Schilddrüse und Schwangerschaft

ao.Univ.Prof.Dr. Michael Krebs

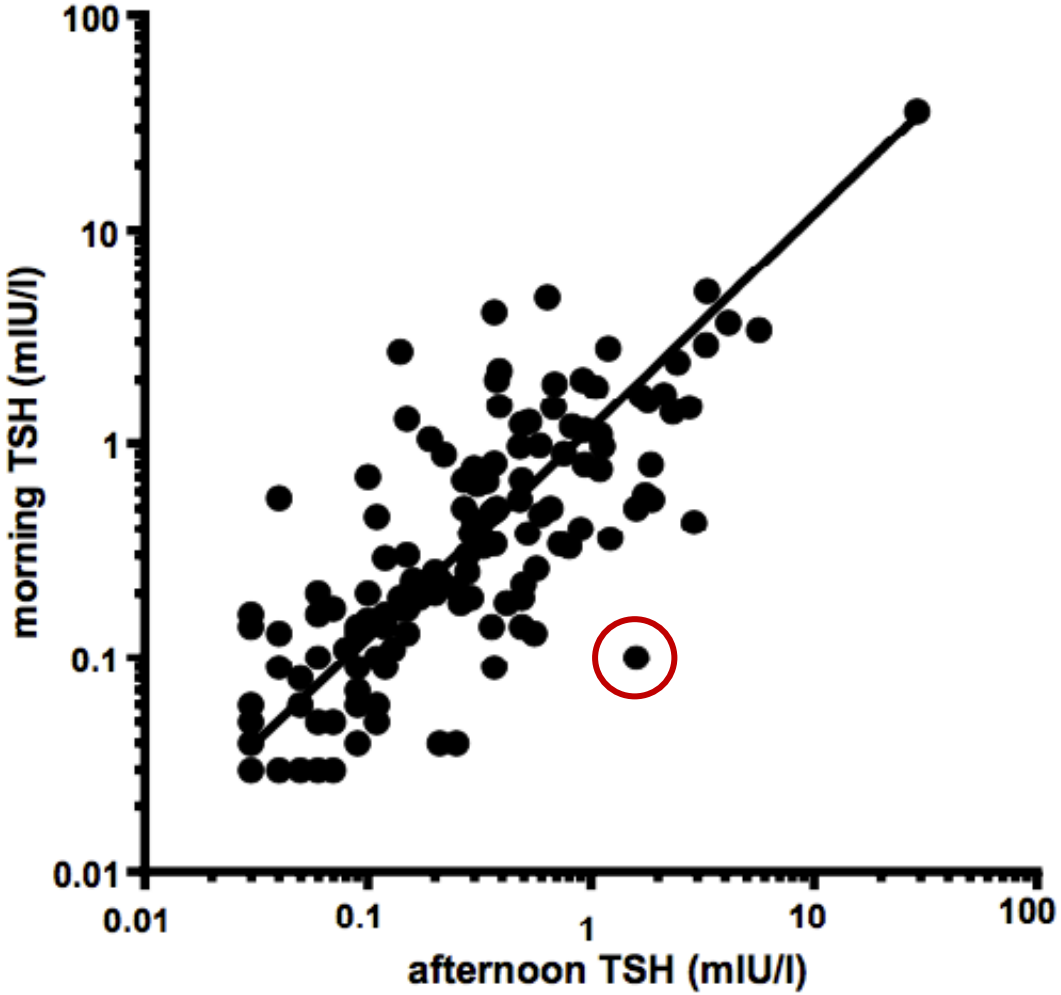
Klin. Abteilung für Endokrinologie und Stoffwechsel, Univ. Klinik für Innere Medizin III,

Med. Univ. Wien

TSH

Was ist „normal“

TSH – Tageszeit



Conte et al., J Endocrinol Invest 2018

TSH

Wer kennt die Werte ?

Normalwerte TSH **2014**

Erwachsene: 0.44 - 3.77 uU/ml
Graubereich: bis 0.1 bzw. 4.0 uU/ml

1.Trimenon: 0.1 - 2.5 uU/ml
2 Trimenon: 0.2 - 3.0 uU/ml
3 Trimenon: 0.3 – 3.5 uU/ml

Lazarus et al., Europ Thyroid Journal 2014

Leitline SD-Schwangerschaft 2014

Europäische SD Gesellschaft 2014

- Eine **latente Hypothyreose bei Frauen mit Kinderwunsch /Schwangerschaft sollte behandelt** werden.
- **„Reasonabe practice to maintain TSH < 2.5 mU/l especially when TPO+“**

Normalwerte TSH
(Labor AKH Wien; Oktober 2019)

Erwachsene: 0.27 - 4,2 uU/ml

1.Trimenon: 0.33 - 4.59 uU/ml
2 Trimenon: 0.35 - 4.1 uU/ml
3 Trimenon: 0.21 - 3.15 uU/ml

Was ist Normal in der Schwangerschaft ?

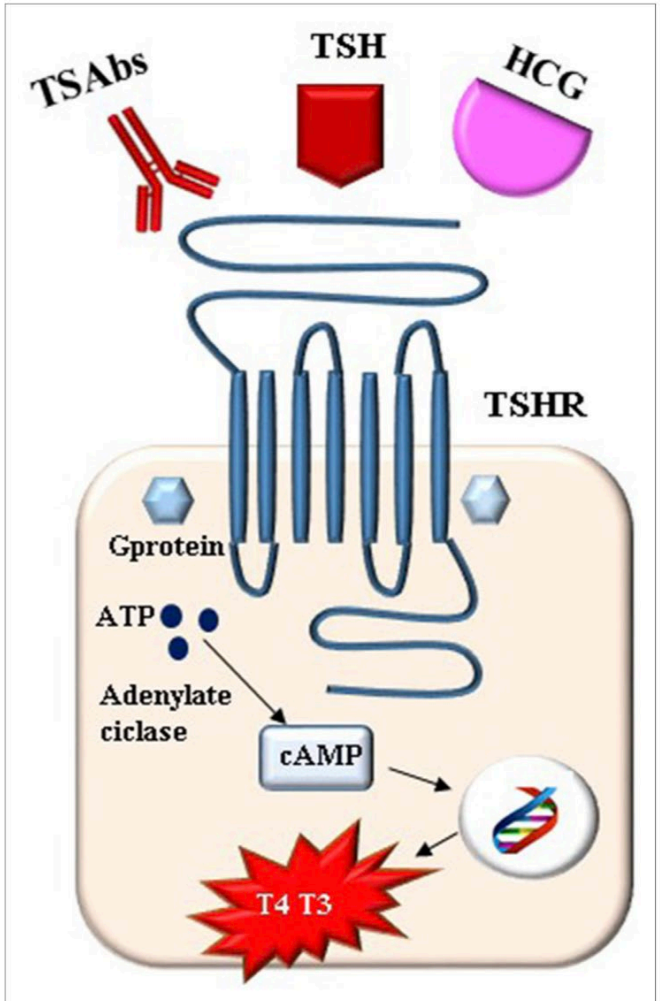
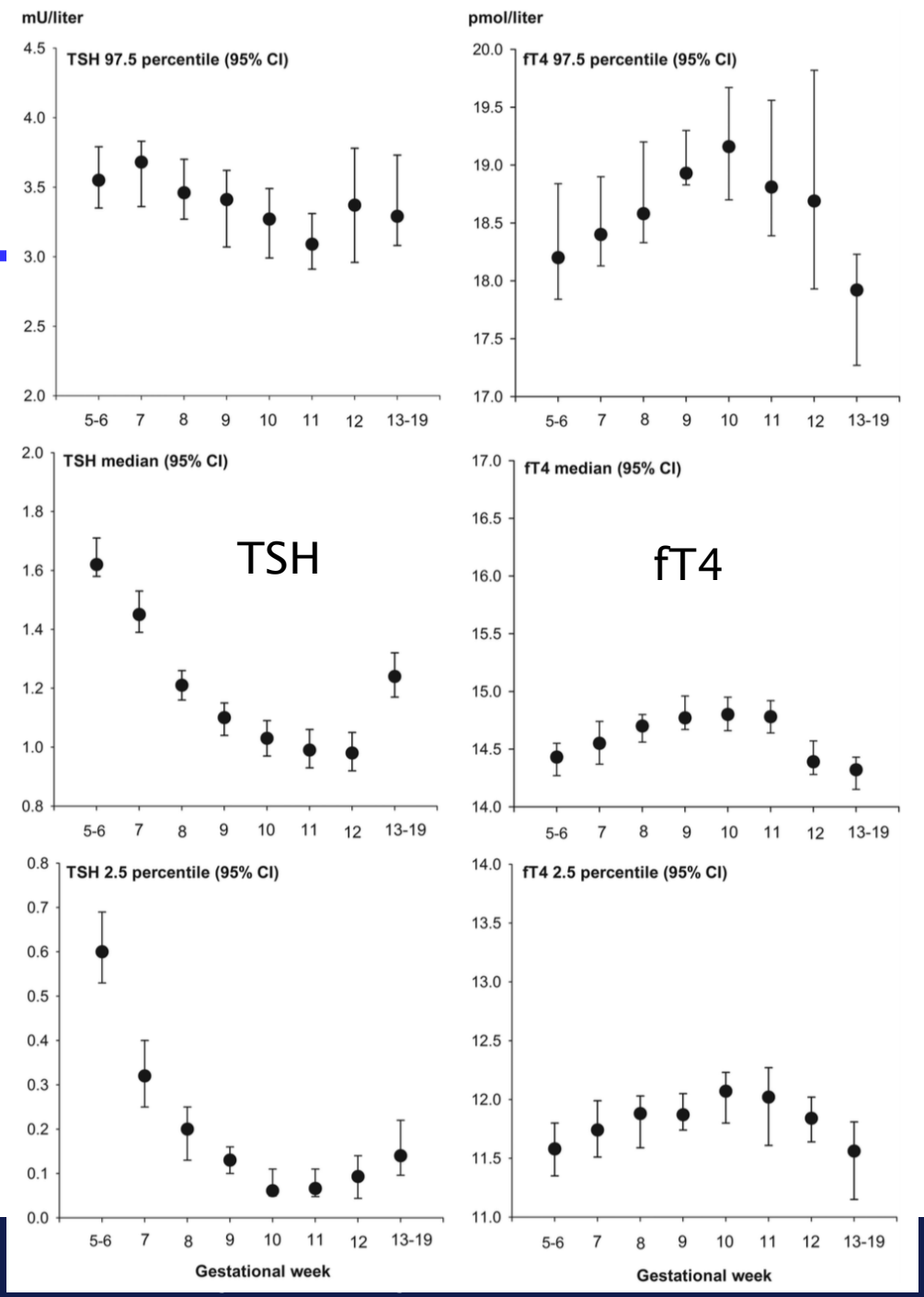


FIGURE 1 | The stimulation of TSH receptor (TSHR) in pregnancy.

Bucci et al., Frontiers in Endocrinology 2017

Normalwerte im **ersten Trimenon**

6671 schwangere Frauen in Dänemark

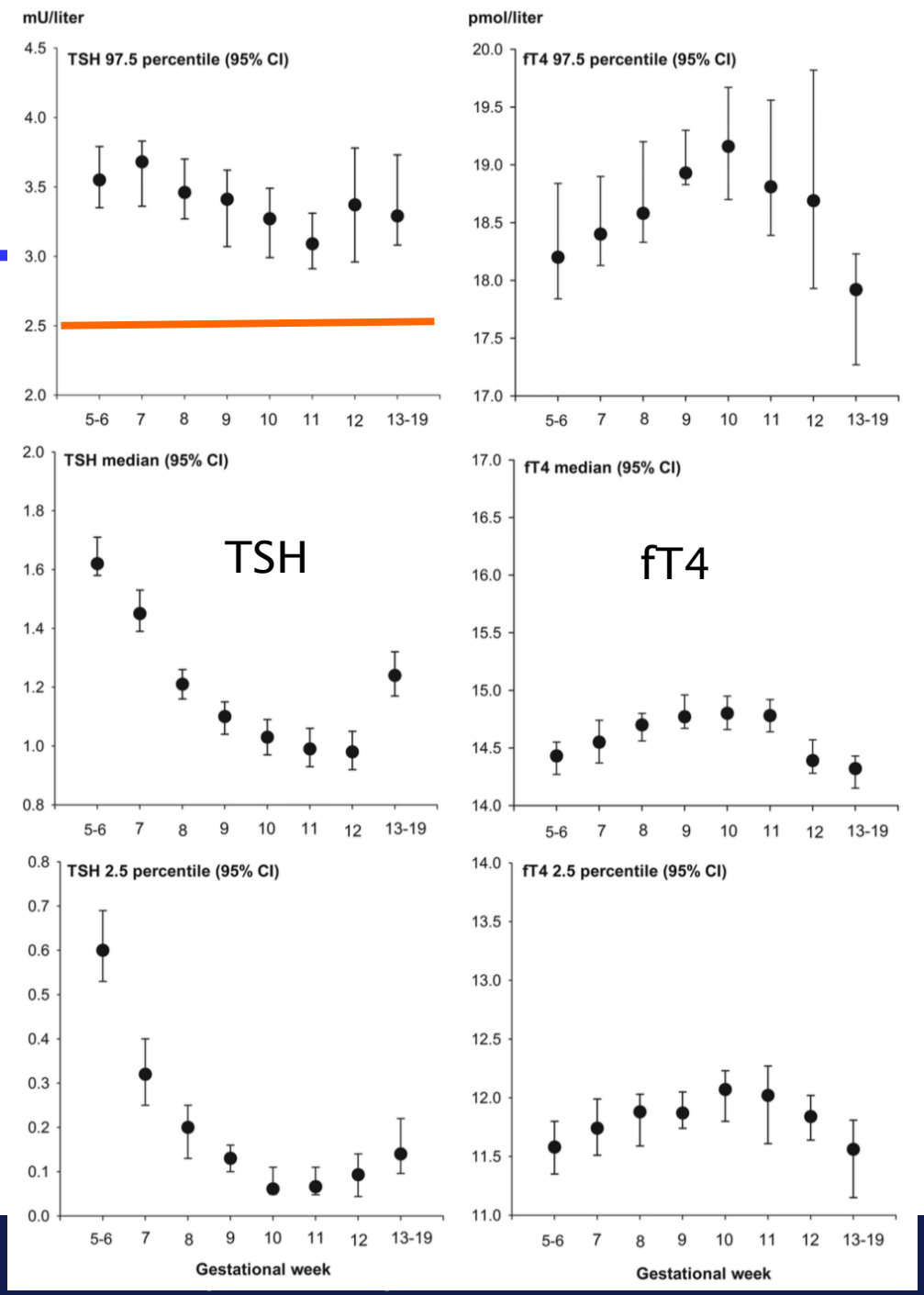


Normalwerte im **ersten Trimenon**

6671 schwangere Frauen in Dänemark

Bei TSH Grenzwert > 2.5 mU/l:

10 % der „gesunden“ Frauen hypothyroid



Lauerberg et al. JCEM 2016

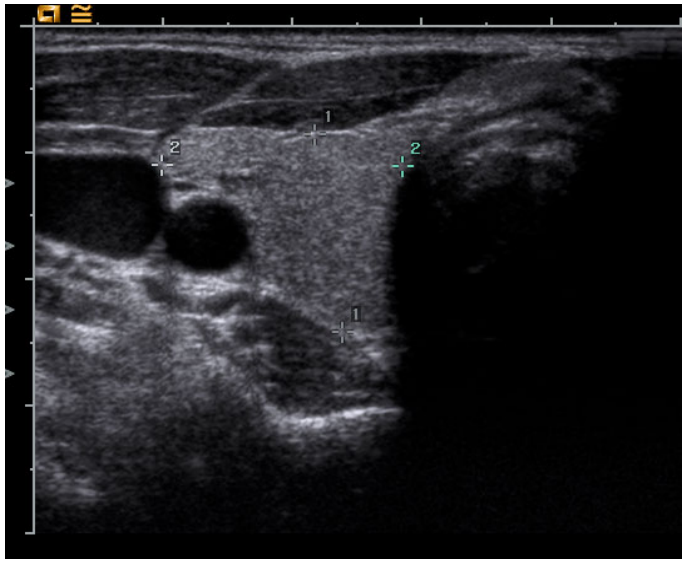
TSH

Normalwert als Therapieziel ?

„Normalität“ in Abhängigkeit von „nachgewiesener“ Begleiterkrankung ?

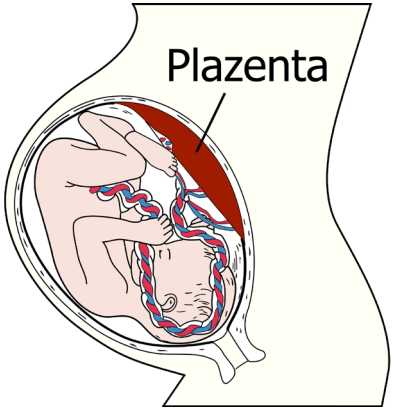
„Haschimoto“ in der Schwangerschaft

Normal:



TPO -

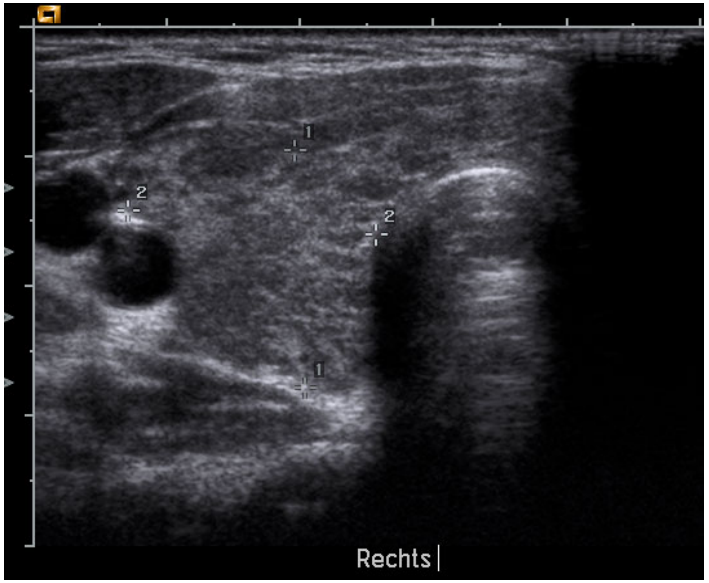
hCG



T4/T3

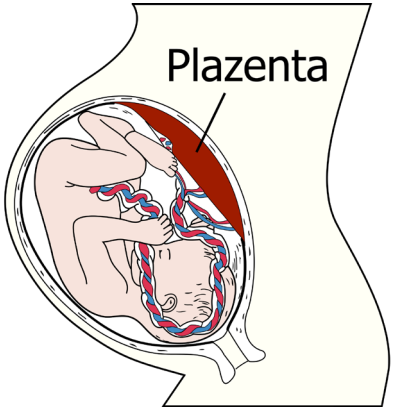
„Haschimoto“ in der Schwangerschaft

Normal:



TPO +

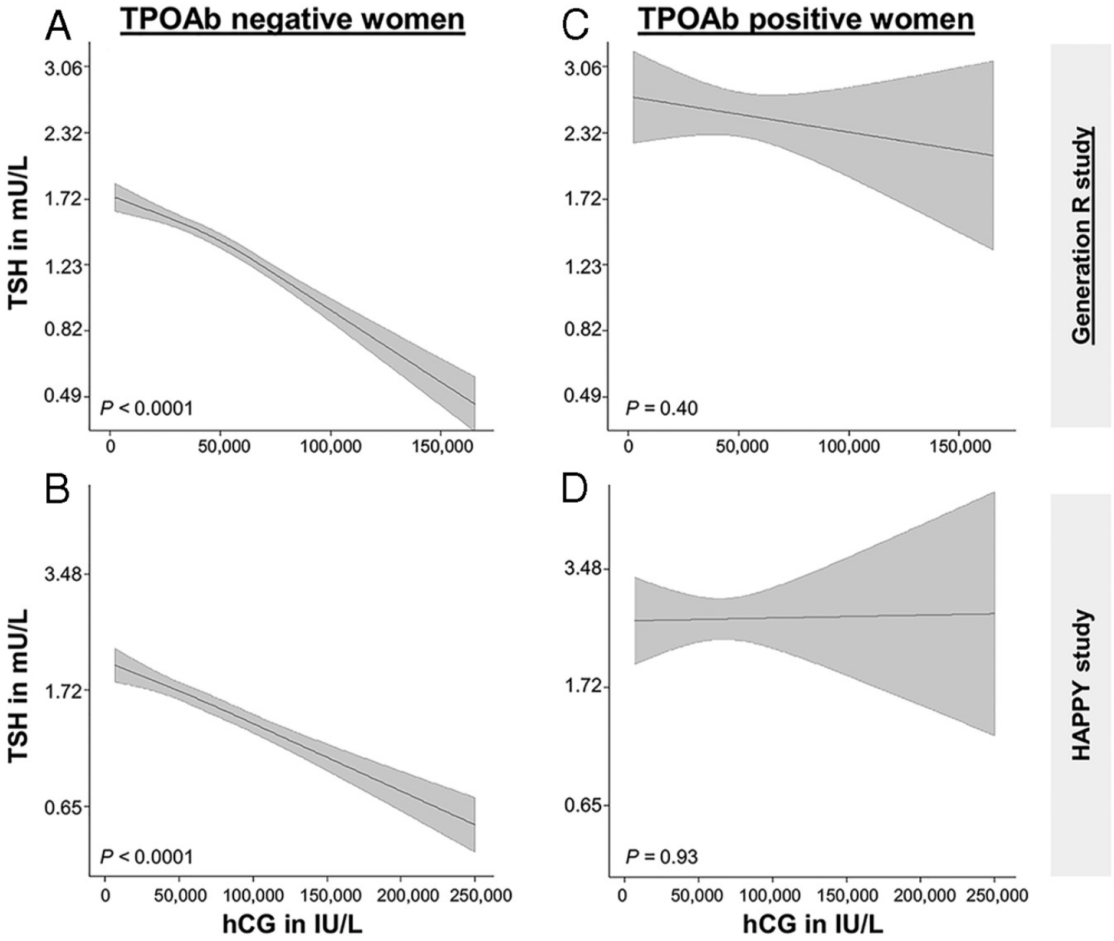
hCG



T4/T3

SD-Antikörper in der Schwangerschaft

TSH



hCG

Korevaar et al., JCEM 2016

Leitlinen SD-Schwangerschaft 2017

Prävalenz SD Antikörper: 2-17 %

Bei **AK-positiven Schwangeren** findet sich in 20 % ein TSH-Anstieg > 4 mU/l

Erhöhtes Risiko für Abortus und Frühgeburt

Recommendation 11: Euthyroid pregnant women who are TPOAb or TgAb positive should have measurement of serum TSH concentration performed at time of pregnancy confirmation and every 4 weeks through midpregnancy.

Alexander et al., Thyroid 2017

Leitlinen SD-Schwangerschaft 2017

ATA 2017

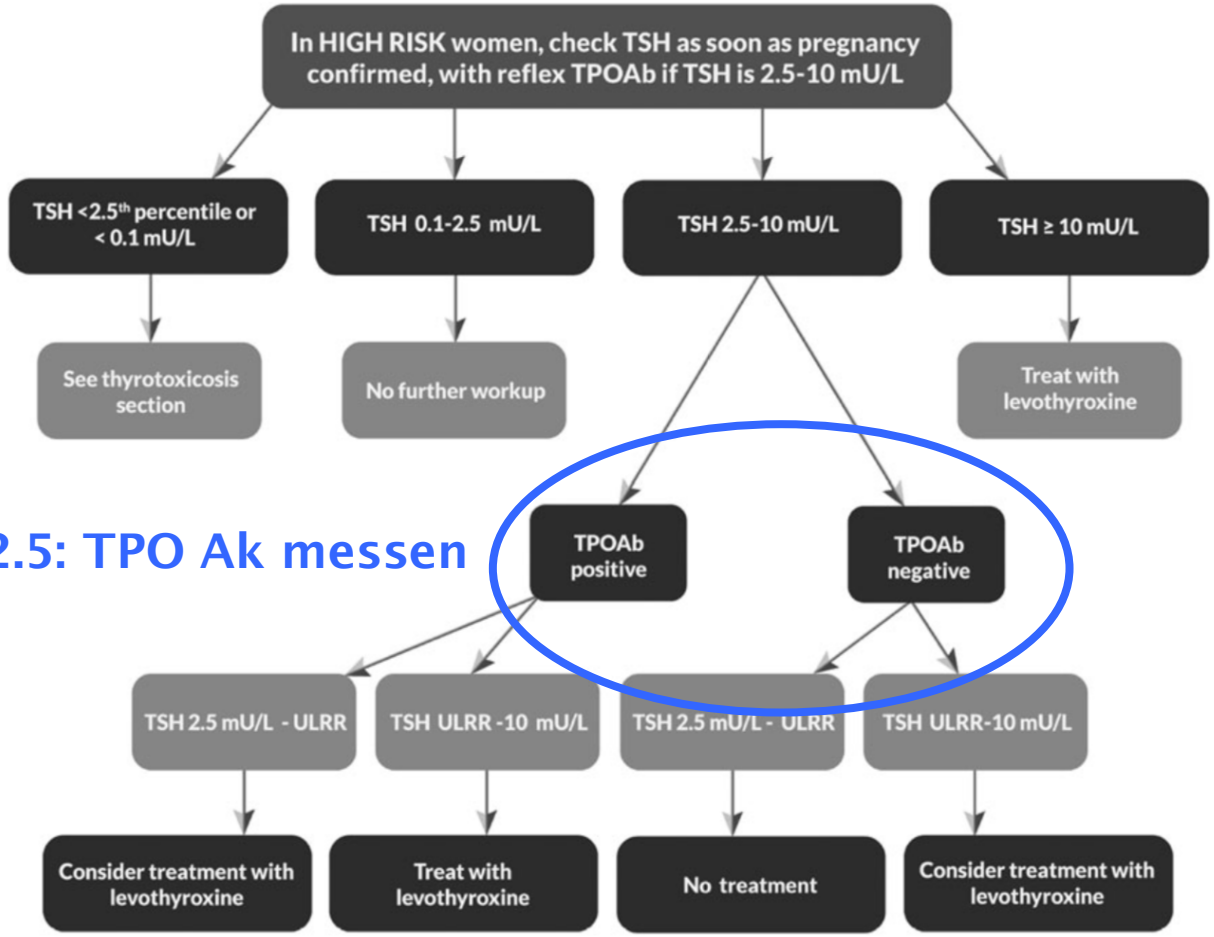
Reccomendation 1: When possible, **population-based trimester-specific reference ranges for serum TSH should be defined through assessment of local population data representative of a health care provider's practice**. Reference range determinations should only include pregnant women with no known thyroid disease, optimal iodine intake, and negative TPOAb status.

Falls nicht verfügbar:

TSH Normalwert:	oberer Normalwert	- 0.5 mU/L (**≈3.7 mU/l**)
Erstes Trimester	unterer Normalwert	- 0.4 mU/L

Alexander et al., Thyroid 2017

Leitline SD-Schwangerschaft 2017



R 28: TSH > 2.5: TPO Ak messen

FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.

Alexander et al., Thyroid 2017

Leitline SD-Schwangerschaft 2017

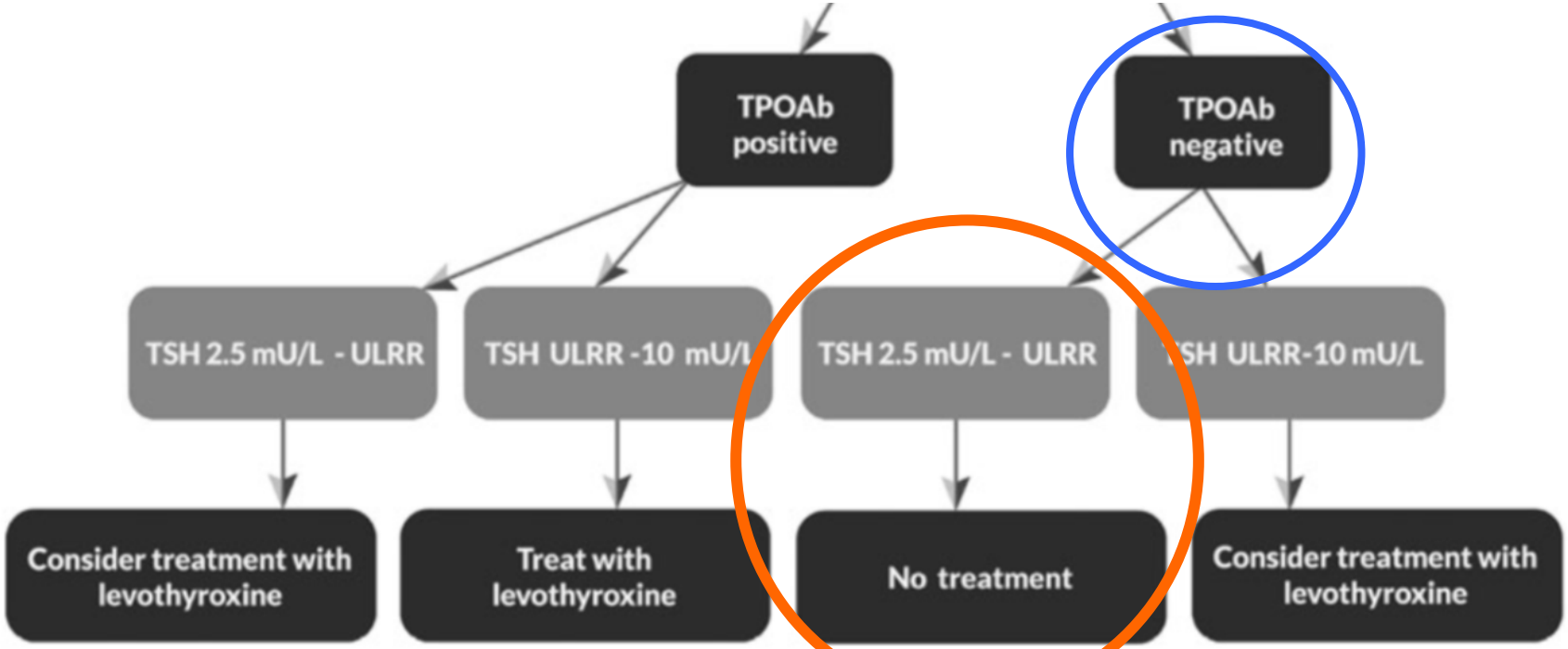


FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.

Alexander et al., Thyroid 2017

Leitline SD-Schwangerschaft 2017

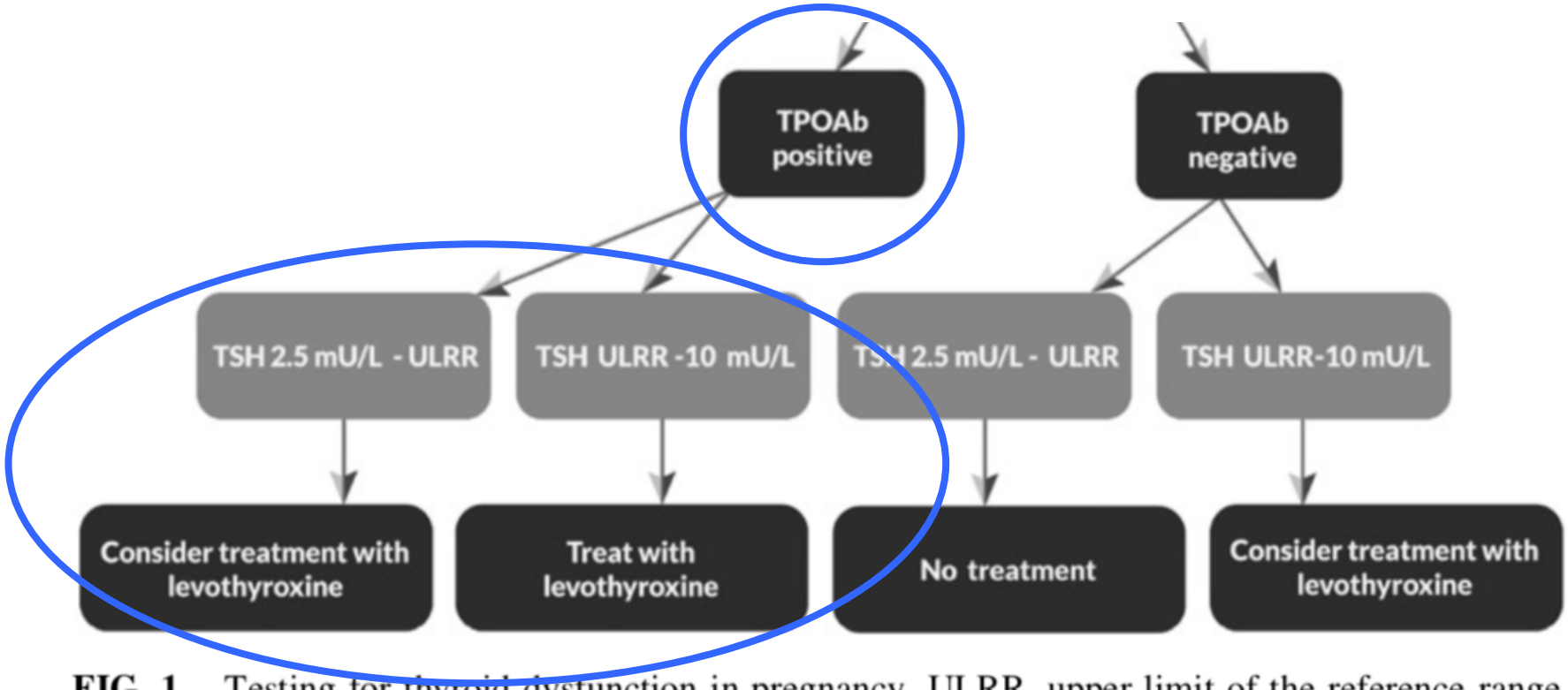


FIG. 1. Testing for thyroid dysfunction in pregnancy. ULRR, upper limit of the reference range.

Alexander et al., Thyroid 2017

T4 Therapie bei Haschimoto ?!

T4-Therapie bei **TPO +** und Kinderwunsch

TPO AK +: höheres Risiko für Fehlgeburten und Frühgeburtlichkeit

Prospektive randomisierte Studie an 952 Frauen mit **positiven TPO AK und einem TSH-Wert von um 2 µU/ml:**

50 µg T4 oder Placebo beginnend vor der Empfängnis

	levothyroxine group	placebo group
Pregnancy:	56.6 %	58.3 %
Live-birth rate:	37.4 %	37.9 %

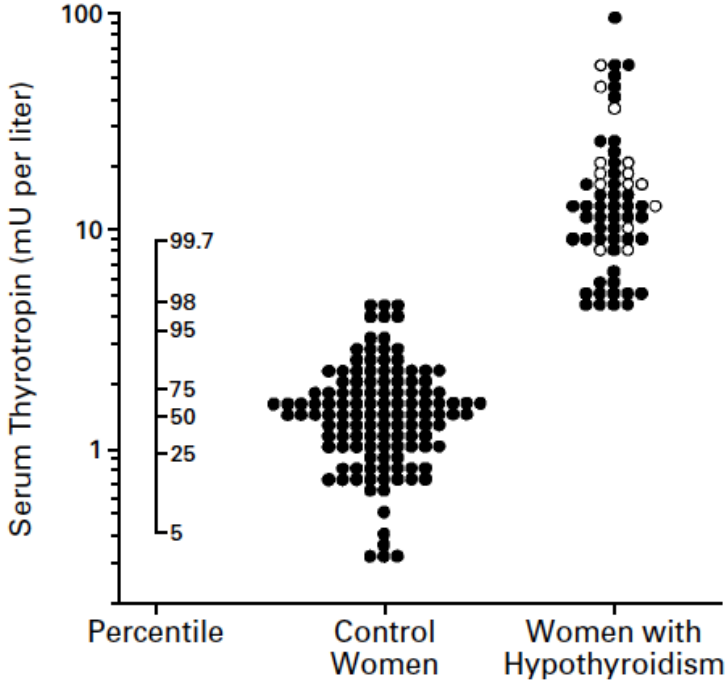
There were **no significant between-group differences** in other pregnancy outcomes, including **pregnancy loss or preterm birth**, or in neonatal outcomes.

TABLET: Dhillon-Smith et al., NEJM 2019

T4 Therapie für den IQ ?!

Hypothyreose: fetale Hirnentwicklung

TSH Messung in der Schwangerschaft (2 Trimester) bei 25.000 Frauen
-> 62 Frauen mit erhöhtem TSH vs. 124 Kontrollen

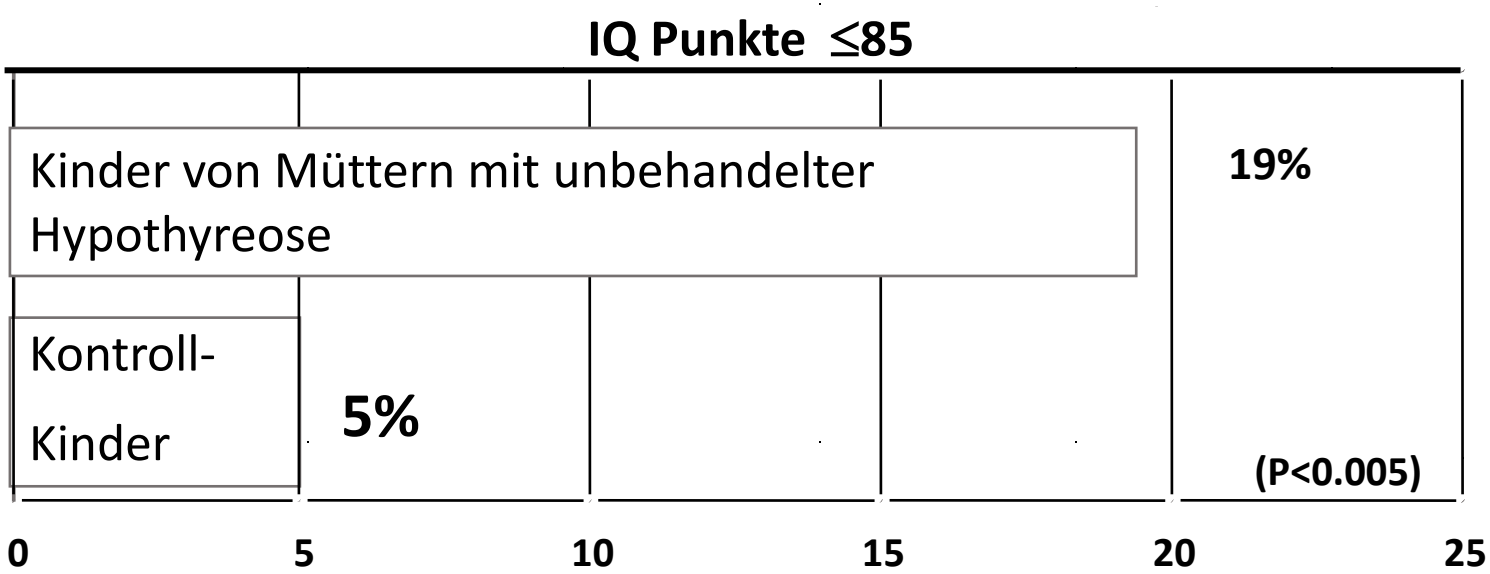


Haddow et al., NEJM 1999

Hypothyreose: fetale Hirnentwicklung

Kinder von Müttern mit unbehandelter Hypothyreose während der Schwangerschaft:

durchschnittlich 7 Punkte weniger bei IQ Test*



***Wechsler Intelligenz Test für Kinder**

Haddow JE, et al. N Engl J Med. 1999.

TSH Screening + Therapie sinnvoll ?

Blutabnahme um die 12 SSW vs. Kontrollgruppe
Falls TSH über 97.5 Perz. oder fT4 unter 2.5 Perz:

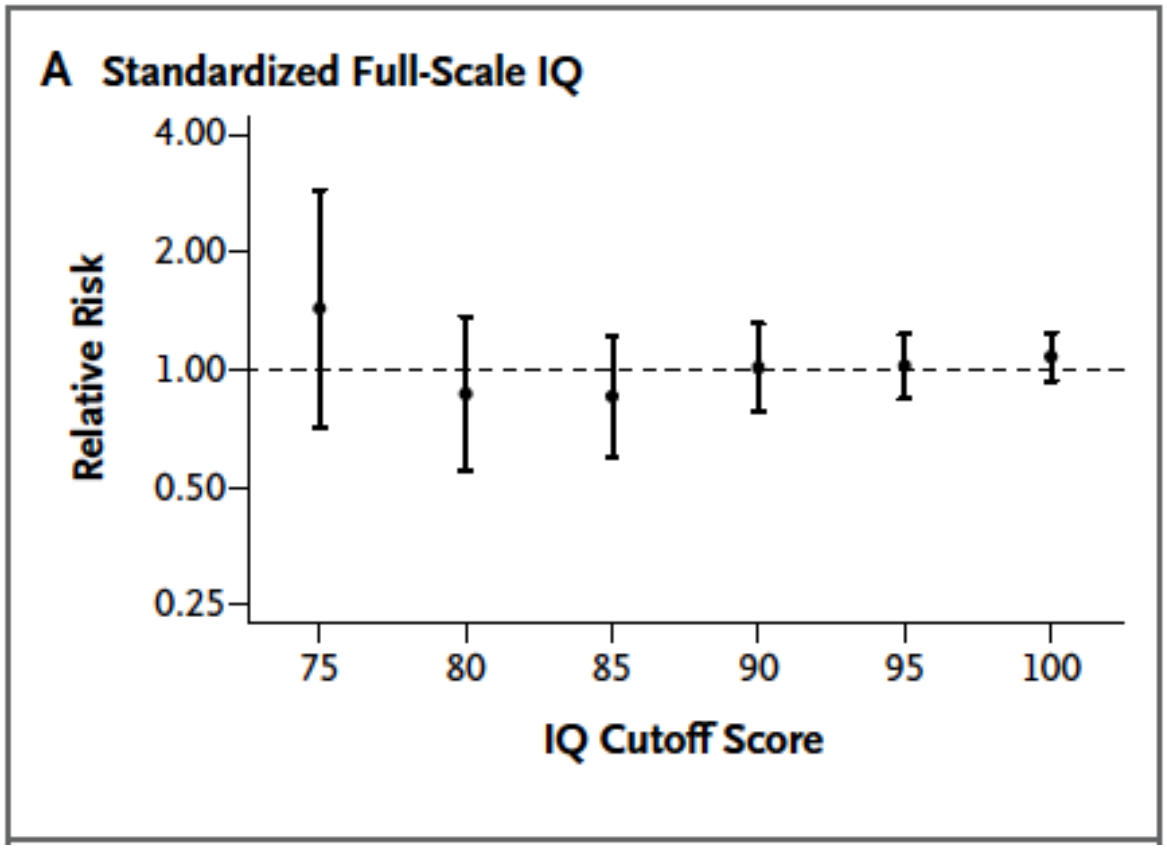
150 µg T4 p.o.TSH Ziel 0.1 – 1 mU/l

	Screening	Kontrollgruppe
TSH (mU/l)	3,5	2,8
fT4 (ng/dl)	0,73	0,73

CATS, Lazarus et al., NEJM 2012

T4 Therapie in der Schwangerschaft

IQ Test der Kinder im 3 LJ



CATS: Lazarus et al., NEJM 2012

T4 Therapie in der Schwangerschaft

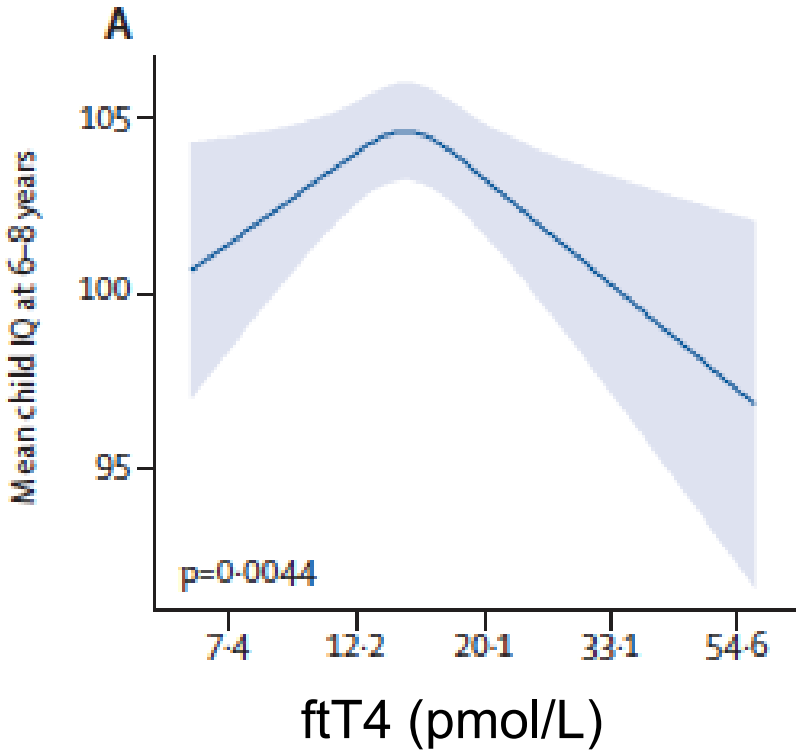
SCH: 677 women, gestational age 16.7 weeks; TSH was 4.5 mU/L; placebo or 100 µg levothyroxine. The treatment goal was a TSH of 0.1-2.5 mU/L;
There was no significant difference in the primary outcome of child IQ at 5 years.

Hypothyroxinemia trial: 526 women, gestational age of 17.8 weeks; placebo or 50 µg levothyroxine; TSH was 1.5 mU/L, free T4 0.8 ng/dL; Treatment goal: free T4 of between 0.86 and 1.90 ng/dL;
There was no difference on the primary outcome of child IQ at 5 years.

Casey et al., NEJM 2017

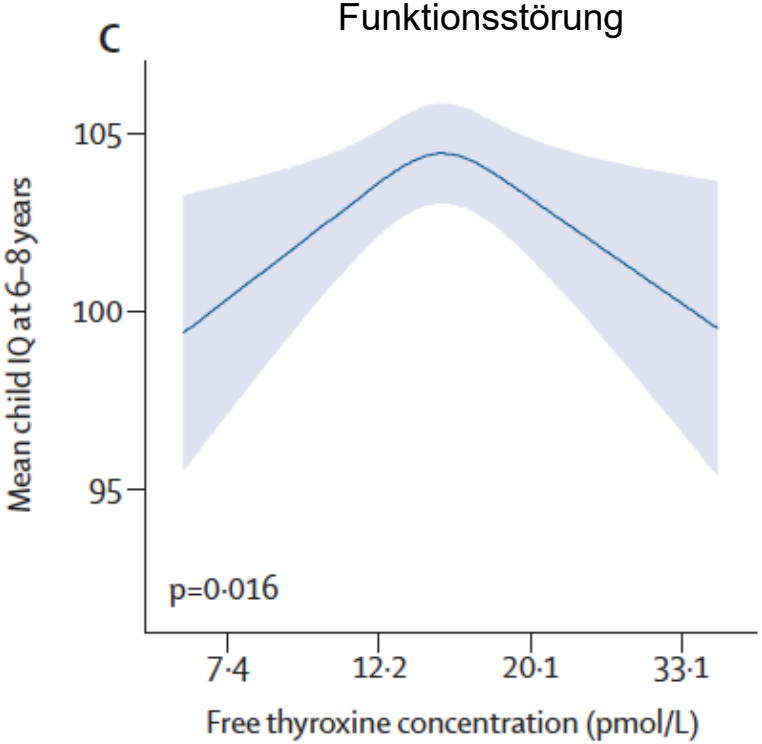
Generation R Study

Generation R Study (Rotterdam)
Blutabnahme in der Schwangerschaft (< 18 SSW)
Nicht verbaler **Intelligenztest der Kinder 6 LJ** (n = 3839)

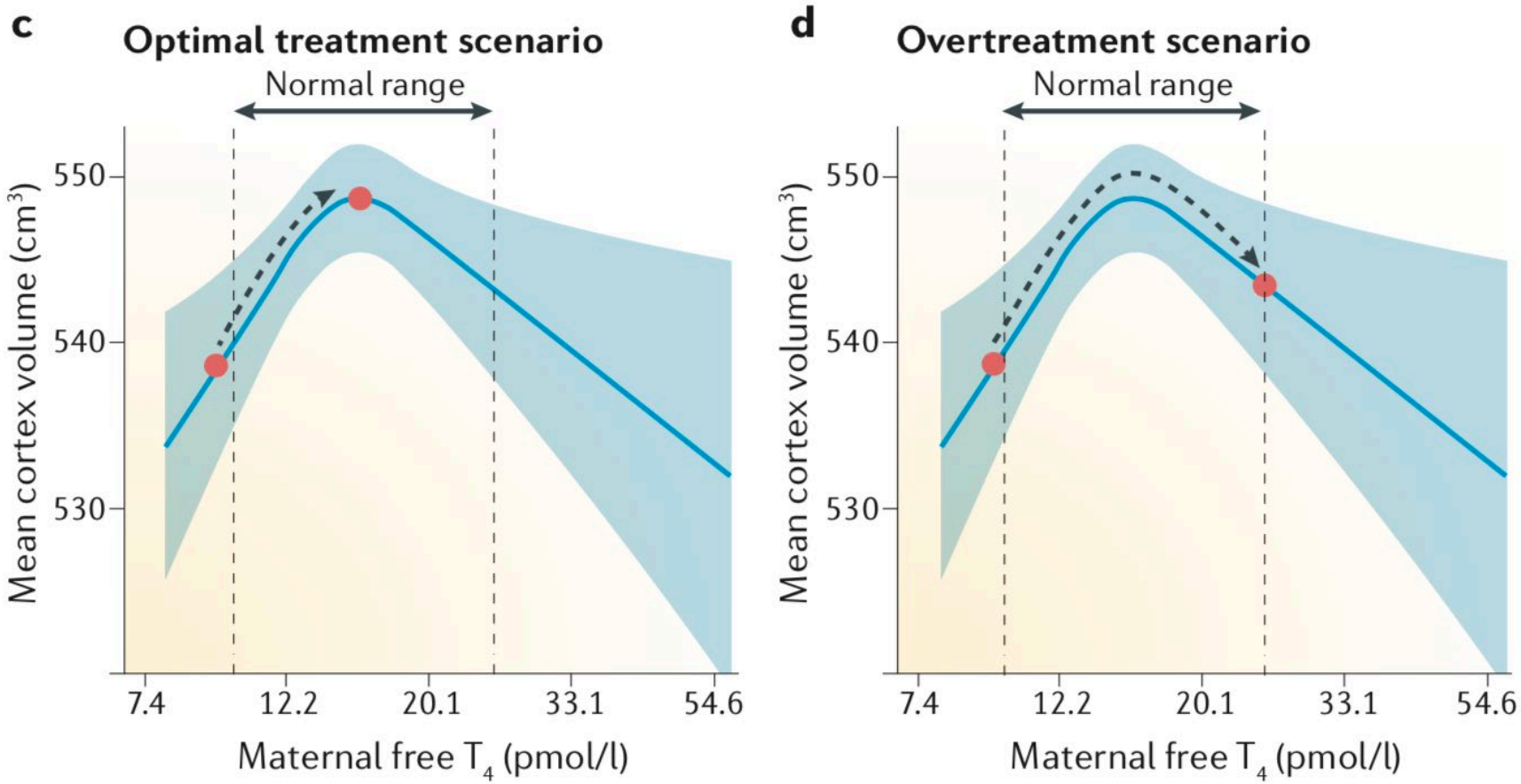


Korevaar et al., Lancet Diabetes Endocrinol 2015

Ohne Mütter mit manifester SD Funktionsstörung



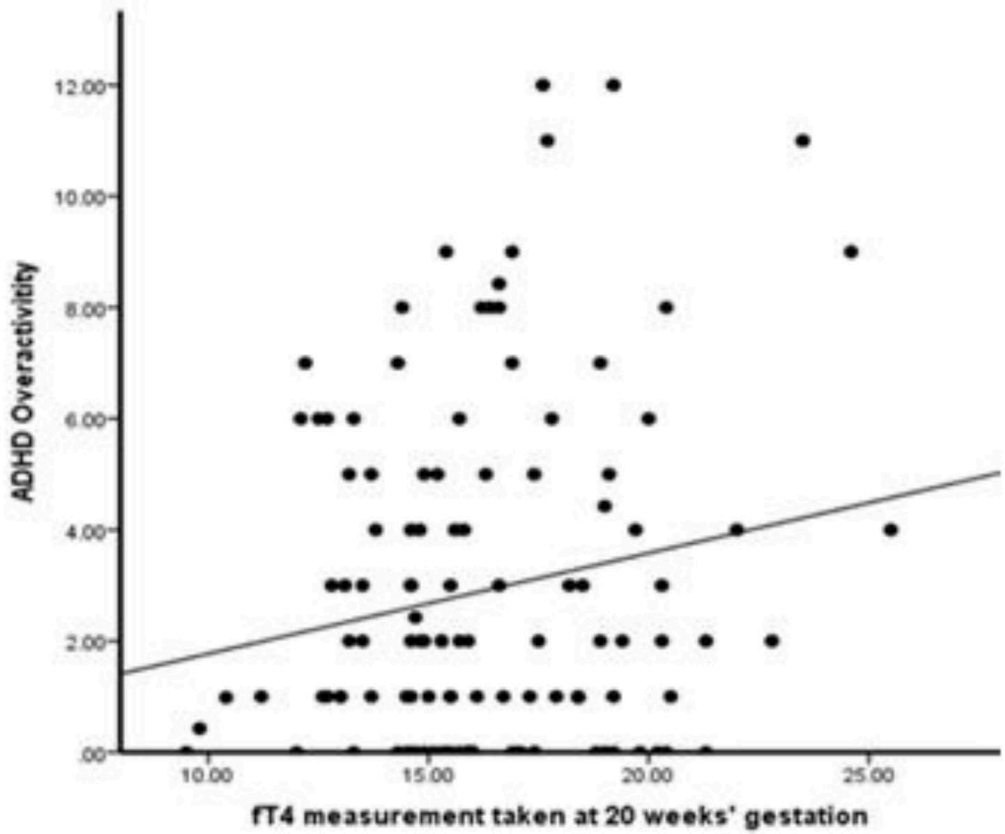
Zu viel ist auch nicht gut !



Korevaar et al., Nature Reviews Endocrinology 2017

CATS follow up

475 Mütter, Fragebögen bzgl. Kinder 9,5 Jahre
Therapie in der Schwangerschaft +/- 150 µg T4,



Children of 'over-treated' mothers:

- **more attention deficit hyperactivity disorder**
- **behavioral difficulties**

Thyroxine supplementation during pregnancy requires monitoring to avoid over- treatment.

Hayes et al., JCEM 2019

Schilddrüse und Hirn

Schilddrüse und Hirn

Rotterdam, 1981 Mutter-Kind Paare, MRI Kinder im 10 LJ

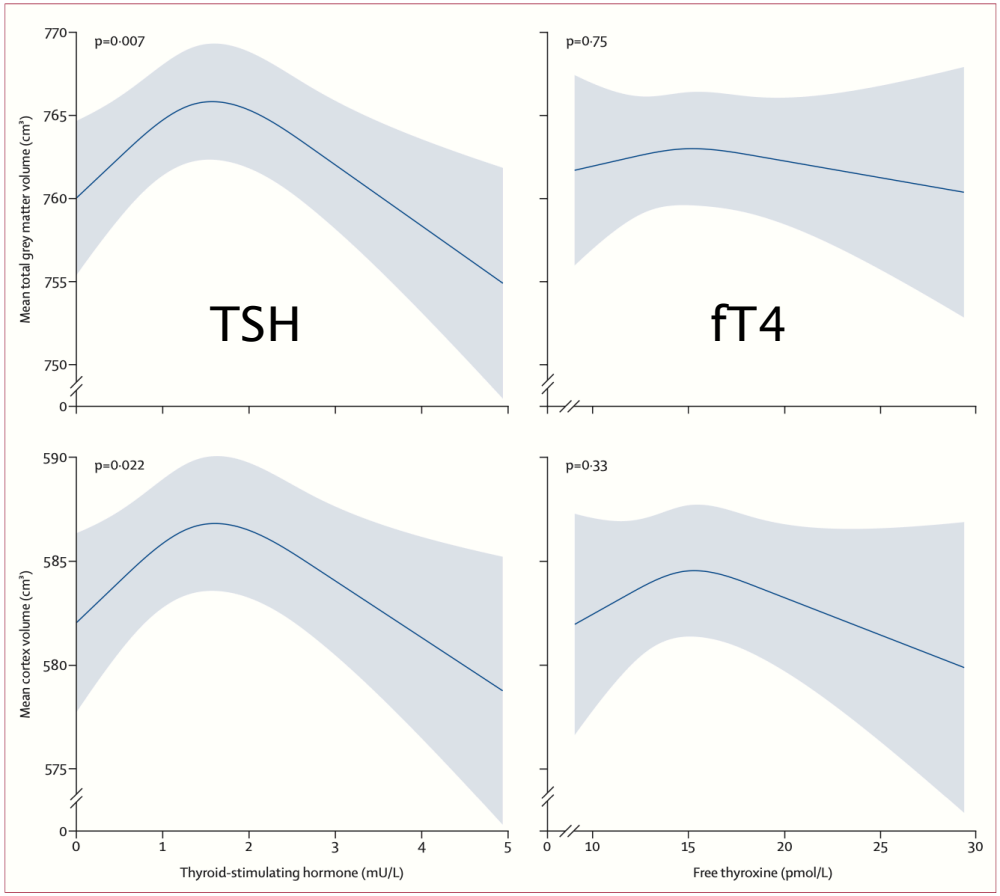


Figure 2: **Association of maternal thyroid stimulating hormone and free thyroxine with offspring brain morphology**
Analyses were adjusted for gestational age at blood sampling, maternal age, ethnicity, education level, smoking, thyroid peroxidase antibody positivity (>60 IU/mL), child sex, age at MRI, and total intracranial volume.

Graue Substanz

Cortex-Volumen

Generation R Study; Jansen et al., Lancet D&E 2019

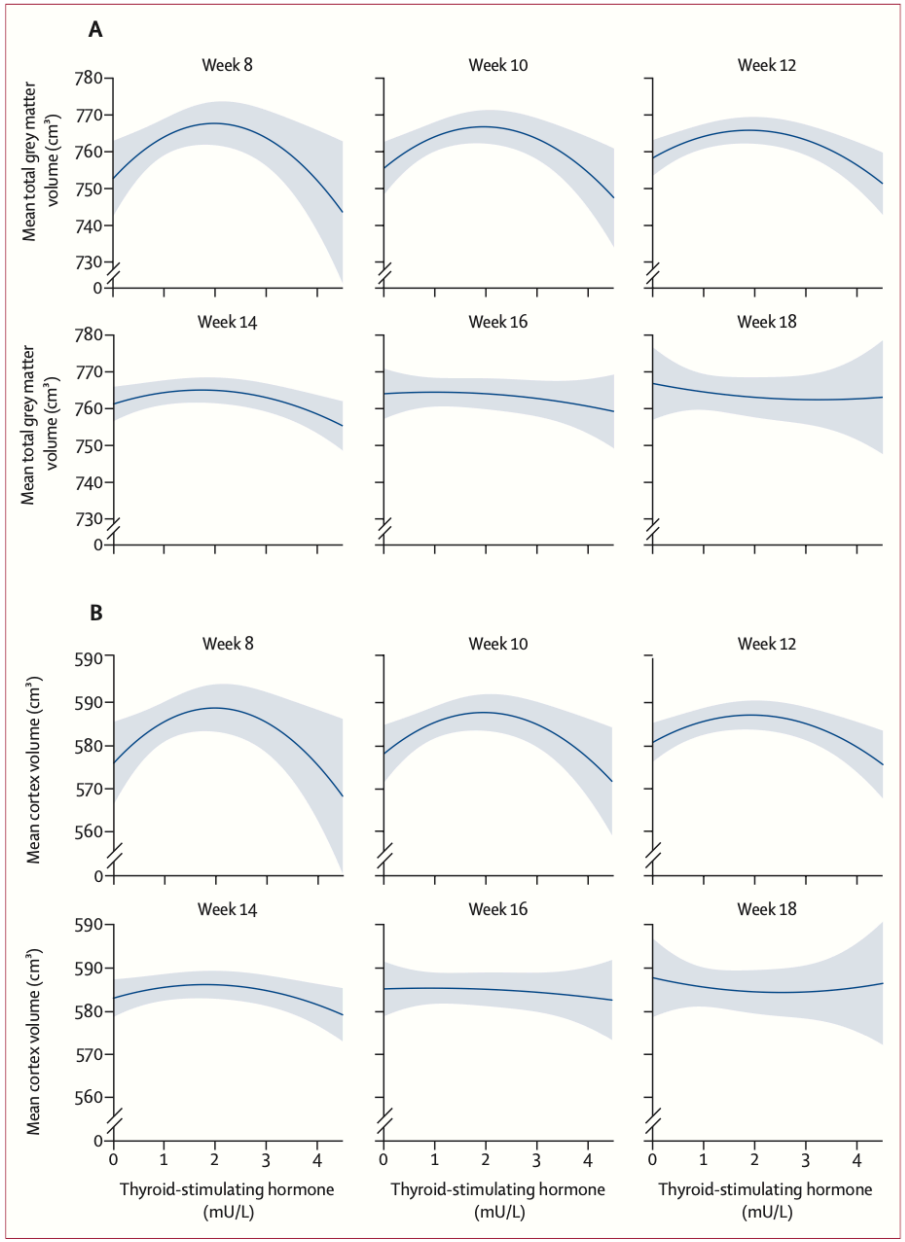


Figure 3: The association of maternal thyroid stimulating hormone with child grey matter volume (A) or cortical grey matter volume (B) stratified by gestational age at blood sampling

Low and high maternal TSH concentrations, particularly in **early pregnancy**, are associated with a smaller volume of total grey matter and cortical grey matter in children aged 9–12 years.

Generation R Study; Jansen et al., Lancet D&E 2019

Therapie

Recommendation 31: Orale LT4 Therapie ist Standard.
T3 and desiccated thyroid not recommended.

Recommendation 33: TSH Messung alle 4 Wochen bis zur Mitte der Schwangerschaft, dann einmal um Woche 30.

Recommendation 36: Eigenständige Steigerung der T4 Dosis um 20-30%: 2 zusätzliche Tabletten pro Woche

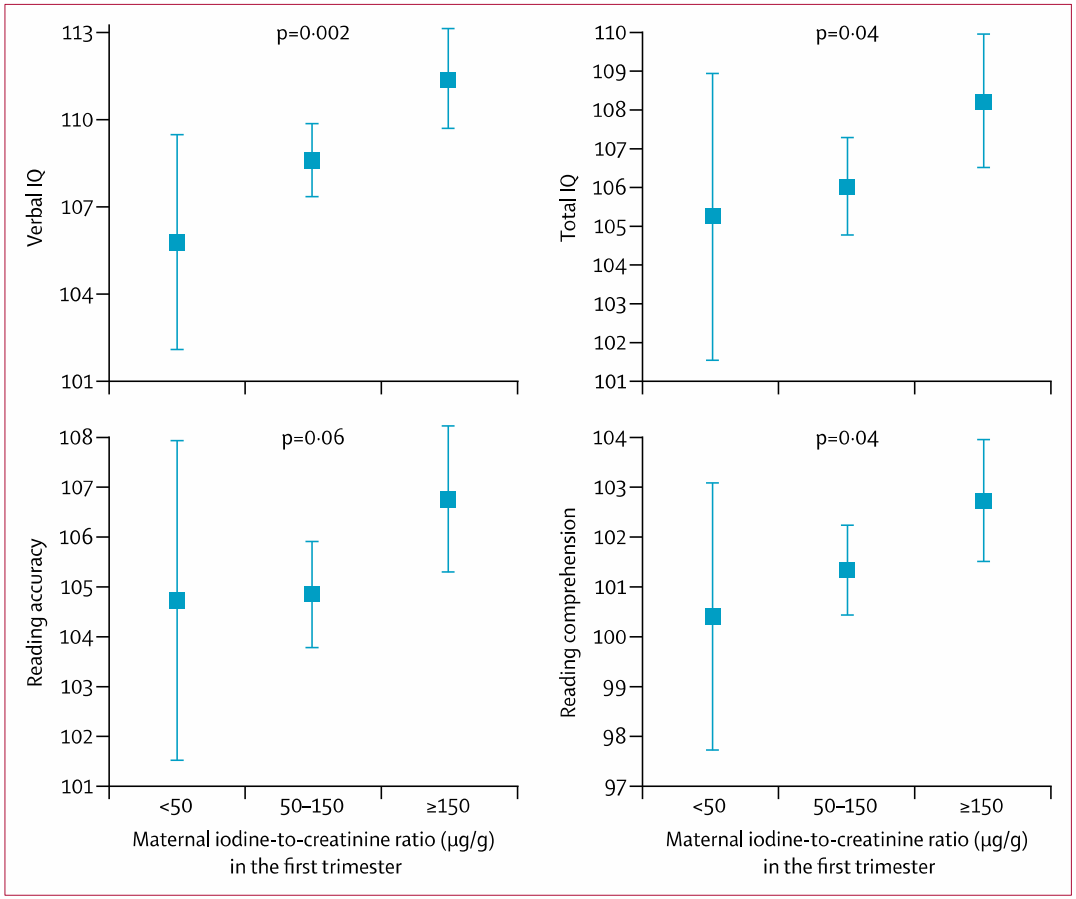
Alexander et al., Thyroid 2017

IQ - Jod in der Schwangerschaft

median UIC (µg/L)	iodine intake	%
0-49	insufficient	21.5
50-99	insufficient	40.2
100-149	insufficient	19.5
150-249	adequate	13.8
250-499	more than adequate	2.8
≥ 500	excessive	2.0

Daten aus Wien: 246 schwangere Frauen

Lindorfer...Gessl, Eur. J. Clin. Nutrition



Daten aus Großbritannien: 1040 schwangere Frauen

Barth et al., Lancet 2013

Vielen Dank !