Thyroid Autoantibodies/ Iodine Deficiency and Pregnancy

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Outline

- Physiologic thyroid changes in pregnancy
- Iodine deficiency and requirement
- AITD
- Disease susceptibility
- Testing for thyroid autoantibody
- Consequence of thyroid disease in pregnancy
- Miscarriage & AITD
- Preterm birth rate & AITD
- Is LT4 a game changer in women with +TPOAb
- ATA Recommendations

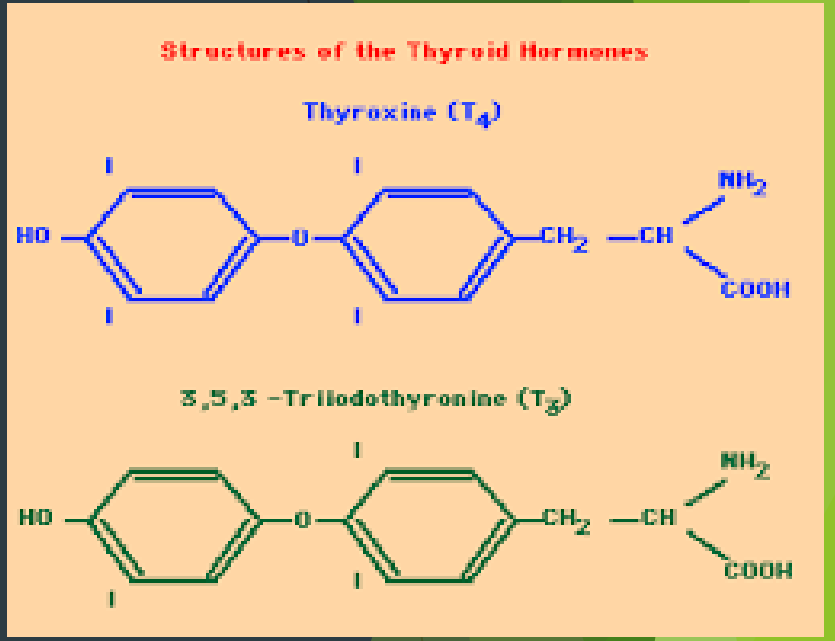
Physiology changes in pregnancy that influence thyroid function

Physiologic changes	Impact on thyroid economy
TBG & half life	Total T4, T3
HCG/ Cross-over for TSH receptor	Free T4, LOW TSH HCG effect impaired in TPOAb poitivity
Plasma volume	T4, T3 pool size
Type III deiodinase activity from placenta	T4, T3 degradiation
Thyroid gland enlargement	Serum Thyroglobulin
Cardiac output, GFR, loss of iodine	Iodine requirement

Need for more thyroid hormone

Iodine nutrition in pregnancy

- Iodine has essential role in thyroid hormone synthesis and is necessary for the prevention of iodine deficiency disorders (IDD)
- Iodine content of the human body is 15-20 mg, of which 70-80% is present in the thyroid gland
- The essential requirement for normal growth is only 100-150 ug/d & 220-290 during pregnancy & lactation
- Is a trace element , so does not occur naturally in specific foods



Impact of Iodine deficiency

- In iodine deficiency thyroid hormone production decreases
- Inadequate thyroid hormone production adversely affects growth and development and in particular damages the developing brain
- It causes:

  Goiter

  Mental retardation,

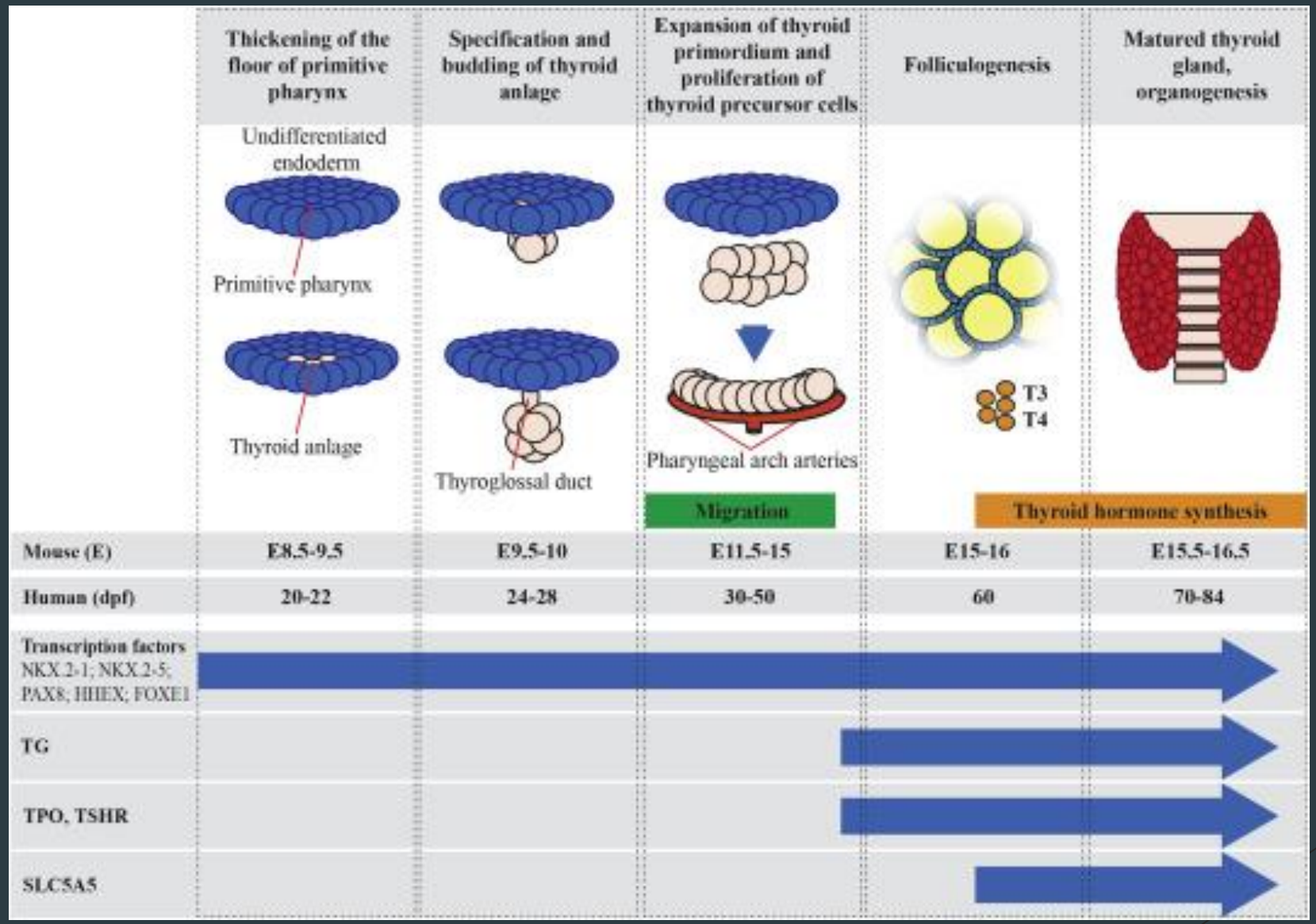
  Growth retardation,

  Reproductive failure,

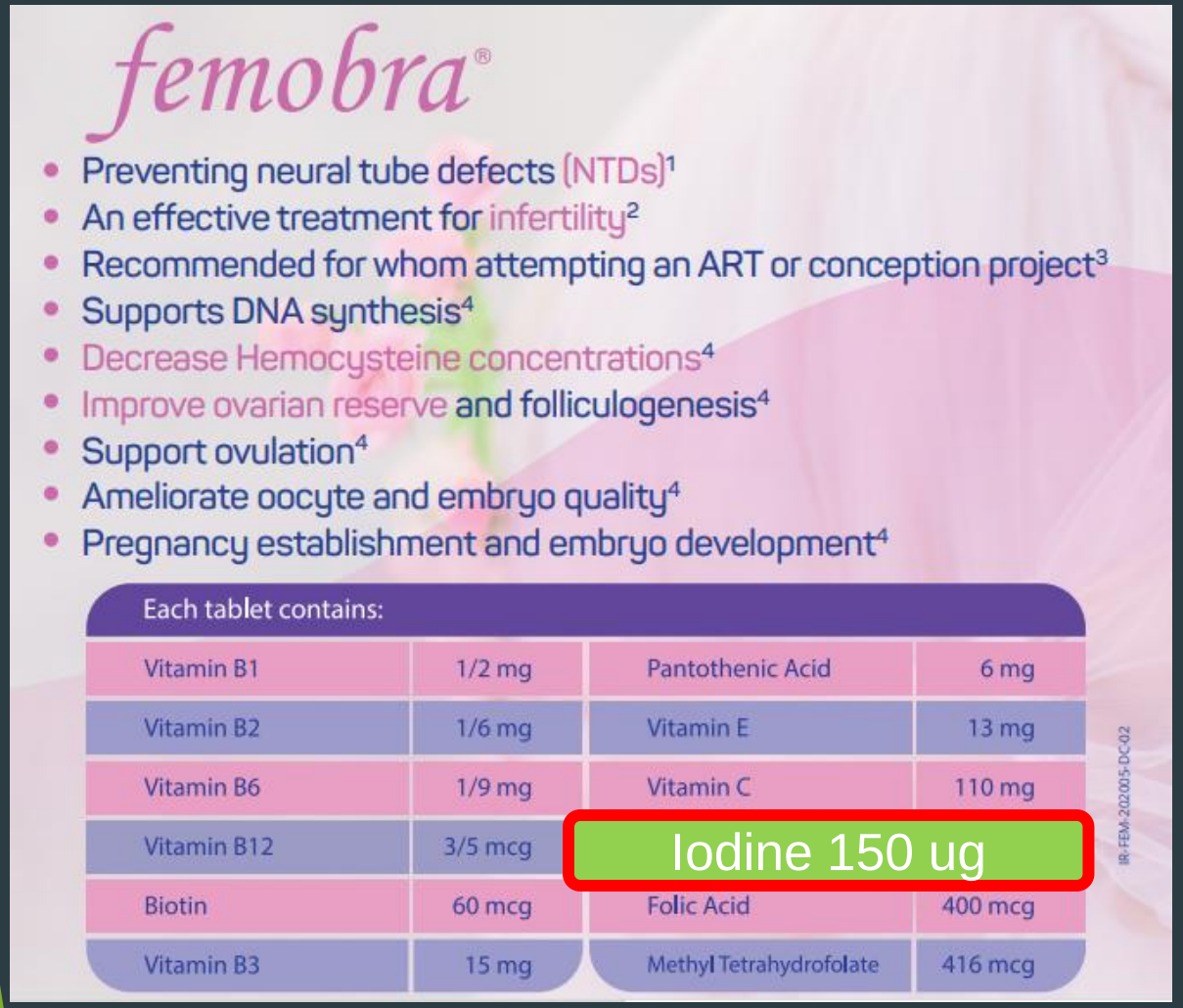
  Childhood mortality

- During the first trimester of pregnancy ; fetal thyroid hormone is from mother thyroid hormones

Thyroid development



Iodine requirement during Pregnancy & Lactation



- WHO & ATA & Endocrine Society recommended 220 -290 ug/d during pregnancy & lactation
- 150 ug iodine daily as dietary supplements for all pregnant women 3 months before conception and during pregnancy and lactation

Thyroid Autoimmunity & pregnancy

Thyroid autoimmune concept origin

- Hashimoto described dense lymphoid infiltration causing goiter and hypothyroidism in 1912

44 y later

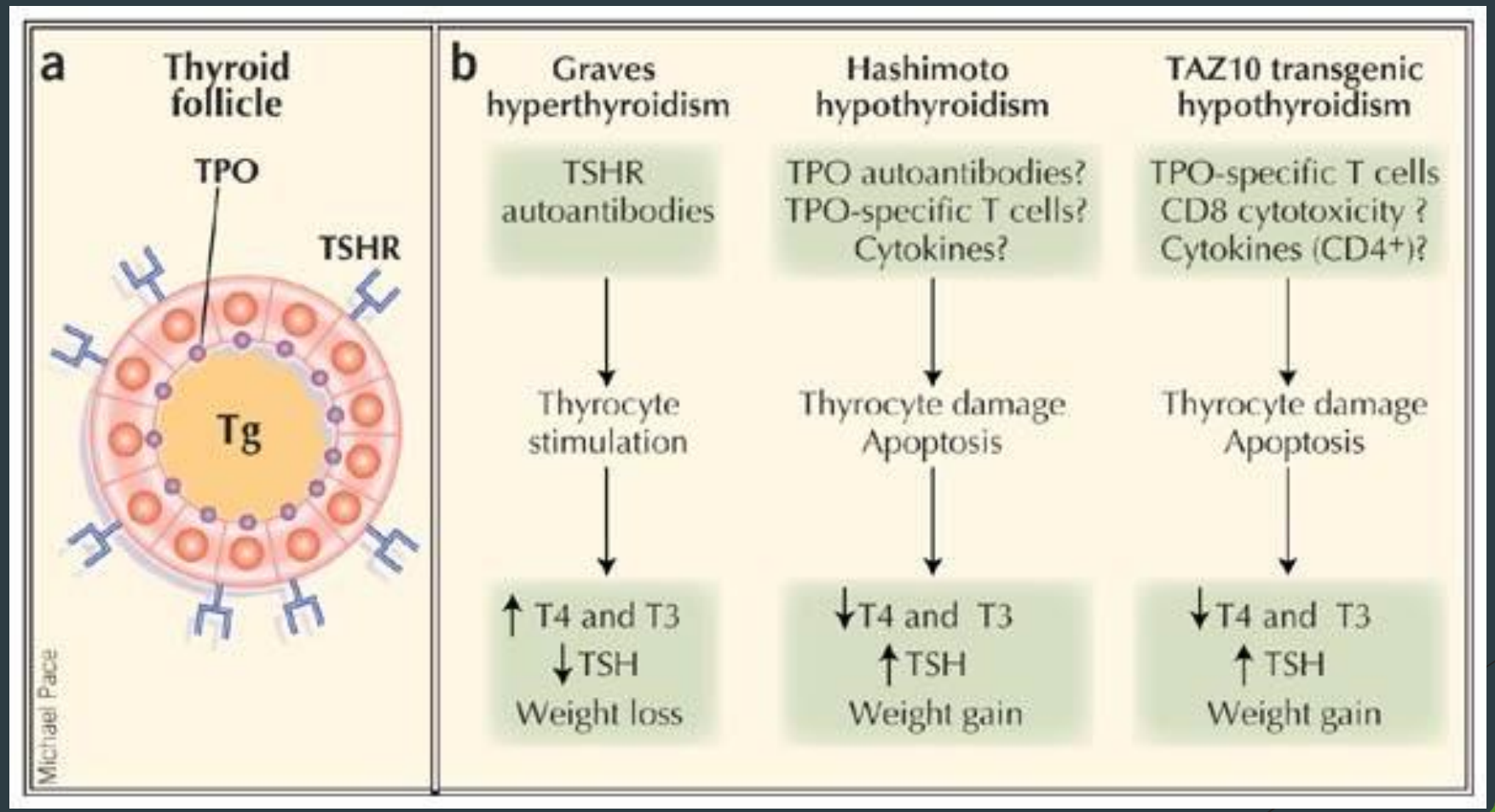
- until 1956 that autoantibodies, anti-thyroiglobulin antibodies (anti-Tg) were detected

52 y later

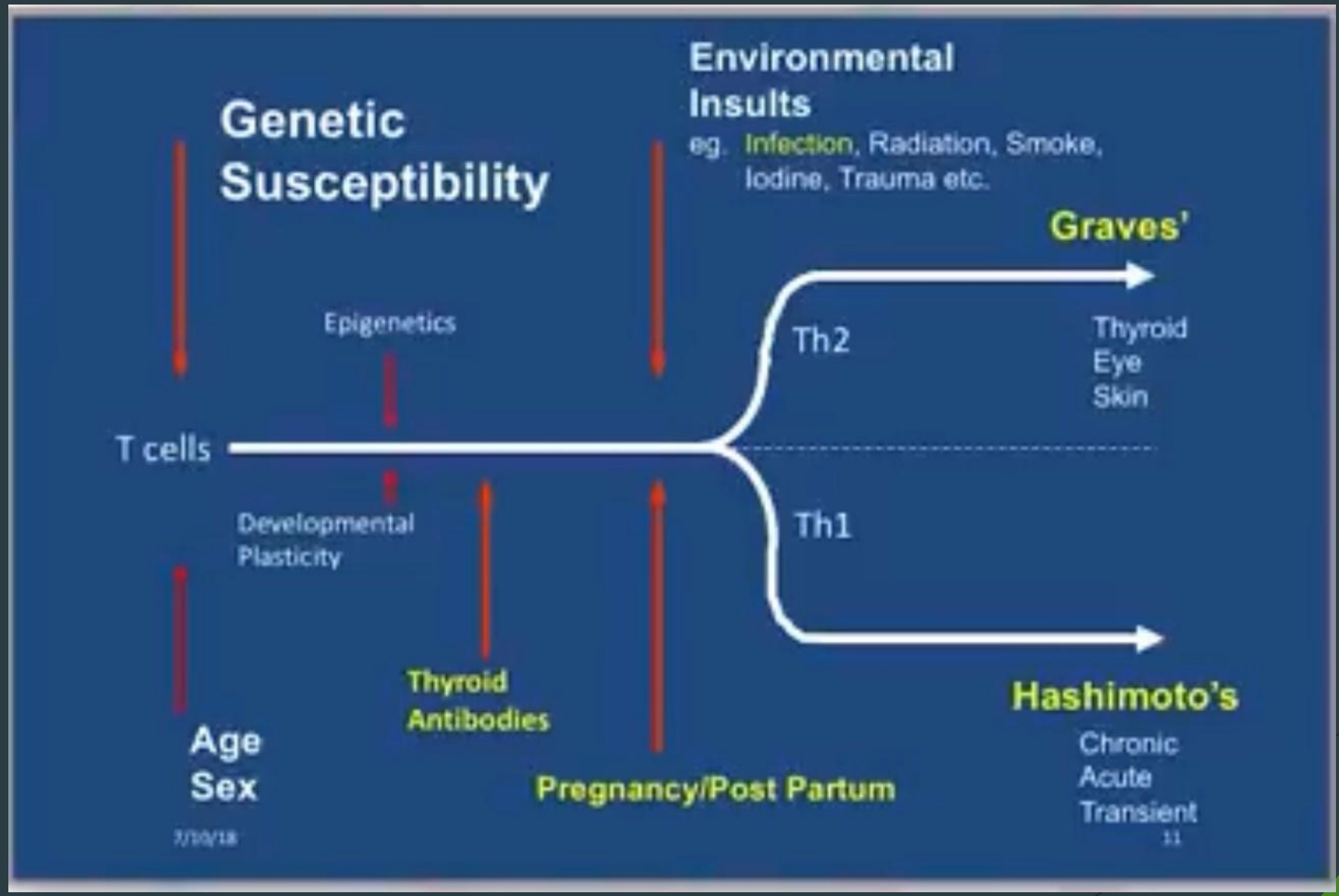
- Discovery of anti-TPO in 1964
- Autoimmune thyroid disease the most common autoimmune condition, 2% of women and 0.2% od men affected at the clinical level, and subclinical disease is 10 fold higher

After more than 100 years, still we have many unanswered questions regarding ATD

Spectrum of Autoimmune Thyroid Disease



Disease Susceptibility



It's all in the family.....

More than 60% of patients will give a family history of Graves' or Hashimoto's diseases

High concordance rate in Graves' twins

Thyroid antigens

- Thyroglobulin (Tg):

  Tissue distribution: thyroid

  Function: thyroid hormone storage

- TPO:

  Tissue distribution: thyroid

  Function: thyroid hormone biosynthesis

- TSH receptor (TSHR):

  Tissue distribution: thyroid, lymphocyte, fibroblasts, adipocytes (retroorbital)

  Function: transduction of signal from TSH

Thyroid Autoantibodies prevalence

Table 2. PREVALENCE OF THYROID AUTOANTIBODIES AND THEIR ROLE IN IMMUNOPATHOLOGY

Antibody	General Population	Graves' Disease	Hypothyroid Autoimmune Thyroiditis
Antithyroglobulin	3% (Table 5)[7]	12% to 30%[7, 144]	35% to 60%[7, 95]
Antimicrosomal/thyroid peroxidase	10% to 15% (Table 5)	45% to 80%[84, 144]	80% to 99%[84, 95]
Anti–TSH receptor	1% to 2%[27, 130]	70% to 100%[27, 130, 150]	6% to 60%[24, 132]
Anti–Na^+/I^- symporter	0%[3]	20%[3]	25%[3]

TSH = thyroid-stimulating hormone.

Endocrinology & Metabolism clinics of North America, 2001

Anti-Thyroglobulin Antibodies

- 99% of sera positive for anti-Tg antibodies are also positive for anti-TPO
- While 65% of sera positive for anti-TPO are negative for anti-Tg
- SO testing for anti-Tg antibodies has been replaced by anti-TPO testing, with exception of screening for interference by anti-Tg antibodies in Tg assays

Prevalence of anti-Thyroid antibodies

Estimated prevalence of antithyroid antibodies (in percent)

Estimated prevalence of antithyroid antibodies (in percent)

Group	Anti-TSHR Ab	Anti-Tg Ab	Anti-TPO Ab
General population	0	3%	8 to 27
Graves' disease	80 to 95	50 to 70	50 to 80
Autoimmune thyroiditis	10 to 20	80 to 90	90 to 100
Relatives of patients with autoimmune thyroiditis	0	30 to 50	30 to 50
Type 1 diabetes	0	30 to 40	30 to 40
Pregnant women	0	Approximately 14	Approximately 14

Anti-TSHR Ab: anti-thyroid-stimulating hormone receptor antibodies; anti-Tg Ab: anti-thyroglobulin antibodies; anti-TPO Ab: anti-thyroid peroxidase antibodies.

- No difference in prevalence of TPO even among high risk populations such as , recurrent miscarriage or subfertility

Clinical Applications of Thyroid Autoantibody Assays

- Thyroid auto-antibodies in 10-15% of women
- Subclinical hypothyroidism in 5-10% of women
- Biochemical hypothyroidism in only 1% of women is present

- Rates in all cases rise with Age, BMI (>34.9), and with increasing TSH

- Once present , thyroid autoantibodies persist; spontaneous disappearance is seen in less than 20% of individuals even after 20 years of follow up

Clinical Applications of Thyroid Autoantibody Assays

- Progression between the different stages of subclinical chronic autoimmune thyroiditis and clinical disease is extremely slow

- Higher the antibody titer and the higher the initial TSH , the more rapid the progression

ATI and female Infertility/Subfertility

- A meta-analysis pooling 4 studies showed that the presence of thyroid antibodies in euthyroid patients is associated with unexplained subfertility (OR 1.5, 95% CI 1.1-2.0)

E. Van den Boogaard, … +2 … , et al. Hum Reprod Update, 2011

- Women with PCOS were found to have an increased prevalence of TAI
- Together with lower TGF-b, low vitamin D levels and the high estrogen-to-progesterone ratio, these factors may contribute to autoimmunity

Thyroid autoimmunity and assisted reproductive technology

- A study by Zhong et al.

Comparing IVF outcome in TAI + and TAI - women revealed:

TAI + women had a significantly lower:

- Fertilization (64.3% vs.74.6%),
- Implantation (17.8% vs. 27.1%) and
- Pregnancy rate (33.3% vs. 46.7%)
- Higher risk of abortion (26.9 vs. 11.8%) .

Indications for Thyroid Autoantibody Testing

- Goiter
- In subclinical hypothyroidism
- In concomitant autoimmune disease; Addison's disease, type 1 diabetes,
- In the first-degree relatives of affected individuals
- In biochemical hypothyroidism
- Postpartum thyroiditis and post natal depression
- Early pregnancy loss and infertility

Thyroid autoimmunity and pregnancy outcomes

- The causes of recurrent first-trimester miscarriages are not fully defined, yet immunologic mechanisms are thought to have a part
- It is seen in 17-33% of women with a history of recurrent miscarriage, and in 10-30% of women with a hx of subfertility

Clinical Endocrinology & Metabolism 2020

Potential Mechanism for Miscarriage in TPO Positive Women

1. Subclinical Hypothyroidism

   Mean TSH 2.1 (TAB+) vs 1.3 (Tab-)

   Failure to mount a normal thyroid response to HCG

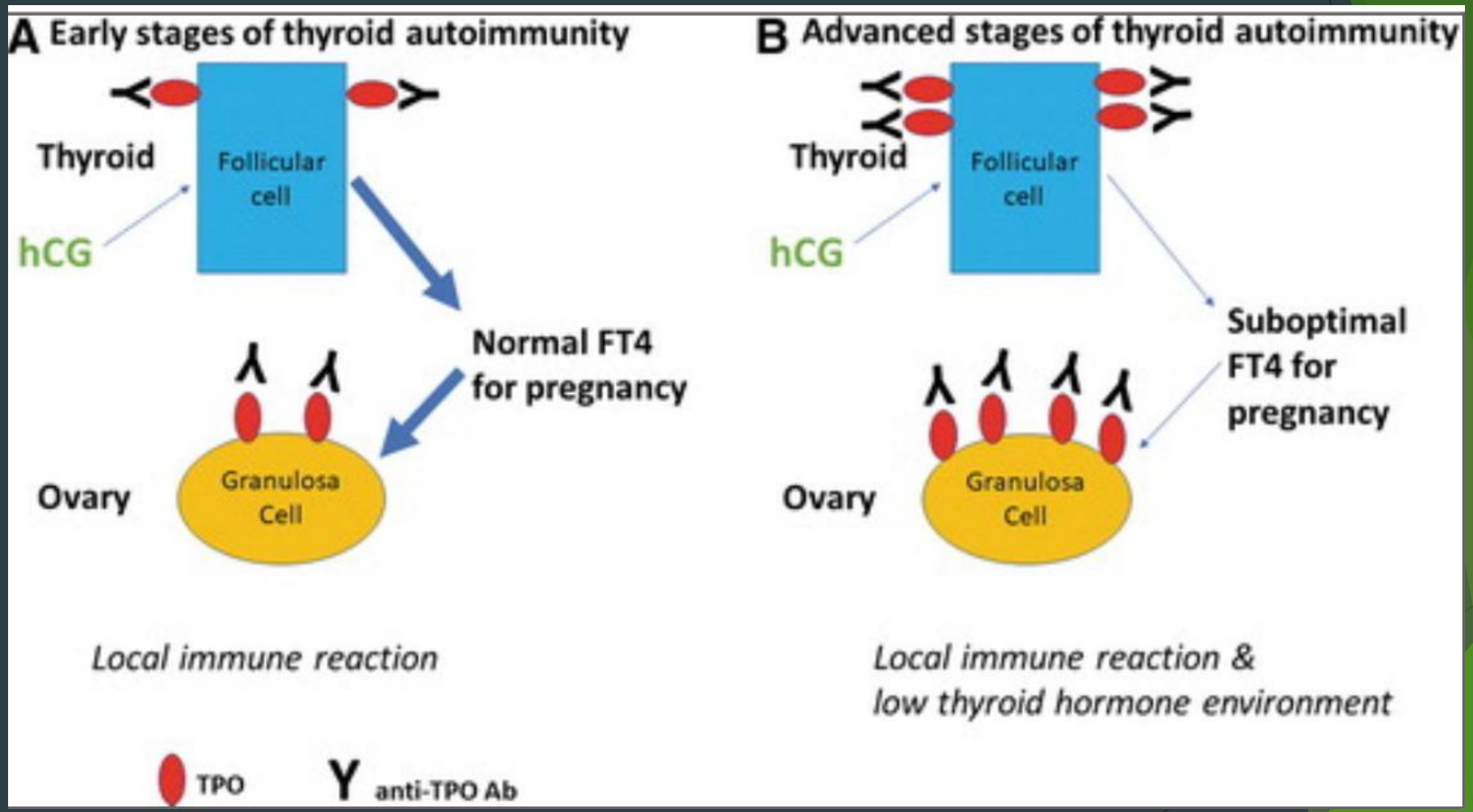
2. Direct effect of thyroid antibodies/Tcells

   mouse model of Tg-Ab immunization

3. Marker of immune failure

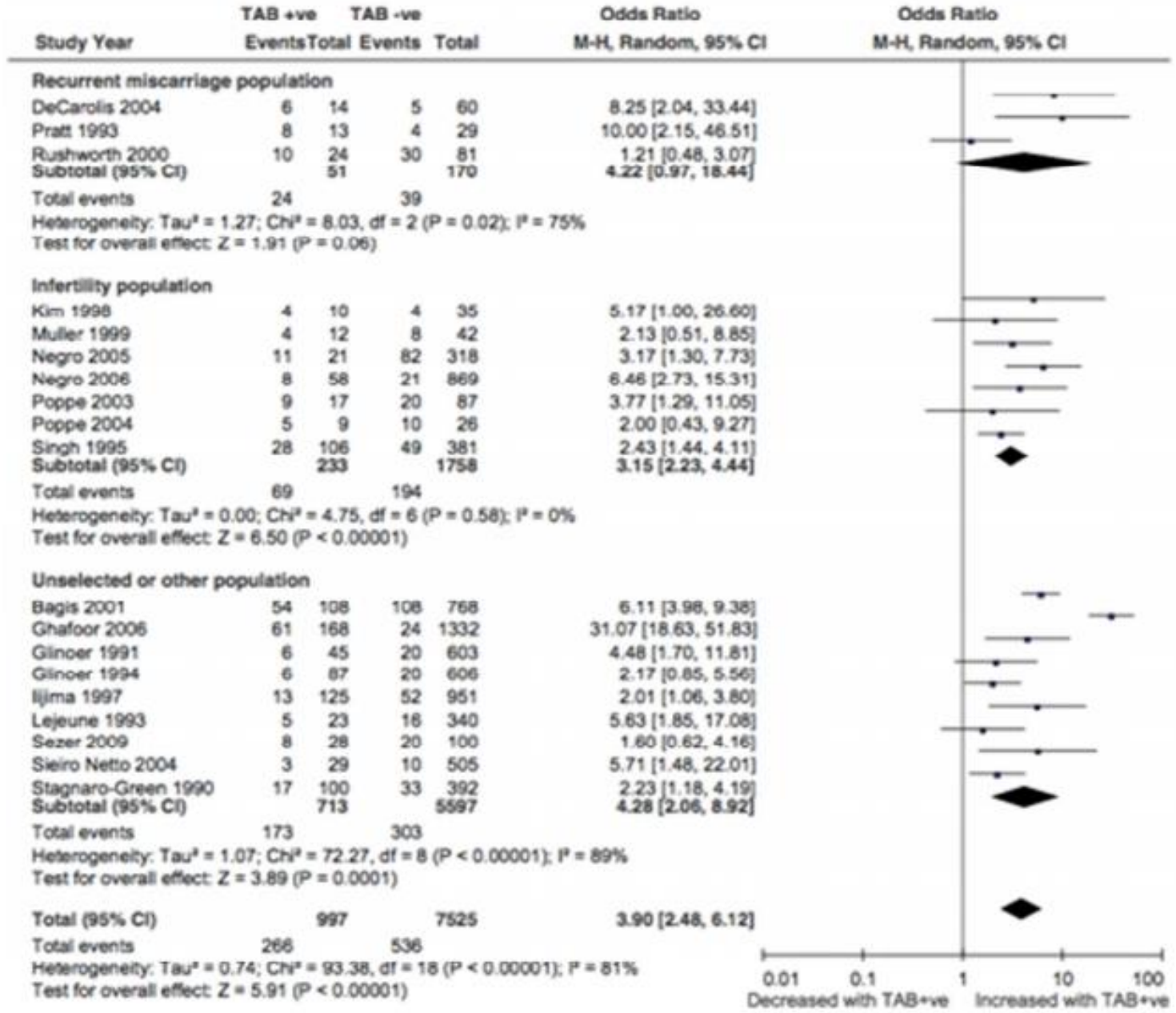
   Immune “instability” Treg inadequacy

4. Age


A Early stages of thyroid autoimmunity
Thyroid
Follicular cell
hCG
Normal FT4 for pregnancy
Ovary
Granulosa Cell
Local immune reaction
B Advanced stages of thyroid autoimmunity
Thyroid
Follicular cell
hCG
Suboptimal FT4 for pregnancy
Ovary
Granulosa Cell
Local immune reaction & low thyroid hormone environment
TPO
anti-TPO Ab

TPOAb and Miscarriage

- A systematic review of 12000 women showed:
- TPO Ab positivity leads to a significantly increased odds of miscarriage OR; 4.22 95%CI: 0.97-18.44 P=0.06



- Recurrent Miscarriage; OR:4.22
- Subfertility; OR: 3.15

BMJ 2011

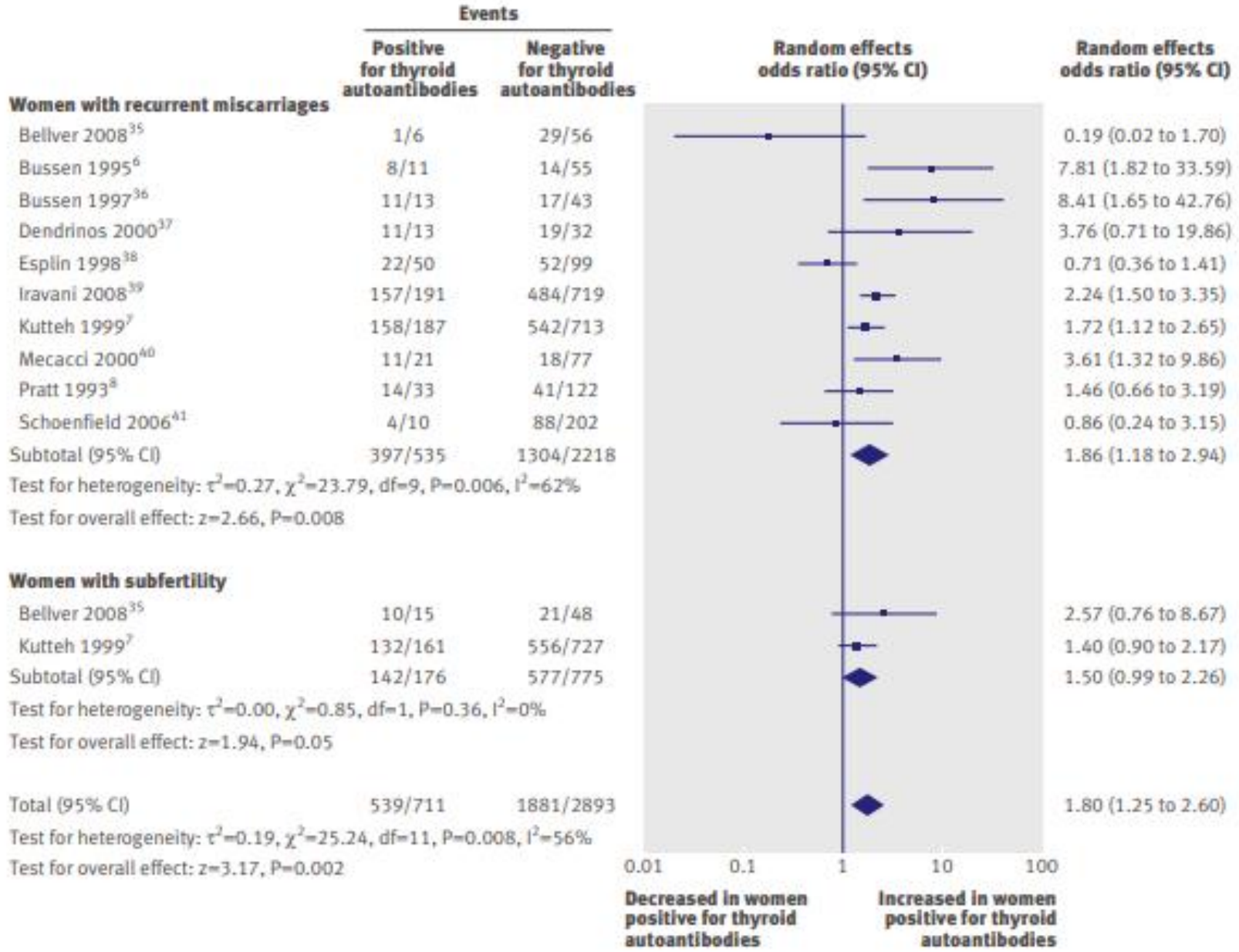


Fig 3 | Association between thyroid autoantibodies and miscarriage in case-control studies

Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth

JAMA | Original Investigation

Association of Thyroid Function Test Abnormalities and Thyroid Autoimmunity With Preterm Birth

A Systematic Review and Meta-analysis

The Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth

IMPORTANCE Maternal hypothyroidism and hyperthyroidism are risk factors for preterm birth. Milder thyroid function test abnormalities and thyroid autoimmunity are more prevalent, but it remains controversial if these are associated with preterm birth.

OBJECTIVE To study if maternal thyroid function test abnormalities and thyroid autoimmunity are risk factors for preterm birth.

From 2526 published reports, 35 cohorts 47 045 pregnant women

Figure 2. Association of Thyroid Function Test Abnormalities With Preterm Birth

	No. of Events/ Total No. (%)	Risk Difference (95% CI), %	Odds Ratio (95% CI)	P Value
Preterm birth (gestational age <37 wk)				
Euthyroid (reference group)	1859/37 202 (5.0)			
Subclinical hypothyroidism	75/1234 (6.1)	1.4 (0 to 3.2)	1.29 (1.01 to 1.64)	.03
Subclinical hyperthyroidism	35/594 (5.9)	1.0 (-0.8 to 3.5)	1.20 (0.84 to 1.70)	.29
Overt hyperthyroidism	13/328 (4.0)	-1.2 (-2.8 to 1.7)	0.76 (0.43 to 1.34)	.35
Isolated hypothyroxinemia	64/904 (7.1)	2.3 (0.6 to 4.5)	1.46 (1.12 to 1.90)	.004
Very preterm birth (gestational age <32 wk)				
Euthyroid (reference group)	289/37 202 (0.8)			
Subclinical hypothyroidism	9/1234 (0.7)	0 (-0.3 to 0.8)	1.03 (0.52 to 2.01)	.92
Subclinical hyperthyroidism	5/594 (0.8)	0 (-0.4 to 1.2)	1.05 (0.43 to 2.58)	.90
Overt hyperthyroidism	1/328 (0.3)[a]			
Isolated hypothyroxinemia	17/904 (1.9)	1.2 (0.4 to 2.5)	2.57 (1.55 to 4.27)	<.001

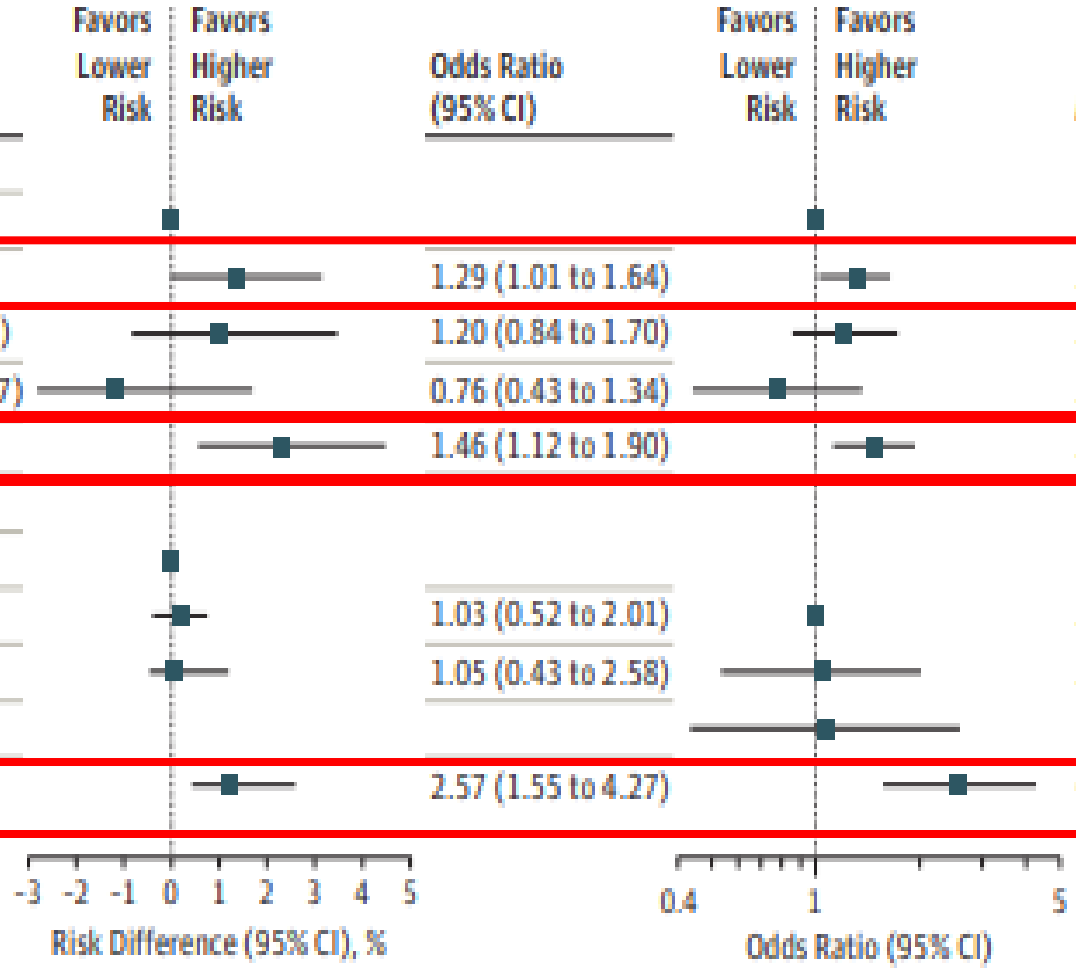
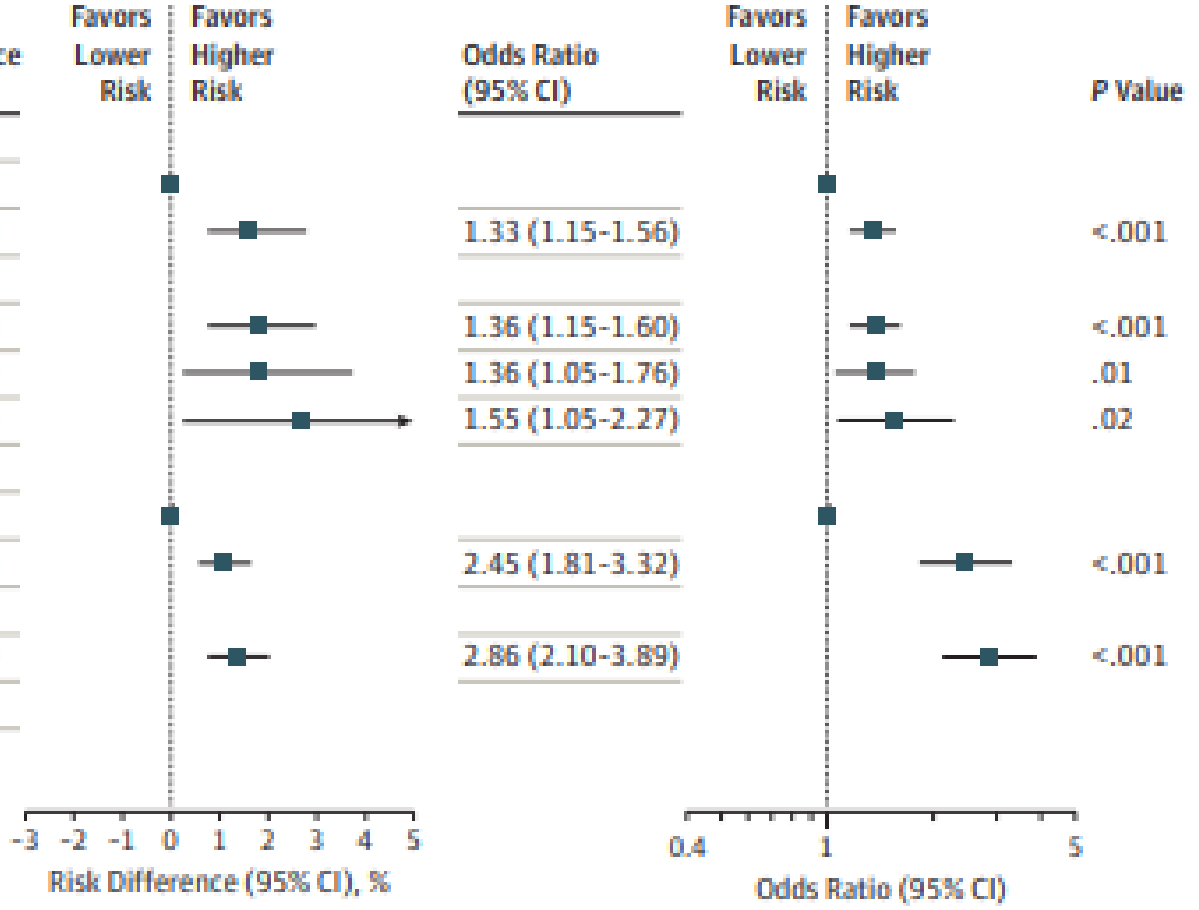


Figure 4. Association of Thyroid Peroxidase (TPO) Antibody Positivity With Preterm Birth

	No. of Events/ Total No. (%)	Risk Difference (95% CI), %	Odds Ratio (95% CI)	*P* Value
Preterm birth (gestational age <37 wk)				
TPO antibody negative (reference group)	1847/37 516 (4.9)			
TPO antibody positive	202/3043 (6.6)	1.6 (0.7-2.8)	1.33 (1.15-1.56)	<.001
TPO antibody positive and				
Thyrotropin within normal range	174/2566 (6.8)	1.8 (0.7-2.9)	1.36 (1.15-1.60)	<.001
Thyrotropin >2.5 mIU/L	64/989 (6.5)	1.8 (0.2-3.7)	1.36 (1.05-1.76)	.01
Thyrotropin >4 mIU/L	29/406 (7.1)	2.7 (0.2-6.3)	1.55 (1.05-2.27)	.02
Very preterm birth (gestational age <32 wk)				
TPO antibody negative (reference group)	268/37 516 (0.7)			
TPO antibody positive	53/3043 (1.7)	1.0 (0.6-1.7)	2.45 (1.81-3.32)	<.001
TPO antibody positive and[a]				
Thyrotropin within normal range	52/2566 (2.0)	1.3 (0.8-2.0)	2.86 (2.10-3.89)	<.001
Thyrotropin >2.5 mIU/L	7/989 (0.7)[b]			
Thyrotropin >4 mIU/L	0/406 (0)[b]			



- Preterm birth was 7.1% vs 5.0% in euthyroid women (absolute risk difference, 2.3% [95% CI,0.6%-4.5%]; OR, 1.46 [95% CI, 1.12-1.90]).
- Each 1-SD higher maternal TSH concentration was associated with a higher risk of preterm birth (absolute risk difference, 0.2% [95% CI, 0%-0.4%] per 1 SD; OR, 1.04 [95% CI, 1.00-1.09] per 1 SD).
- TPO antibody–positive women had a higher risk of preterm birth vs TPO antibody–negative women (6.6% vs 4.9%, respectively; absolute risk difference, 1.6% [95% CI, 0.7%-2.8%]; OR, 1.33 [95% CI, 1.15-1.56]).

TPOAb and Preterm labor
BMJ 2011

	Events			
	Positive for thyroid autoantibodies	Negative for thyroid autoantibodies	Random effects odds ratio (95% CI)	Random effects odds ratio (95% CI)
Ghafoor 2006[28]	27/100	8/100		4.25 (1.82 to 9.92)
Glinoer 1994[29]	14/87	48/606		2.23 (1.17 to 4.24)
Haddow 2010[43]	90/1247	543/8423		1.13 (0.90 to 1.42)
Iijima 1997[30]	5/125	29/951		1.32 (0.50 to 3.49)
Negro 2006[44]	13/58	71/869		3.25 (1.67 to 6.30)
Total (95% CI)	149/1617	699/10 949		2.07 (1.17 to 3.68)

Test for heterogeneity: $\tau^2=0.31$, $\chi^2=18.12$, df=4, P=0.001, $I^2=78\%$

Test for overall effect: z=2.48, P=0.01

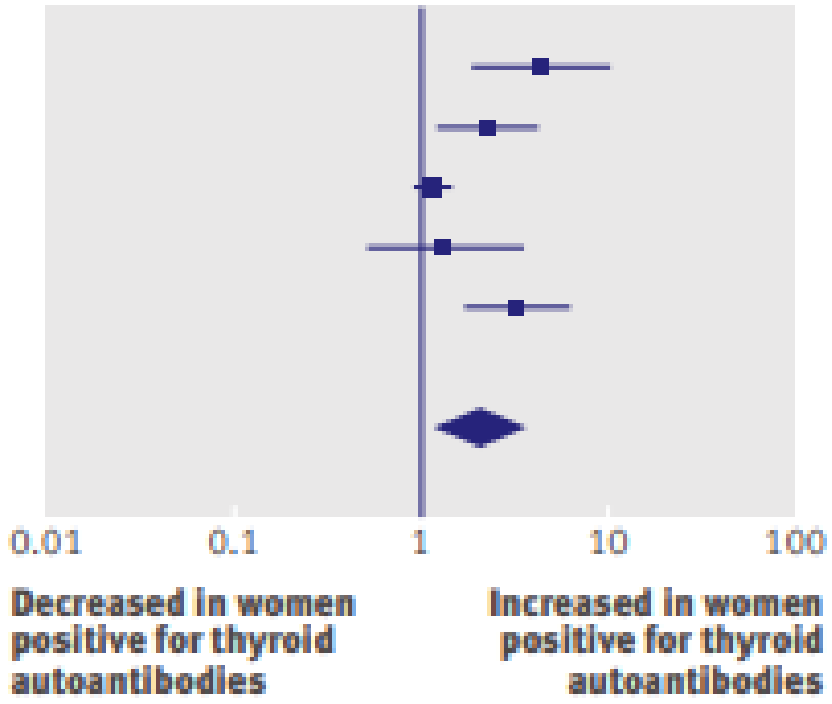


Fig 6 | Association between thyroid autoantibodies and preterm births

Thyroid and association with preterm birth

Among pregnant women without overt thyroid disease;

- Subclinical hypothyroidism,
- Isolated hypothyroxinemia, and
- TPO antibody positivity

Were significantly associated with higher risk of preterm birth

NO association between Tg antibody and preterm birth

TPOAb and thyroid disease in pregnancy

- TPO Ab positive women who are euthyroid are more likely to develop SCH and also overt hypothyroidism

TPO Ab & antenatal adverse events association

- The present studies suggest a link between TPOAb positivity and placental abruption; 3 fold increased. Obstet Gynecol 2011, Haddow et al
- Polyhydramnios: incidence was higher in TPOAb+ women compared to TPOAb-. (15% vs 2.7%) Int J Wndocrinol 2016
- Premature rupture of membranes Haddow et al 2011

NO CONFIRMED association between TPOAb and Pre-eclampsia or GDM

TPOAb & Post-partum complications

TPOAb positivity has been associated with a significantly increased risk of PPT.

The meta-analysis showed a statistically significant increased pooled odds of developing PPT ; OR: 11.54 95% CI 5.44-23.88. Van de Boogard

TPOAb & behavioural/ intellectual development

- ADHD
- Hearing loss
- Higher rates of babies needing NICU admission
- Neonatal respiratory distress
- Autism 6%

Effect of LT4 Tx in reducing miscarriage in women with NL TFT & Thyroid Abs

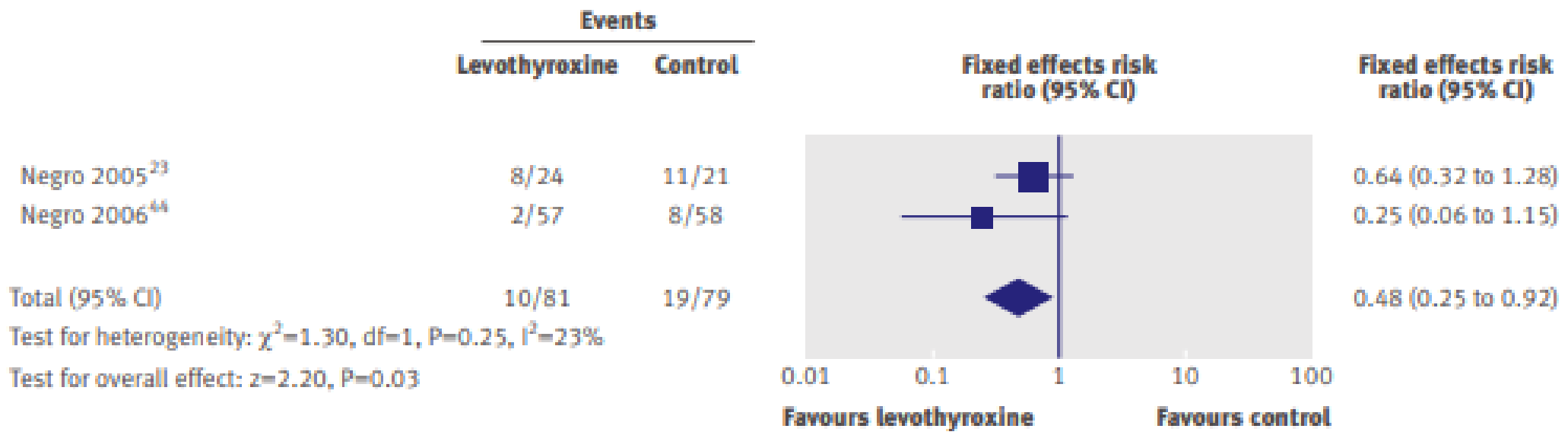


Fig 7 | Effect of levothyroxine treatment in reducing miscarriage in women with normal thyroid function and thyroid autoantibodies

TABLET Study

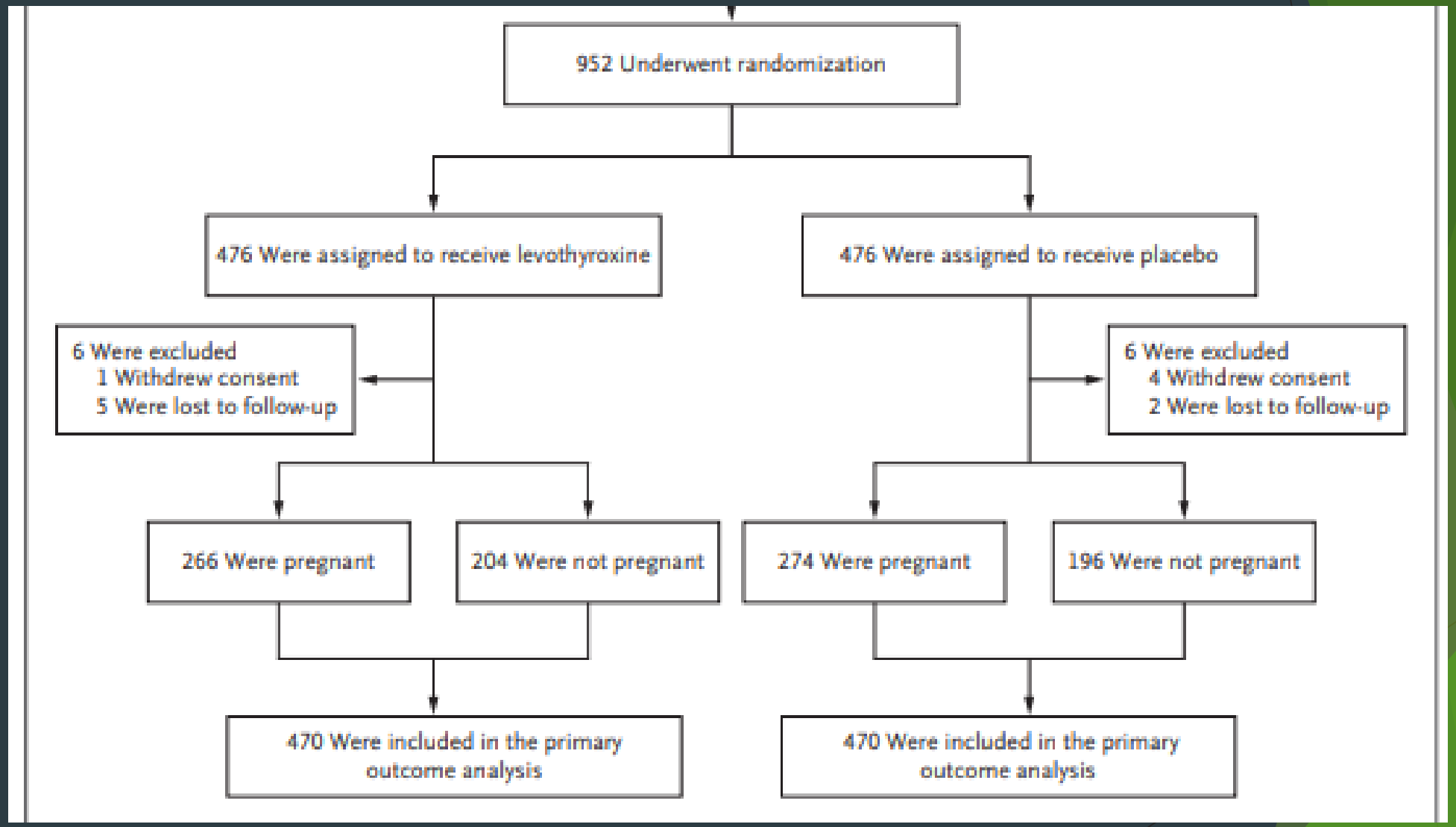
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception

METHODS

We conducted a double-blind, placebo-controlled trial to investigate whether levothyroxine treatment would increase live-birth rates among euthyroid women who had thyroid peroxidase antibodies and a history of miscarriage or infertility. A total of 19,585 women from 49 hospitals in the United Kingdom underwent testing for thyroid peroxidase antibodies and thyroid function. We randomly assigned 952 women to receive either 50 μg once daily of levothyroxine (476 women) or placebo (476 women) before conception through the end of pregnancy. The primary outcome was live birth after at least 34 weeks of gestation.


952 Underwent randomization
476 Were assigned to receive levothyroxine
476 Were assigned to receive placebo
6 Were excluded
1 Withdrew consent
5 Were lost to follow-up
6 Were excluded
4 Withdrew consent
2 Were lost to follow-up
266 Were pregnant
204 Were not pregnant
274 Were pregnant
196 Were not pregnant
470 Were included in the primary outcome analysis
470 Were included in the primary outcome analysis

LT4 group Placebo

Pregnancy history		
Nulliparous — no./total no. (%)	141/476 (29.6)	131/473 (27.7)
Previous miscarriages — no./total no. (%)†		
0	166/476 (34.9)	165/476 (34.7)
1 or 2	219/476 (46.0)	213/473 (45.0)
≥3	91/476 (19.1)	95/476 (20.0)
No. of previous miscarriages — median (IQR)		
In women with ≥1 miscarriage	2 (1–3)	2 (1–3)
First-trimester miscarriage (<14 wk) in women with ≥1 miscarriage	2 (1–3)	2 (1–3)
Previous preterm births at <34 wk — no./total no. (%)	11/476 (2.3)	10/473 (2.1)
Current treatment for infertility — no. (%)†	216 (45.4)	213 (44.7)
Prerandomization thyroid hormone concentrations		
Serum thyrotropin level†		
≤2.5 mIU/liter — no. (%)	329 (69.1)	330 (69.3)
>2.5 mIU/liter — no. (%)	147 (30.9)	146 (30.7)
Median level (IQR) — mIU/liter	2.10 (1.51–2.74)	2.01 (1.45–2.70)
Level on log scale — mIU/liter	0.674±0.422	0.652±0.418
Mean serum free thyroxine level — pmol/liter	14.6±1.9	14.5±2.0
Median serum thyroid peroxidase antibody level (IQR) — IU/ml§	170 (83–428)	202 (94–417)

Results

Table 2. Primary Outcome and Secondary Outcomes.*

Outcome	Levothyroxine Group	Placebo Group	Relative Risk or Mean Difference (95% CI)†
Primary outcome			
Live birth at ≥34 wk — no./total no. (%)	176/470 (37.4)	178/470 (37.9)	0.97 (0.83 to 1.14)
Secondary outcomes			
Pregnancy at ≤12 mo after enrollment — no./total no. (%)	266/470 (56.6)	274/470 (58.3)	0.97 (0.88 to 1.07)
Pregnancy outcomes — no./total no. (%)			
Clinical pregnancy at 7 wk‡	237/266 (89.1)	248/274 (90.5)	0.98 (0.93 to 1.04)
Ongoing pregnancy at 12 wk‡	194/266 (72.9)	200/274 (73.0)	1.00 (0.90 to 1.11)
Miscarriage at <24 wk§	75/266 (28.2)	81/274 (29.6)	0.95 (0.73 to 1.23)
Stillbirth: intrauterine death at ≥24 wk	1/266 (0.4)	0/274	—
Ectopic pregnancy	3/266 (1.1)	6/274 (2.2)	0.50 (0.13 to 1.99)
Termination of pregnancy¶	1/266 (0.4)	0/274	—
Live birth			
At <34 wk	10/266 (3.8)	10/274 (3.6)	1.02 (0.43 to 2.42)
At ≥34 wk	176/266 (66.2)	178/274 (65.0)	1.02 (0.90 to 1.15)
Neonatal outcomes among women with live births			

LT4 in euthyroid women with +TPO did not result in a higher rate of live births than placebo

RESULTS

The follow-up rate for the primary outcome was 98.7% (940 of 952 women). A total of 266 of 470 women in the levothyroxine group (56.6%) and 274 of 470 women in the placebo group (58.3%) became pregnant. The live-birth rate was 37.4% (176 of 470 women) in the levothyroxine group and 37.9% (178 of 470 women) in the placebo group (relative risk, 0.97; 95% confidence interval [CI], 0.83 to 1.14, P=0.74; absolute difference, −0.4 percentage points; 95% CI, −6.6 to 5.8). There were no significant between-group differences in other pregnancy outcomes, including pregnancy loss or preterm birth, or in neonatal outcomes. Serious adverse events occurred in 5.9% of women in the levothyroxine group and 3.8% in the placebo group (P=0.14).

CONCLUSIONS

The use of levothyroxine in euthyroid women with thyroid peroxidase antibodies did not result in a higher rate of live births than placebo. (Funded by the United Kingdom National Institute for Health Research; TABLET Current Controlled Trials number, ISRCTN15948785.)

ATA Recommendation

- Population-based trimester-specific reference ranges for TSH should be defined
- All pregnant women should ingest approximately 250 ug iodine daily. & 150 ug supplement in form of KI
- There is no need to initiate iodine supplementation in pregnant women who are being treated for hyperthyroidism or who are taking LT4 (Weak recommendation)
- Selenium supplementation is not recommended for the treatment of TPOAb positive women during pregnancy

Recommendations (ATA)

- Euthyroid pregnant women who are TPOAb or TgAb positive should have TSH measurement at time of pregnancy confirmation and every 4 weeks through pregnancy
- Treatment with LT4 should only be commenced if abnormality in TFT is detected
- LT4 may be considered for TPOAb positive women with TSH>2.5 and below the upper limit of the pregnancy specific range
- In euthyroid women with a prior history of pregnancy loss, treatment with T4 may be considered, 25 ug of LT4

ATA Recommendation

- The cut-off value of 4 mIU/L for TSH emerges as the intervention level for treatment of SCH in women with and without TAI in ART
- Insufficient evidence exists to determine whether LT4 therapy improves the success of pregnancy following ART in TPOAb- positive euthyroid women however, LT4 maybe considered in these cases . 25-50 ug/d

- **IVIG** treatment of euthyroid women with a hx of recurrent pregnancy loss is not recommended
- **Glucocorticoid** therapy is not recommended for thyroid autoantibody-positive euthyroid women undergoing ART

- Isolated hypothyroxinemia should not be treated
- TPO-Ab positive women offered TFT 6 weeks following delivery

Take home message

- So far we do not have any modality to decrease Anti TPO level, and we do not treat TPO Ab
- TFT should be checked every 4 weeks in TPOAb positive pregnant women during pregnancy , 6 weeks after delivery
- LT4 may be considered for TPOAb positive women with TSH>2.5 and below the upper limit of the pregnancy specific range
- In euthyroid women with a prior history of pregnancy loss, treatment with T4 may be considered, 25-50 ug of LT4

Hyperthyroidism & Pregnancy

Maternal

- Gestational HTN
- Preeclampsia x 4.7
- CHF
- Thyroid storm

Obstetrical

- Miscarriages
- Premature delivery x 16.5%
- Placental abruption
- Premature rupture of membrane

Hypothyroidism & Pregnancy

- Preterm delivery x 1.8
- Pregnancy loss x 1.8
- Caesarian rate x 2.8
- Fetal distress x 3.6
- Low birth weight x 3.1
- Hypertension x 2.24