854

Exophtalmus

Goitre



Tachycardia

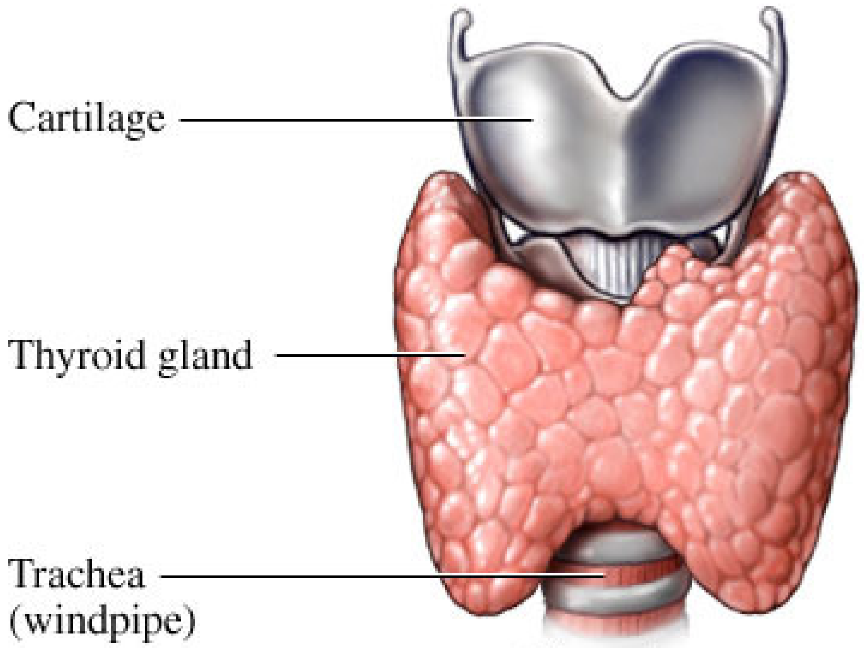
History

1886 *Paul Julius Moebius: M. Basedow is a thyroid gland disease*

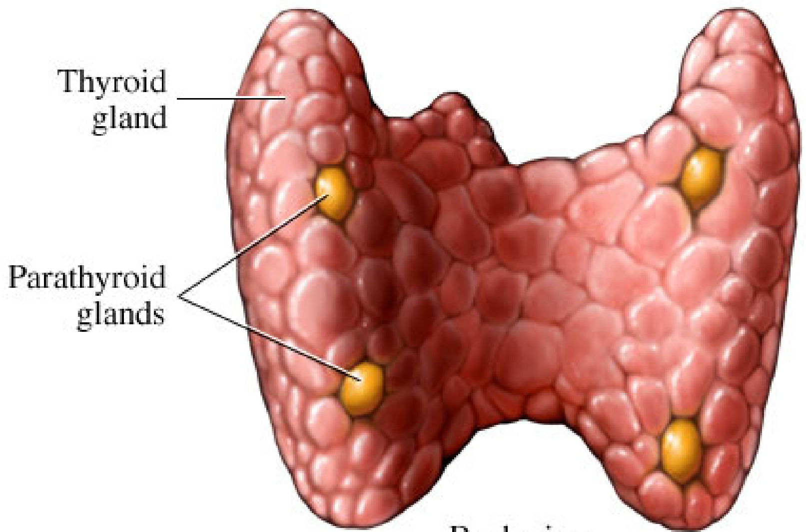
1912 *Hakaru Hashimoto: first described auto-immune thyreoditis (Struma lymphomatosa)*

1926	*Harington:*	*T4*
1932	*Junkmann:*	*TSH*
1952	Gross, Pitt-Rivers:	T3
1969	Schally, Guillemin:	TRH

Thyroid gland



Front view

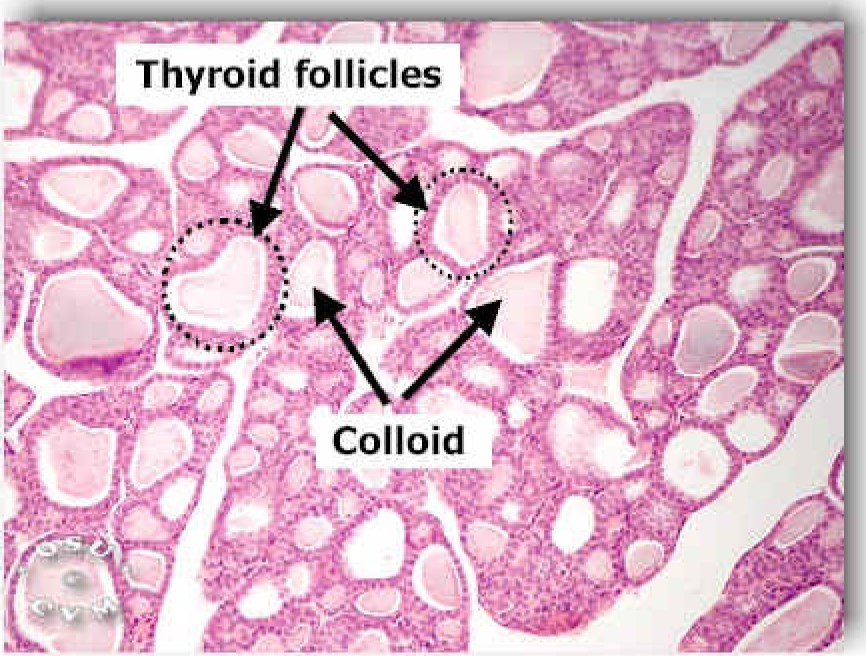


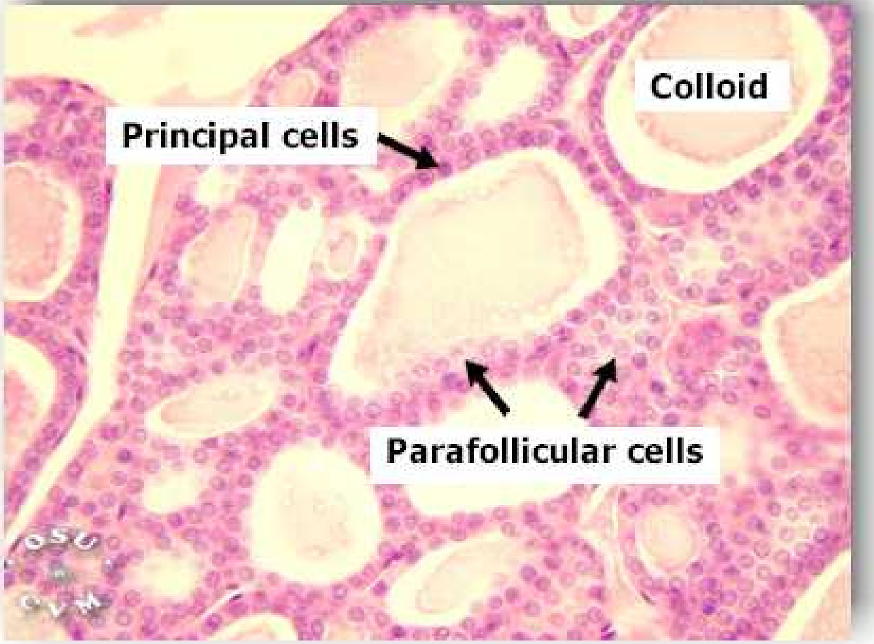
Back view

Weight: 18-60 g

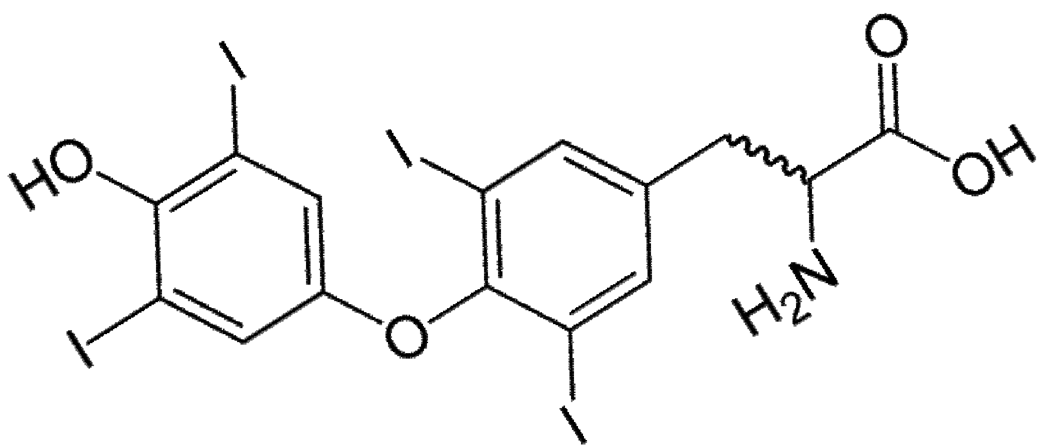
Volume: 18-25 ml

Thyroid gland: histology

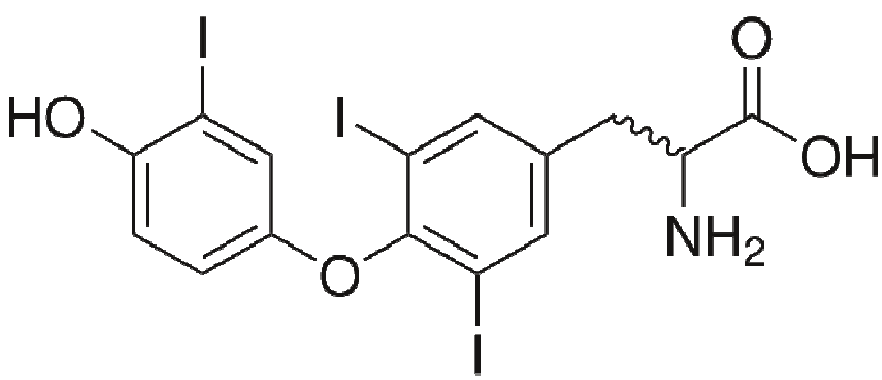




Thyroid hormones



T4 (thyroxin)



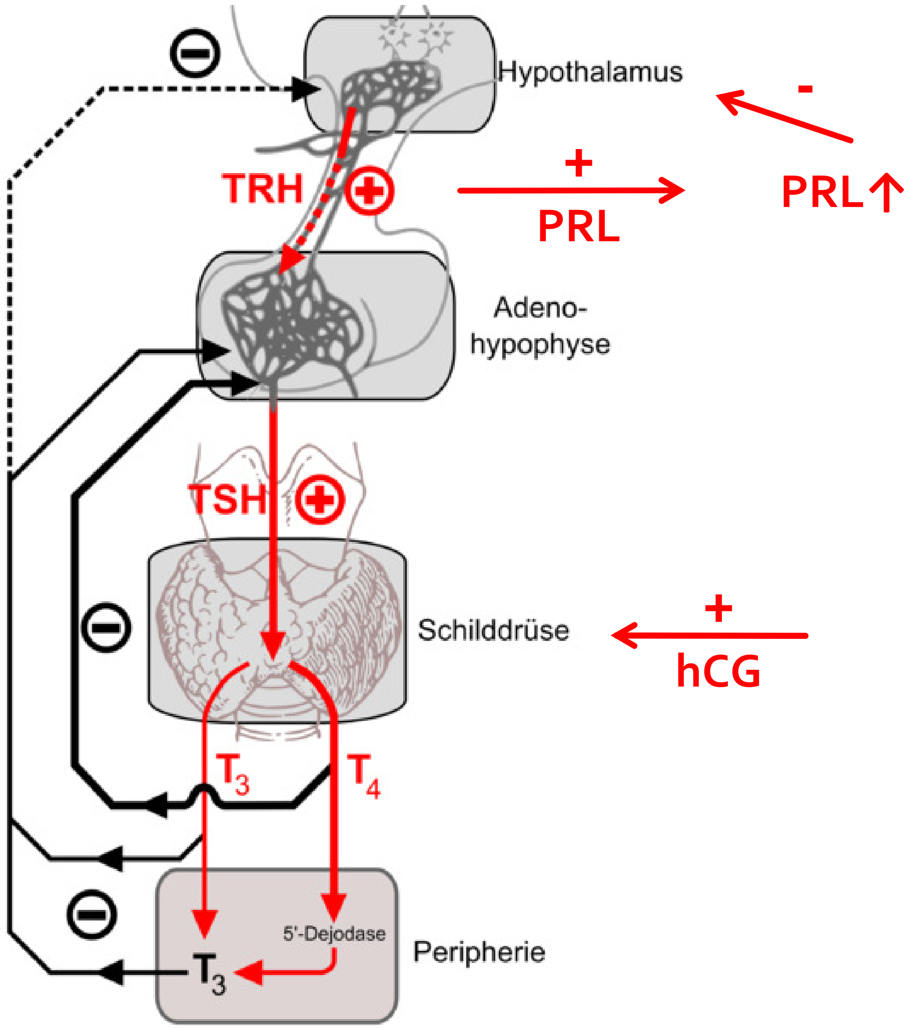
T3 (triiodothyronin)

Reference ranges

Parameter	Referenzwerte	Beschreibung
TSH	0,40–4,00 mU/ml[a]	Thyreotropin
fT4	8,0–17,0 pg/ml	Freies Thyroxin
fT3	2,00–4,20 pg/ml	Freies Trijodthyronin
TPO-AK	<35,0 U/ml Graubereich: 35,0–120,0 U/ml	Antikörper gegen thyreoidale Peroxidase
TRAK	<9,0 U/l Graubereich: 9,0–14,0 U/l	Antikörper gegen TSH-Rezeptor

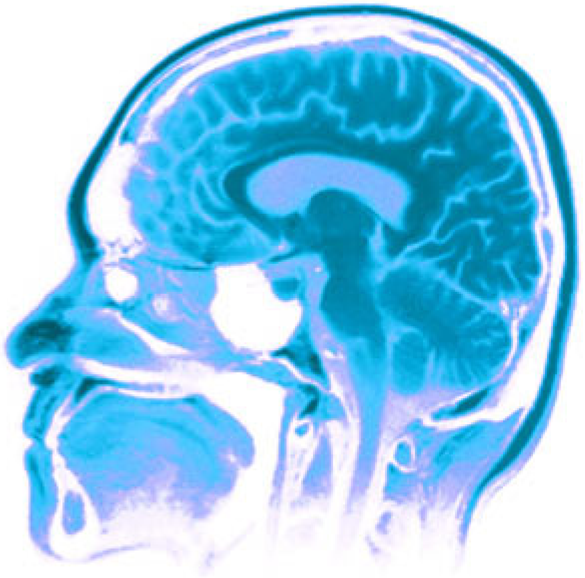
a) more recently the upper reference value for TSH is 2,5 mIU/ml

Thyroid hormone feedback

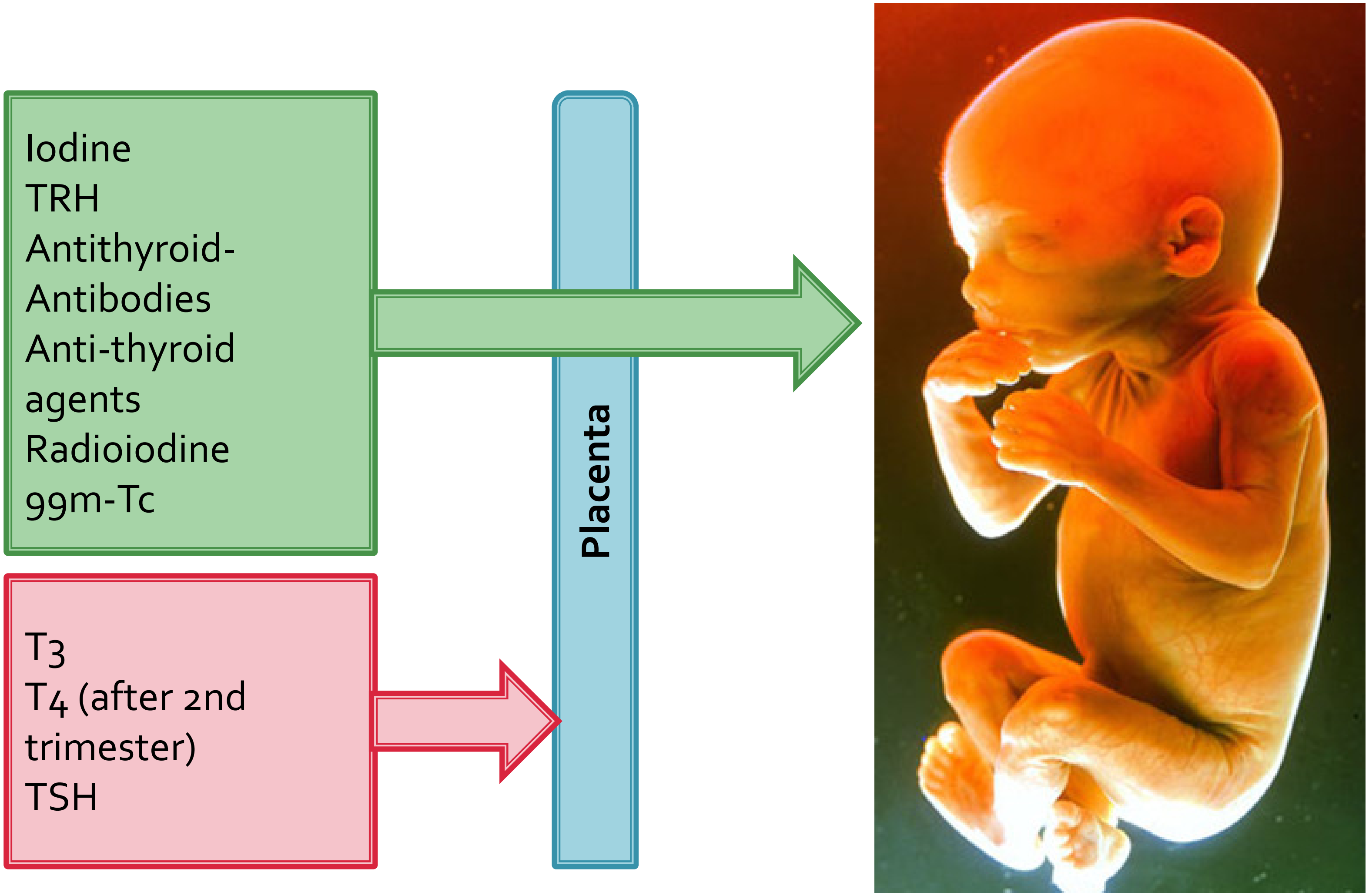


Thyroid hormone effects and target organs

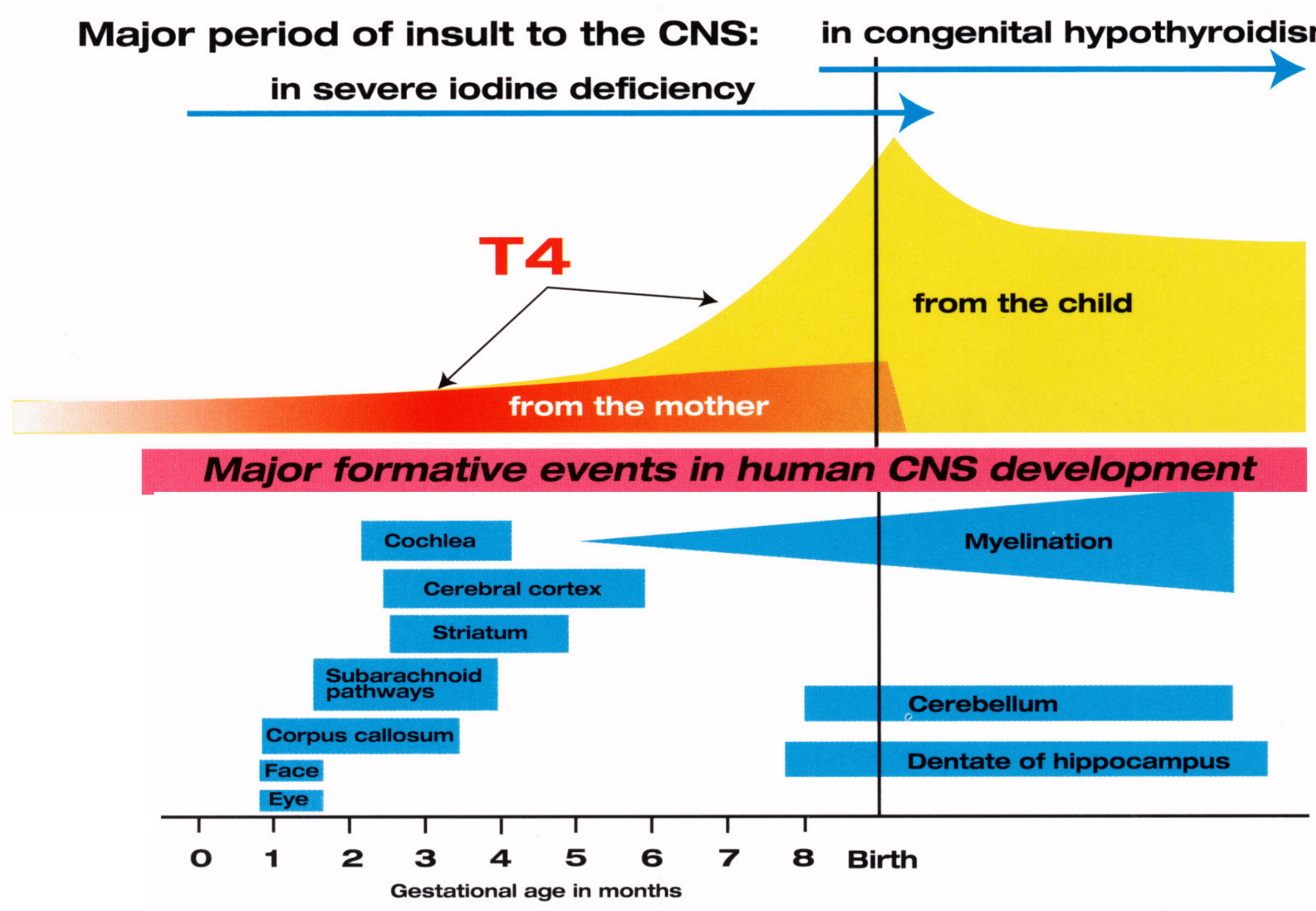
- Growth and development
  - crucial role in brain development during fetal life!
- Metabolism
- Catecholamine like effects



Human placental transfer



Thyroid hormones & CNS development



Neuropsychological development in children of women with hypothyreoidism

Test	Children of Women with Hypothyroidism (N=62)	Control Children (N=124)	Mean Difference†	P Value
Intelligence				
WISC-III full-scale IQ score	103±15	107±12	–4.1±2.1	0.06
WISC-III full-scale IQ score ≤85 (%)	15	5	3 (1–8)	0.08
Attention				
WISC-III freedom-from-distractibility score	98±13	102±13	−3±2	0.08
Continuous Performance Test score >8 (%)‡	37	19	3 (1–5)	0.01
Language				
Test of Language Development score				
Word articulation	10.1±2.5	10.2±2.4	−0.2±0.4	0.80
Word discrimination	10.5±2.9	11.4±2.4	−0.9±0.4	0.04
WISC-III verbal IQ score	103±16	107±16	−4.2±2.2	0.06
Reading ability and school performance				
PIAT-R reading-recognition score	96±14	100±16	−3.8±2.5	0.14
PIAT-R reading-comprehension score	98±17	101±17	−3.0±2.6	0.20
School difficulties and learning problems (%)‡	23	11	2 (1–6)	0.06
Repeated a grade (%)‡	8	4	2 (0.6–7)	0.40
Visual–motor performance				
Score on Developmental Test of Visual–Motor Integration	96±13	97±11	−1±2	0.40
WISC-III performance IQ score	101±16	105±13	−4±2	0.08
Pegboard-test score				
Dominant hand‡	86±16	83±15	3±2	0.10
Nondominant hand‡	94±22	89±16	5±3	0.10

Haddow et al., NEJM 1999

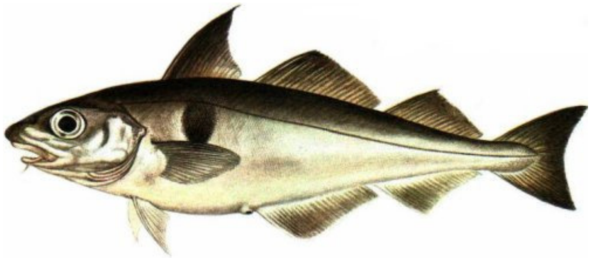
Iodine requirements

	iodine (µg/d)
Baby < 4 months	40
Baby 4-12 months	80
Children 1-3 years	100
Children 4-6 years	120
Children 7-9 years	140
Children 10-12 years	180
13-50 years	200
>51 years	180
Pregnant woman	230
Lactating woman	260

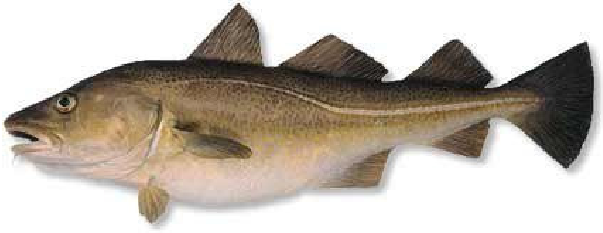
Deutsche Gesellschaft für Ernährung

Iodine in food

Plaice: 250 µg/100g



Haddock: 250 µg/100g



Cod: 120 µg/100g

Iodine requirements in pregnancy

- Increased maternal metabolism
- Increased distributional volume
- Increased renal excretion
- Higher TBG and albumin binding of T3 and T4
- Higher TSH secretion
- Higher T3 and T4 production but also higher binding

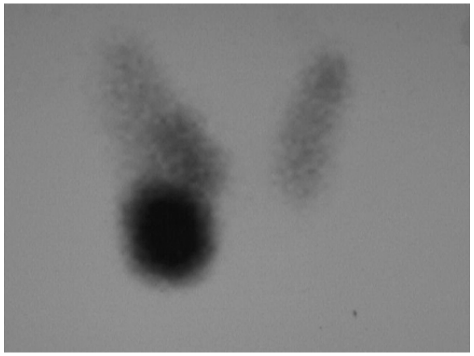
- → pregnancy & lactation:

  100 - 150µg/d supplementation

Arbeitskreis Jodmangel
American Thyroid Society, 2006

Are there any risk of iodine supplementation?

- Induced hyperthyreosis in case of autonomously functioning thyroid nodules



- Induced hypothyreoidism in the fetus (Wolff-Chaikoff phenomenon)

But not at common (100-250µg/d) doses,
„safe“ up to 500µ/d (WHO)!

Overdosing of iodine

- Burger with pig thyroid glands
- Iodine solution vaginal flushing
- Excessive ingestation of algae

- Avoid lack and excess of iodine in pregnancy!

Hypothyreoidism

- most common primary causes:
  - autoimmune (Hashimoto)
  - after radioiodine treatment

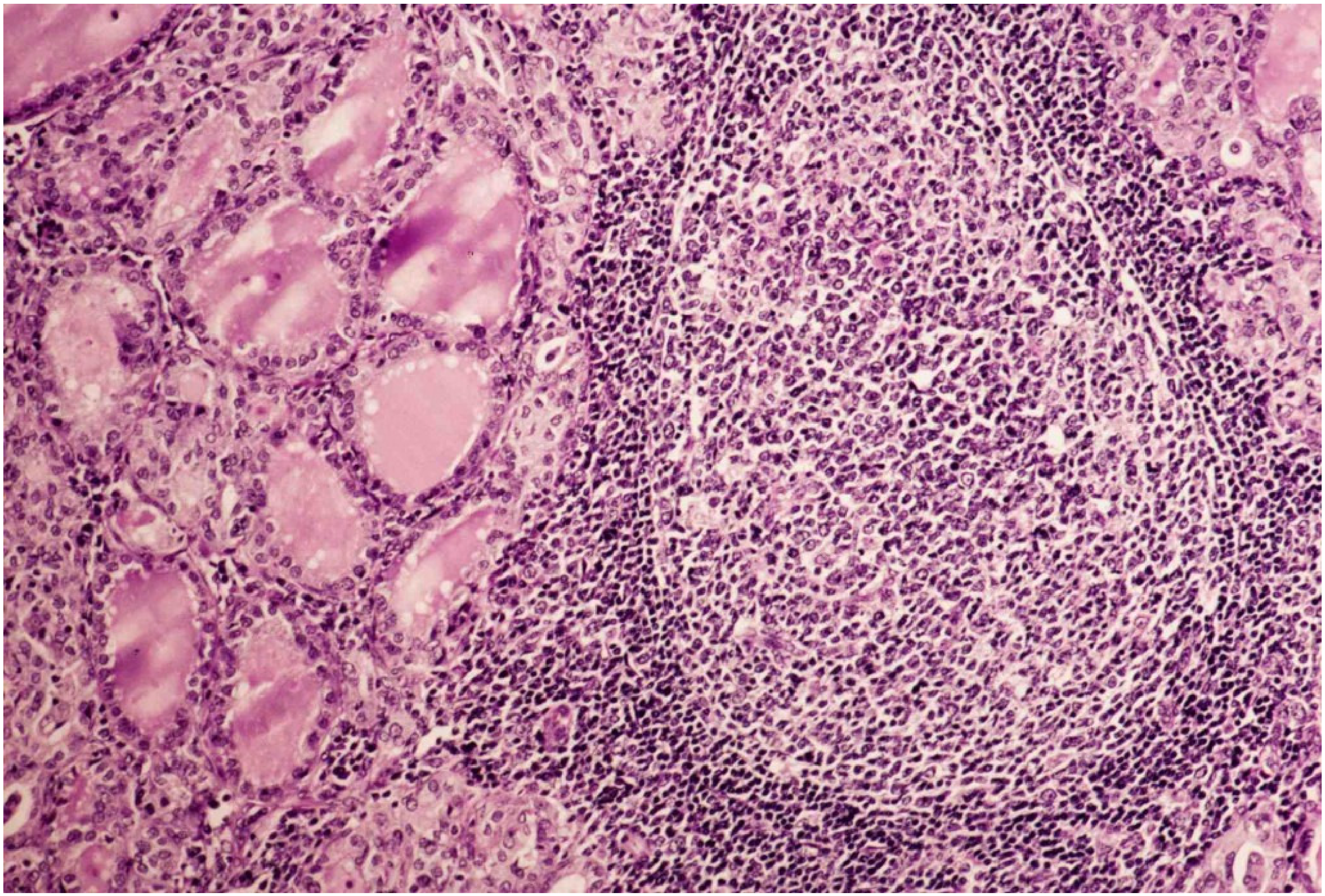
- Prevalence overall: 2-4%
- Prevalence women (age 18-40): 0,5-0,7%

- Subclinical hypothyroidism: TSH ↑ fT4↔
- Hypothyreoidism: TSH ↑ fT4↓

Autoimmune Hypothyreoidism

- women:men = 5-10:1
- common endocrine disease at reproductive age (prevalence 5-10%)
- Enlarged, non-tender gland
- T cells recognize the patient’s own thyroid antigens as foreign. The T cells (cytotoxic) stimulate B cells to make anti-thyroid antibodies (*TPO & TG*), which block thyroid receptors
- Initially hyperthyreosis, then hypothyreosis
- Progressive, chronic disease

Hashimoto disease



Hypothyreoidism and subfertility

- TRH ↑ → PRL ↑
- → Pulsatile GnRH release ↓
- → LH release ↓
- → Corpus luteum deficiency, irregular cycle

Prevalence of subclinical hypothyroidism in infertile women

Table 3 Prevalence of subclinical hypothyroidism in infertile women.

Study	Study design	Prevalence of SCH in patients (% [*n*/total])	Prevalence of SCH in controls	Definition of SCH
Bohnet *et al.* (1981)[80]	Prospective	11% (20/185)	No controls	Basal TSH >3 mIU/l or peak TSH >15 mIU/l[d]
Gerhard *et al.* (1991)[35]	Prospective	43% (80/185)[a]	No controls	Peak TSH >20 mIU/l[d]
Shalev *et al.* (1994)[81]	Retrospective	0.7% (3/444)	No controls	Basal TSH >4.5 mIU/l
Arojoki *et al.* (2000)[82]	Retrospective	1.3% (4/299)	2–3%[b]	Basal TSH >5.5 mIU/l
Grassi *et al.* (2001)[37]	Prospective	4.6% (6/129)	No controls	Basal TSH >4.5 mIU/l
Poppe *et al.* (2002)[31]	Prospective	0.9% (4/438)	<1%[c]	Basal TSH >4.2 mIU/l
Raber *et al.* (2003)[83]	Prospective	34.0% (96/283)	No controls	Basal TSH >4 mIU/l or peak TSH >15 mIU/l[d]
Abalovich *et al.* (2007)[33]	Retrospective	10.2% (25/244)	1.9%[c]	Basal TSH >5 mIU/l

[a]1/185 (0.5%) patients had a basal serum TSH >6 mIU/l. [b]Prevalence in the Finnish population. [c]Fertile women. [d]Peak serum TSH after thyrotropin-releasing hormone stimulation test. Abbreviation: SCH, subclinical hypothyroidism.

Poppe et al., 2008

Risk of infertility associated with thyroid autoimmune disorder

Table 1 Studies on the risk of infertility associated with thyroid autoimmune thyroid disorder.

Study and country	Thyroid antibodies measured	Cause of infertility	Control	Number positive for thyroid antibody (*n*/total)		Relative risk (95% CI)	*P* value
				Patients	Controls		
Wilson *et al.* (1975),[25] UK	Microsomal and thyroglobulin	OD	Age-matched, postpartum	8/77	11/77	0.7 (0.3–1.9)	NS
Roussev *et al.* (1996),[26] US	Microsomal and thyroglobulin	Idiopathic, OD, endometriosis	Healthy, nonpregnant	5/63	0/15	1.2 (0.1–11)	NS
Geva *et al.* (1997),[27] Israel	Microsomal and thyroglobulin	Idiopathic, tubal disorders	Age-matched, healthy, nulligravidae	15/80	2/40	3.8 (0.8–17.3)	NS
Kutteh *et al.* (1999),[28] US	Peroxidase and thyroglobulin	Idiopathic, OD, tubal disorders, endometriosis	Reproductive age, parous	132/688	29/200	1.3 (0.9–2.1)	NS
Kaider *et al.* (1999),[29] US	Peroxidase and thyroglobulin	Idiopathic, OD, endometriosis	Fertile	51/167	16/109	2.1 (1.1–3.9)	0.02
Reimand *et al.* (2001),[30] Estonia	Microsomal	Idiopathic, OD, endometriosis	Unselected population	2/108	15/392	0.5 (0.1–2.2)	NS
Poppe *et al.* (2002),[31] Belgium	Peroxidase	All causes	Age-matched, fertile	61/438	8/100	1.7 (0.9–3.5)	NS
Janssen *et al.* (2004),[32] Germany	Peroxidase and thyroglobulin	OD (PCOS)	Age-matched, no PCOS	47/175	14/168	3.2 (1.9–5.6)	<0.0001
Abalovich *et al.* (2007),[33] Argentina	Peroxidase	All causes	Age-matched, fertile	62/244	10/69	1.8 (1.0–3.2)	NS
Petta *et al.* (2007),[34] Brazil	Peroxidase and thyroglobulin	Endometriosis	Fertile, no endometriosis	13/148	25/158	0.5 (0.3–1.0)	NS

Abbreviations: NS, not significant; OD, ovulatory dysfunction; PCOS, polycystic ovary syndrome.

Poppe et al., 2008

Thyroid autoimmunity & miscarriage

Case-control studies

Table 1 Meta-analysis of case–control studies on the association between miscarriage and the presence of antithyroid autoantibodies.

Reference	Patients No. of Ab +ve (%)	Controls No. of Ab +ve (%)	Odds ratio	95% CI
Pratt *et al.* (8)	≥3 abortions 14/45 (31 %)	Blood donors 19/100 (19%)	1.93	0.86–3.37
Bussen & Steck (9)	≥3 abortions 8/22 (36 %)	No abortions 3/44 (7%)	7.81	1.82–33.6
Bussen & Steck (10)	≥3 abortions 11/28 (39 %)	No abortions 2/28 (7%)	8.41	1.70–42.8
Esplin *et al.* (11)	≥3 abortions 22/74 (29%)	≥3 pregnancies 28/75 (37%)	0.71	0.50–1.01
Kutteh *et al.* (12)	≥2 abortions 158/700 (23%)	Blood donors 29/200 (15%)	1.72	1.12–2.65
Mecacci *et al.* (13)	≥2 abortions or ≥1 fetal death 20/51 (39%)	Unknown 10/69 (15%)	3.81	1.95–9.14
Dendrinos *et al.* (14)	≥3 abortions 11/30 (37 %)	≥1 pregnancies 2/15 (13%)	3.76	0.71–19.87
Bagis *et al.* (15)	≥1 abortion 54/162 (33%)	No abortions 54/714 (8%)	5.98	3.98–9.38
Total	298/1112 (27 %)	147/1245 (12%)	2.73	2.20–3.40

heightened autoimmune state affecting the fetal allograft, of which thyroid antibodies are just a marker?

Prummel et al., 2004

Thyroid autoimmunity & miscarriage

longitudinal studies

Table 2 Meta-analysis of prospective studies analyzing abortion rates among women with thyroid autoantibodies (Ab +ve) versus women without antibodies (Ab −ve).

Reference	Abortion rate in Ab +ve women	Abortion rate in Ab −ve women	Odds ratio	95% CI
Stagnaro-Green *et al.* (16)	17/100 (17%)	33/392 (8%)	2.23	1.19–4.20
Glinoer *et al.* (17)	6/45 (13%)	20/603 (3%)	4.48	1.70–11.81
Lejeune *et al.* (18)	5/23 (22%)	16/340 (5%)	5.63	1.82–17.1
Pratt *et al.* (19)	8/13 (62%)	12/42 (29%)	10.0	2.20–46.5
Singh *et al.* (20)	28/87 (32%)	49/301 (16%)	2.44	1.42–4.20
Iijama *et al.* (21)	13/125 (10%)	52/951 (5%)	2.01	1.06–3.80
Kim *et al.* (22)	4/10 (40%)	4/35 (11%)	5.17	2.72–26.54
Muller *et al.* (23)	4/12 (33%)	8/42 (19%)	2.13	0.51–8.87
Rushworth *et al.* (24)	10/24 (42%)	30/77 (39%)	1.12	0.44–2.84
Poppe *et al.* (25)	9/17 (53%)	20/87 (23%)	3.77	1.34–10.63
Total	104/456 (23%)	336/2957 (11%)	2.30	1.80–2.95

But:

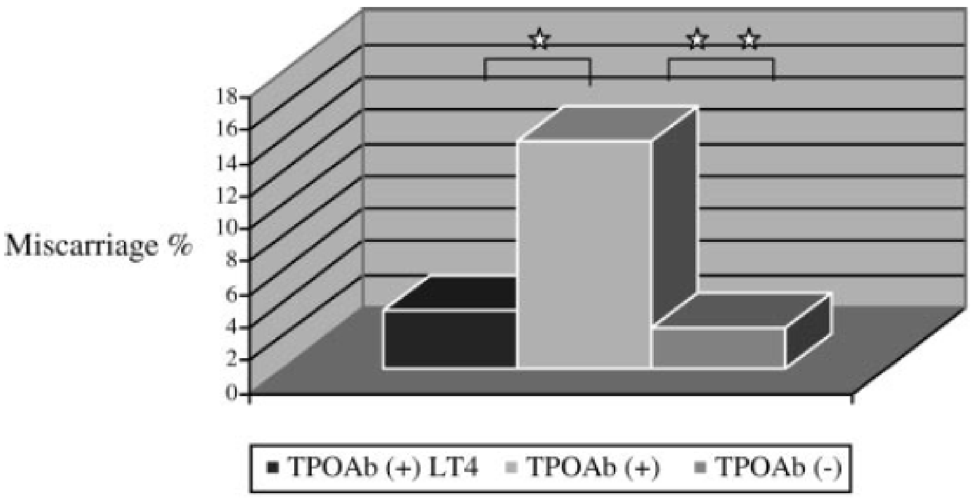
Ab+ women on average older (+0.7 years, p<0.01)

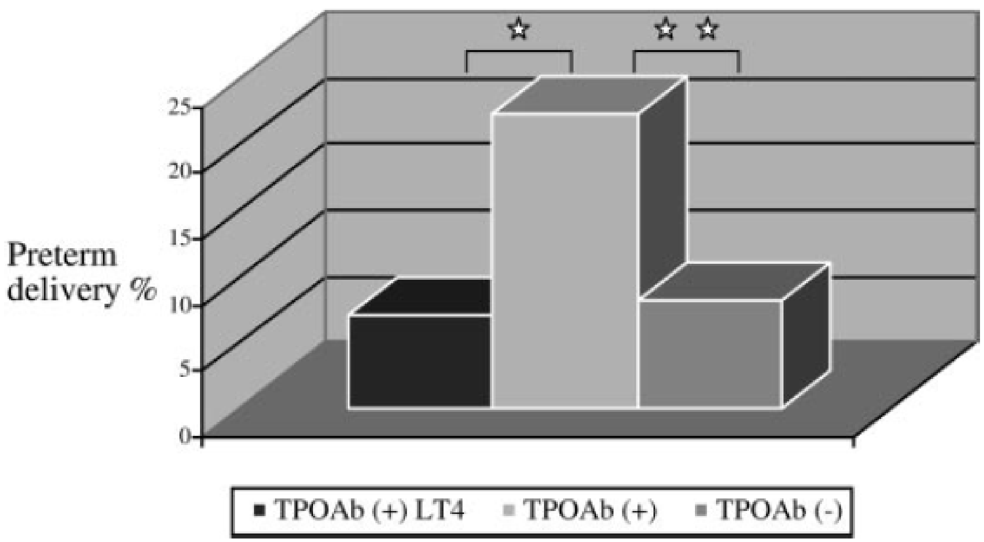
Ab+ women more often show mild thyroid failure (+0.7 IU/L TSH, p<0.01)

→ RCTs needed!

Prummel et al., 2004

LT4 supplementation in pregnancy in TPO+ patients





Non-randomized, prospective, interventional study:

Group A (n=57) TPO+, treated with LT4
Group B (n=58) TPO+, not treated.
Group C (n=869) TPO- (control group)

Negro et al., JCEM 2006

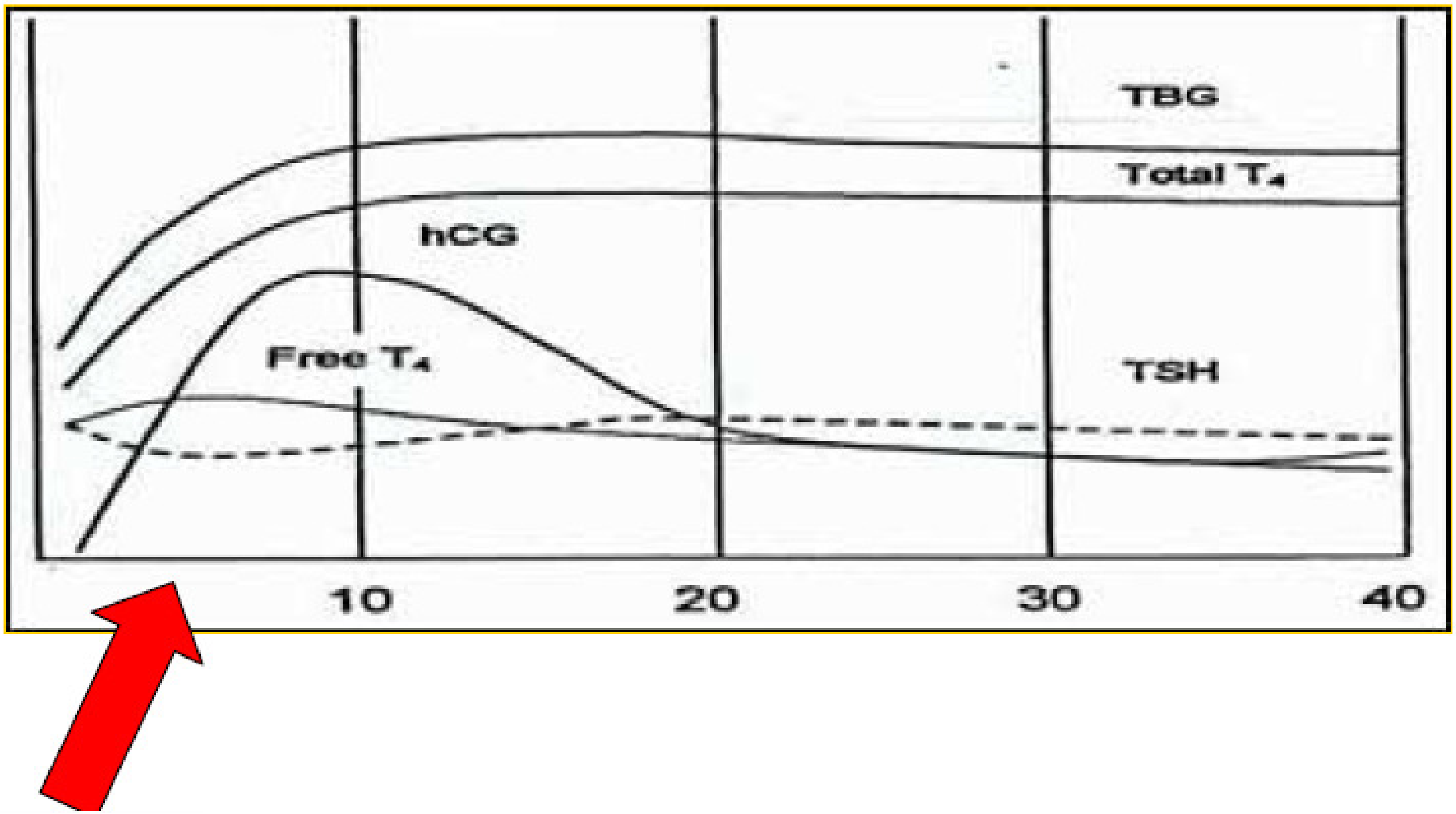
Hypothyreoidism & subfertility: treatment

- LT_4 supplementation (initiation typically 50µg/d)
- Aim: TSH 0.5-1.5 mIU/ml (1.0?)
  (TSH will normalize only after ~6 weeks!)

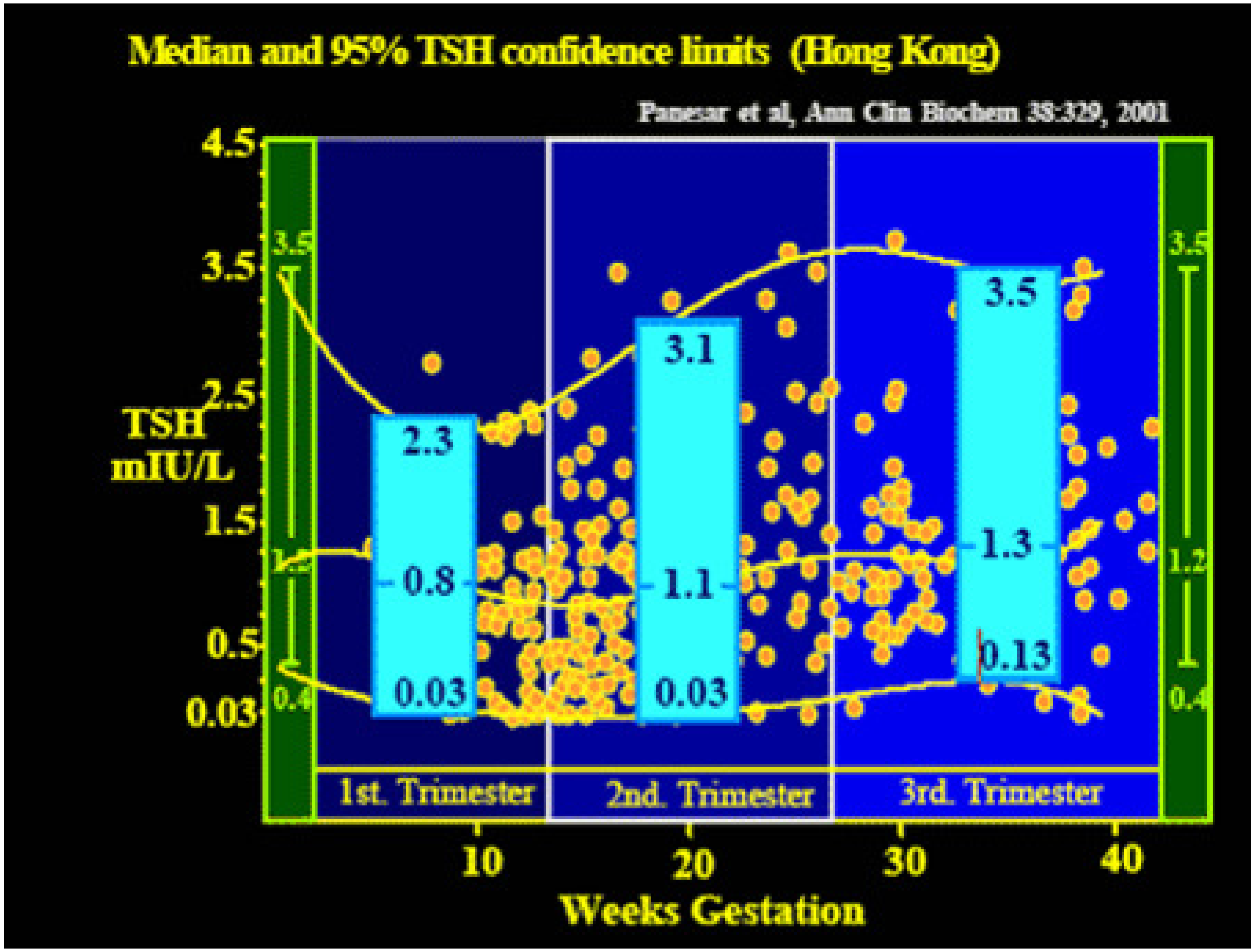
If pregnant: control TSH, fT_4, TPO-Ab at 2-3 monthly intervals

If pregnant: higher demand (30-50%) of LT_4 in the course of pregnancy, peak demand reached by 16th GW, do not forget iodine, even in Hashimoto

Thyroid gland & pregnancy



TSH in pregnancy



Panesar et al., 2001

Thyroid gland & pregnancy

- Thyreotropic effect of hCG → transient mild hyperthyreosis -- thyreotoxicosis (twins, molar pregs)
- TSH reference values overall lower (0.02–2.15 mU/l vs. 0,4–4,0 mU/l)
- no generally accepted upper TSH limit
- Recommendation: TSH in 1st trimester pregnancy <2.5 mIU/l
- Beware of false diagnosis of subclinical hyperthyreoidism during pregnancy!

Postpartum thyroid dysfunction

- Prevalence: 3–8% within 6 months pp

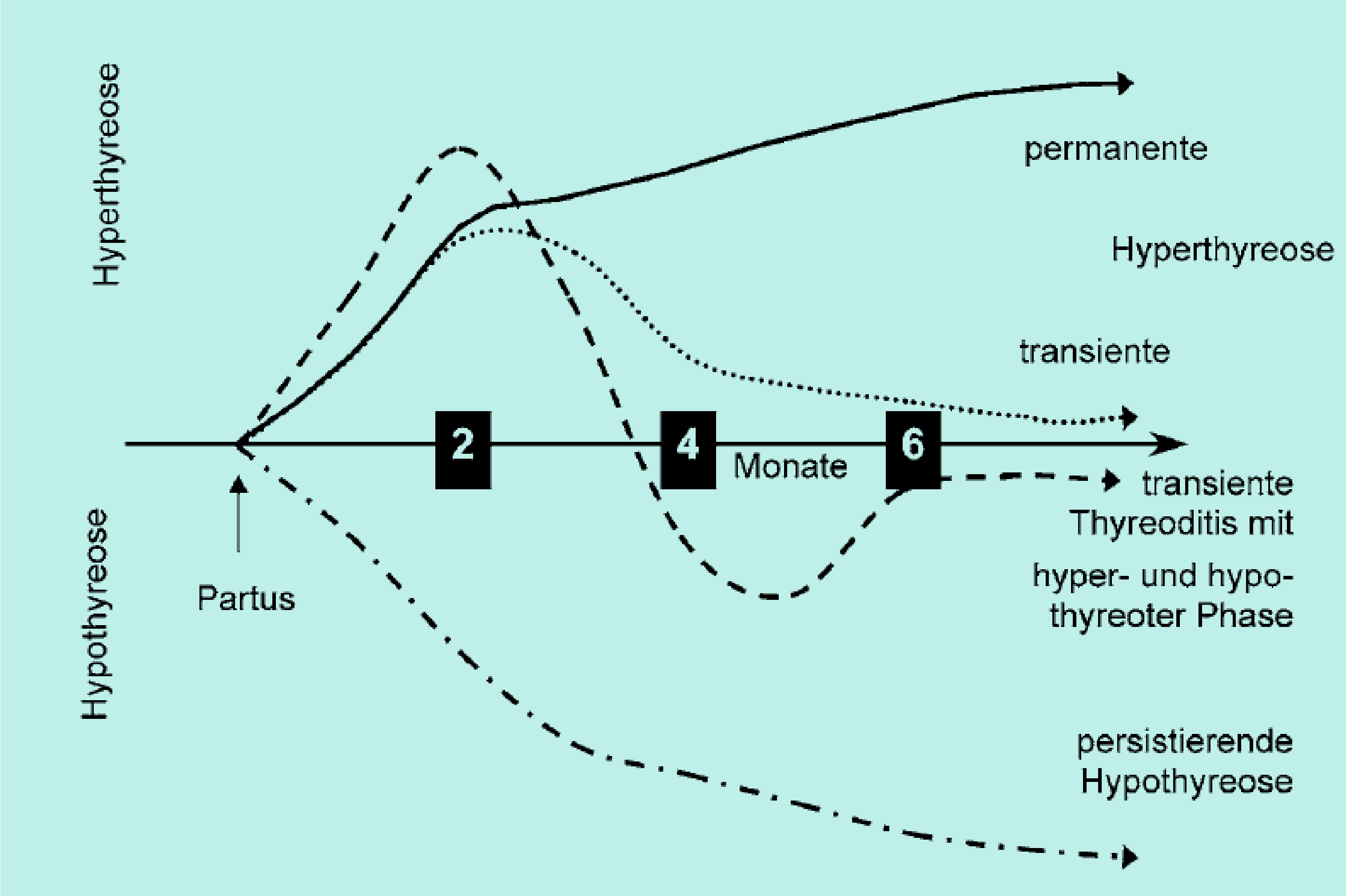
- TPO Ab+: risk 40-60%
- TPO Ab- : risk 1:10-1:100
- Increased risk in diabetes!

- Sonography: hypodense

- Painless!

- 80% remission within 1 year
- 30% manifest hypothyreoidism
- In creased recurrence in subsequent pregnancy

Postpartum thyroid dysfunction



Meng and Ziegler, 2003

Postpartum thyroid dysfunction treatment

- Hyperthyreoidism milder than in Basedow
- Monitoring at regular intervals
- Beta-blocker in case of hyperthyreoidism
- Antithyroid drugs useless
- LT_4 in case of hypothyreoidism

Hyperthyroidism (M. Basedow, Graves disease)

- Most frequently autoimmune cause (TSH-receptor Ab), rare: hCG induced or autonomous process
- TSH↓ (<0.02 mIU)   fT3 ↑   fT4 ↑ or ↔
- Typcially no effect on menstrual cycle

Treatment of M. Basedow

- Medical therapy
- Radioiodine therapy
- Operation (only after medical treatment)

Medical treatment of M. Basedow

	Initially [mg]	Continous daily [mg]
Thiamazol	**10–15**	**2.5–10**
Carbimazol	**15–20**	**5–15**
Propylthiouracil	**200–300**	**50–150**

Treatment of hyperthyreoidism in pregnancy and lactation

- No radioiodine!
- Thyreostatics in low doses
- 1st choice: Propycil®
- M. Basedow: immunomodulation of pregnancy → dose reduction often possible
- In severe cases: operation in 2nd trimester
- Aim of therapy:
  - Wellbeing of patient
  - Normal fetal development
  - Normal values of fT_3 and fT_4

Monitoring of hyperthyreoidism in pregnancy and lactation

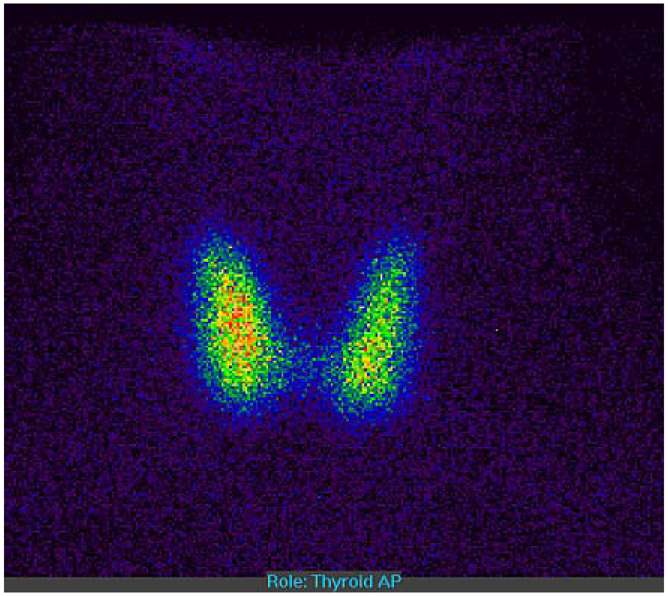
- fT_3, fT_4, TSH every 4-6 weeks
- Postpartum: every 3 months
- check TRAK in receptor Ab+

- Lactation: Propycil < 200-300mg/d
- Intake after breast feeding

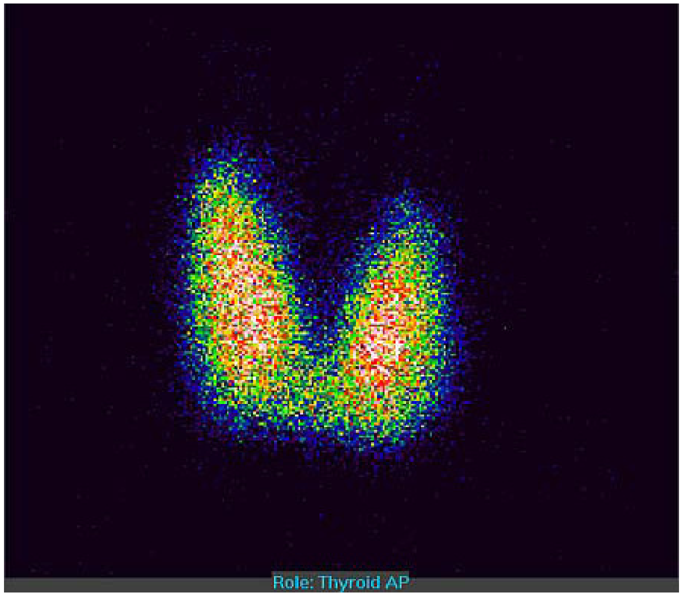
Hyperemesis gravidarum

- Potential danger of thyreotoxicosis!
- Always screen fT_4, TSH in hyperemesis patients!

Thyroid scintigraphy (99tm Tc)



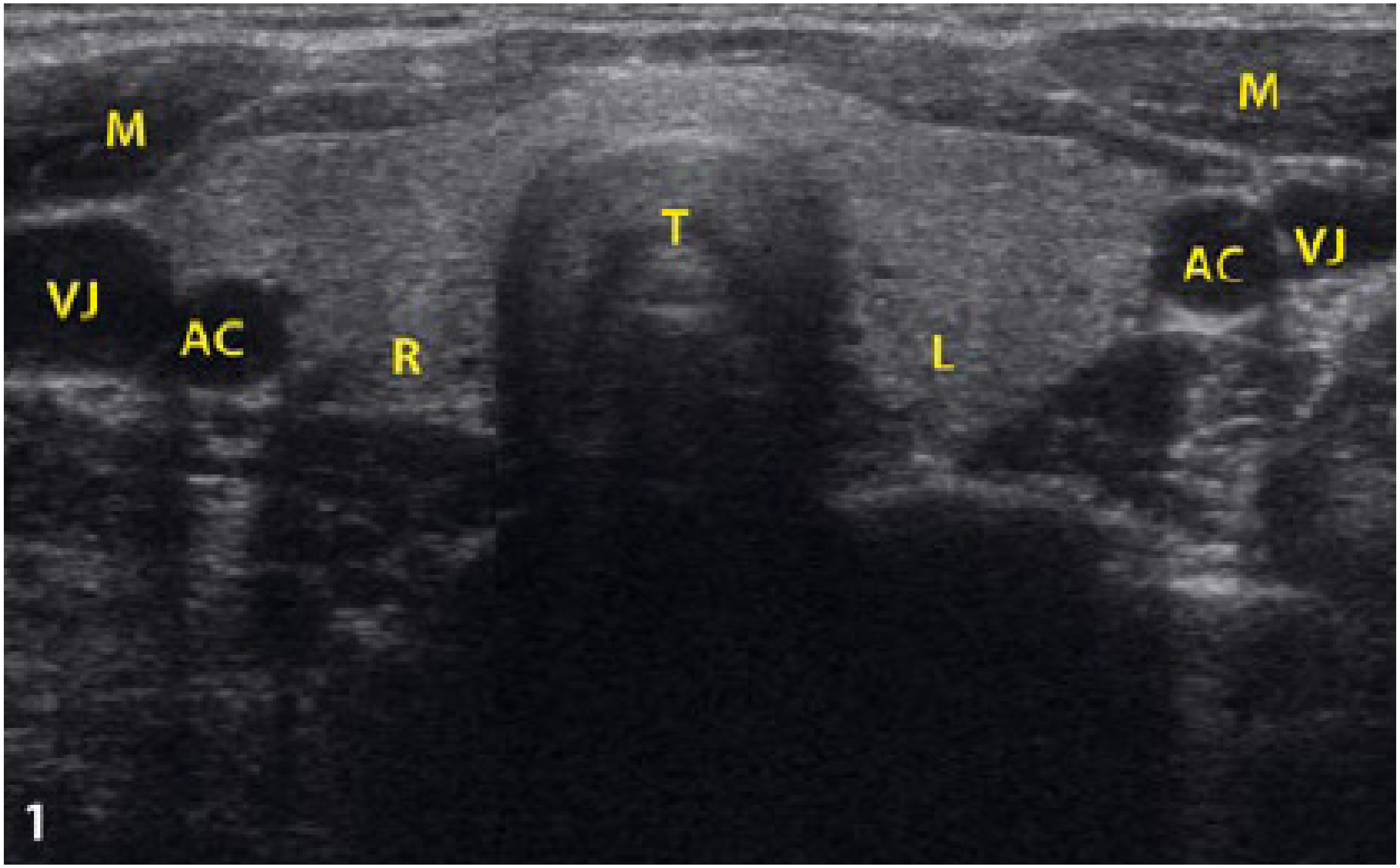
normal



hyperthyreoidism (M. Basedow)

Distinction between focal process - adenoma - vs. diffuse process (Basedow)
„Cold“ nodule: carcinoma? (risk ~10%)

Thyroid sonography



Courtesy of O. Janßen, Hamburg

Fine needle aspiration

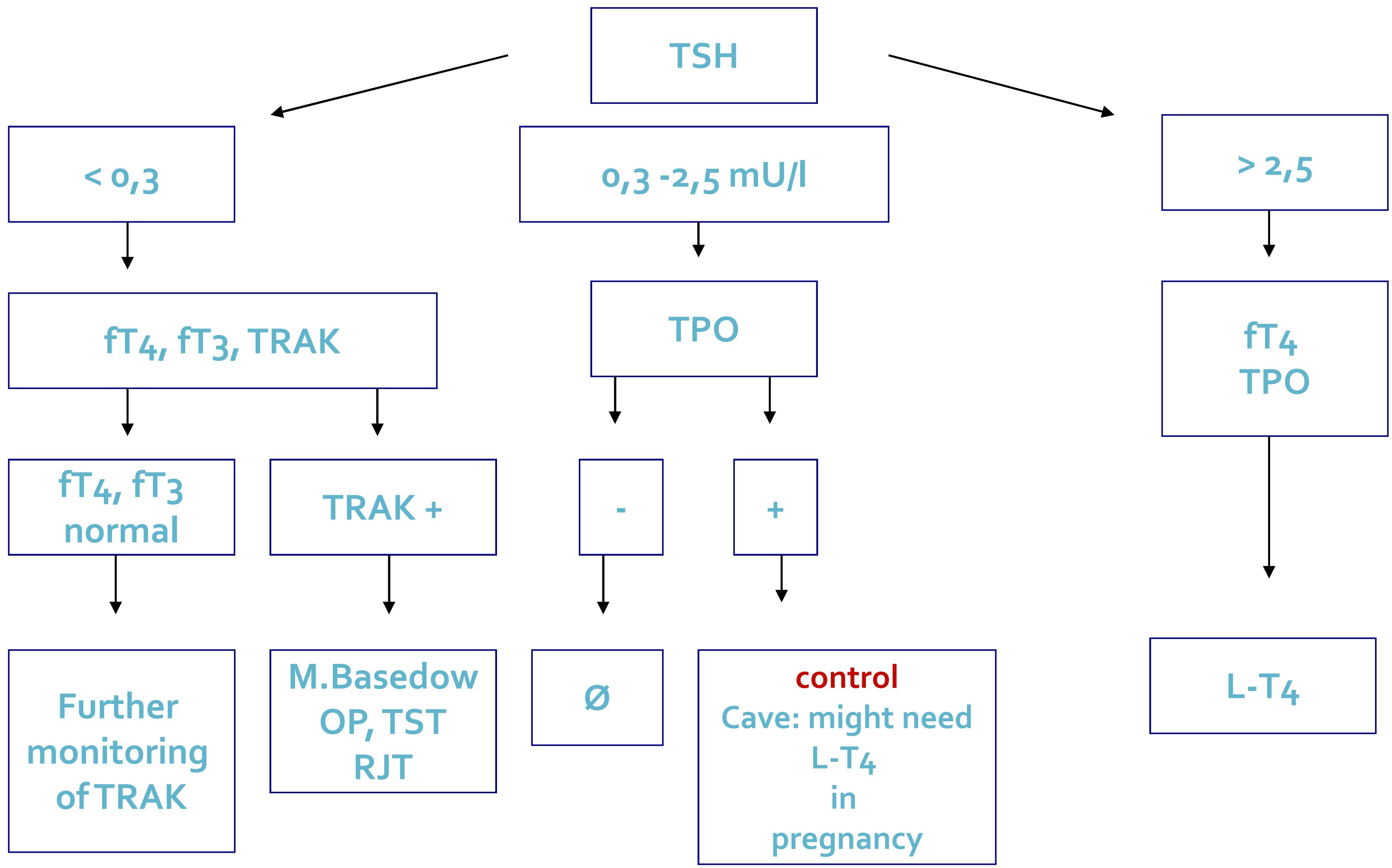
Courtesy of O. Janßen, Hamburg

Premature ovarian failure

- autoimmune etiology of POF
- frequent association with autoimmune thyroid diseases & Addison's disease described

- Implantation failure?
- Other?

Conclusion:
Simplified lab-analysis algorithm



Conclusion cont'd

1. Iodine supplementation in pregnancy 100-200µg/d
2. Routine screening of thyroid disorders in subfertile women, TSH <1-1.5 mU/l
3. Routine screening of thyroid disorders in 1st trimester
4. Increase LT4 dosage in pregnancy by 30-50%
5. Do not forget iodine in pregnancy even in TPO Ab+
6. Beware of post partum thyroid disorder in TPO Ab+ patients
7. Thyreostatic drugs and LT4 are no contraindication to breastfeeding

Thank you!

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