

Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial)

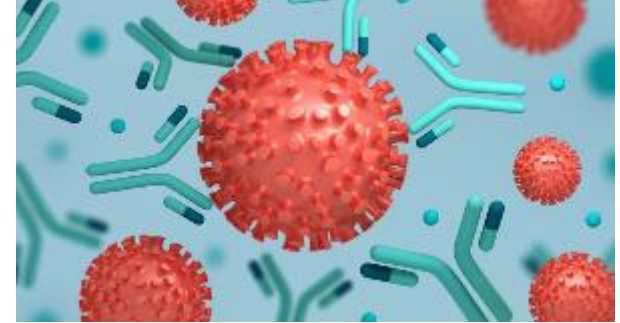
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Disclosure of speaker's interest

(Potential) conflict of interest	None
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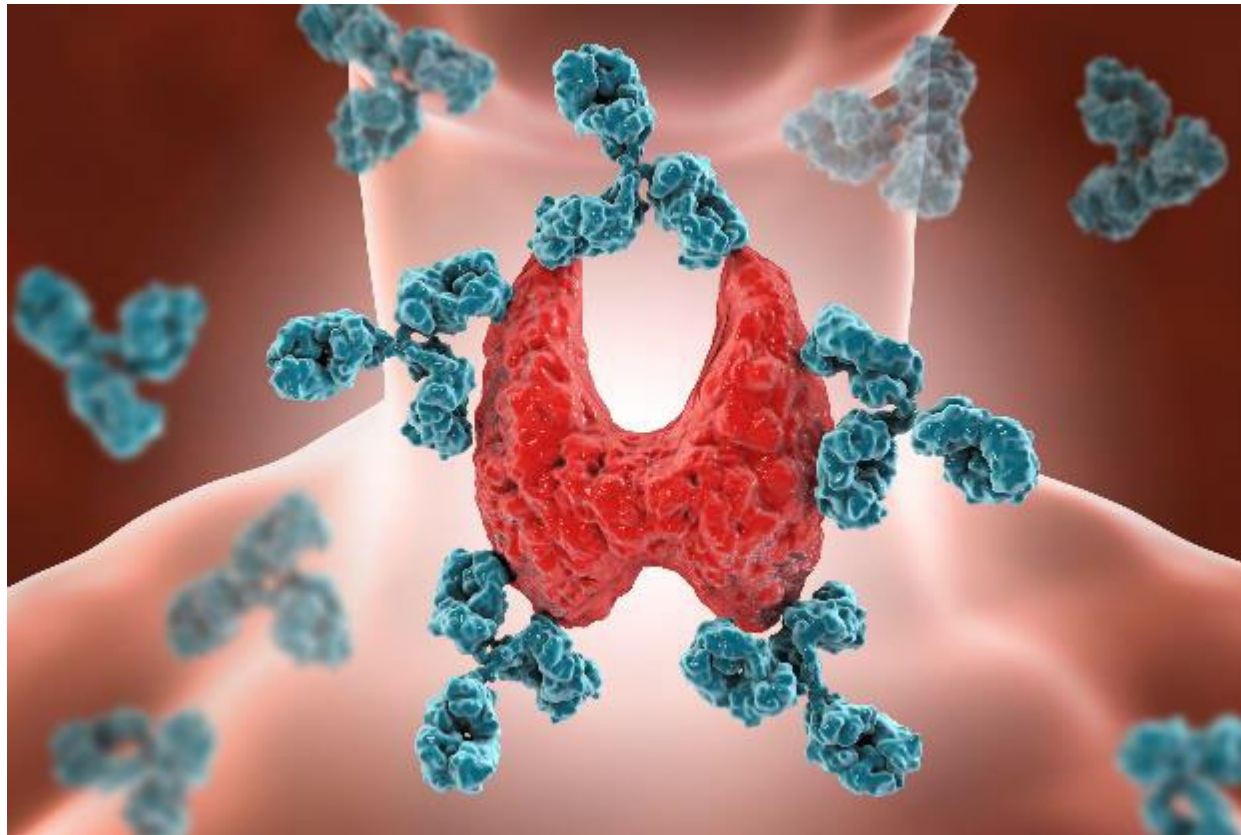


Background

- Women positive for thyroid peroxidase antibodies (TPOAb) higher risk:
 - single pregnancy loss OR 3.7, 95% CI 1.8-7.6
 - recurrent pregnancy loss OR 1.9, 95% CI 1.4-2.6
 - unexplained subfertility OR 1.5, 95% CI 1.1-2.0
 - preterm birth OR 1.9, 95% CI 1.1-3.5
 - postpartum thyroiditis OR 11.5, 95% CI 5.6-24



Background





Aim

- To determine if levothyroxine increases live birth rates in women who are TPO-Ab positive with recurrent pregnancy loss and normal thyroid function





Design

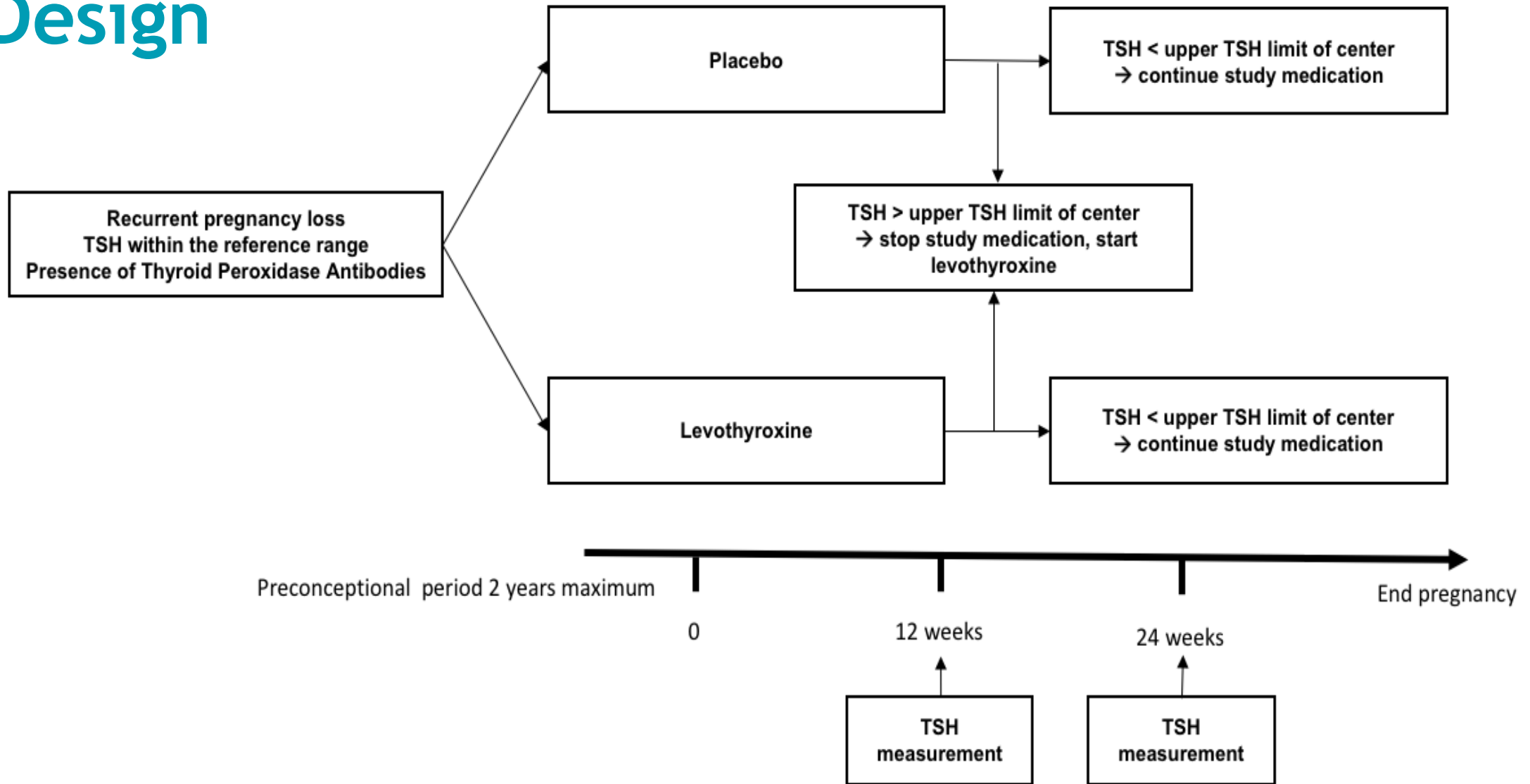
- Randomised, doubleblind, placebo-controlled trial
- 15 hospitals
 - 13 hospitals in the Netherlands
 - 1 university hospital in Belgium
 - 1 university hospital in Denmark
- Randomly assigned (1:1) to receive levothyroxine or placebo



Participants

- Women with recurrent pregnancy loss
 - TSH concentration within the centres' reference range
 - Positive for TPO-Ab
 - Aged 18-42 years
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- Exclusion criteria: antiphospholipid syndrome, other autoimmune diseases, thyroid disease, previous enrolment in this trial, or contraindications for levothyroxine

Design





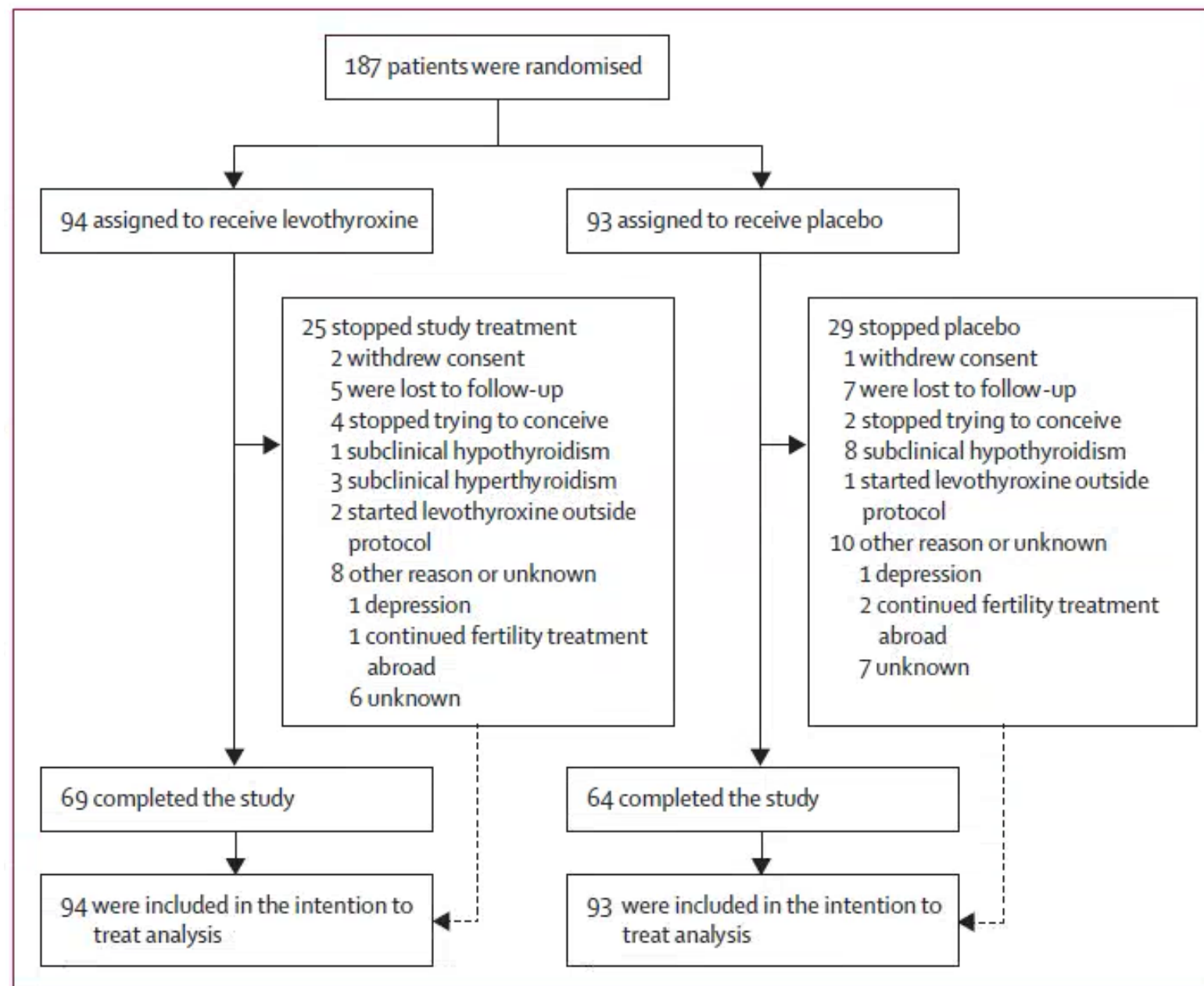
Outcomes and SAP

- Primary outcome: live birth
- Secondary outcomes: ongoing pregnancy at 12 weeks, pregnancy loss, preterm delivery, adverse events, serious adverse events, time to pregnancy
- Intention-to-treat principle



Results - Participants

- Between Jan 1, 2013, and Sept 19, 2019, 187 women consented to participate
- Prematurely stopped because of slow recruitment
 - 78% of 240 predefined patients
- Follow-up data available for the primary outcome in 172/187 (92%)





Baseline characteristics

Characteristic	Levothyroxine (N = 94)	Placebo (N = 93)
General demographic characteristics		
Female age - mean ($\pm$ SD)	34.9 $\pm$ 4.2	33.7 $\pm$ 4.7
BMI - mean ($\pm$ SD)	25.3 $\pm$ 5.5	24.8 $\pm$ 4.3
Smoking, no. (%)	9 (9.6)	12 (12.9)
Pregnancy history		
Nulliparous – no./total no. (%)	53 (56.4)	56 (60.2)
No. of previous miscarriages - median (range)	3 (2 - 7)	3 (2 - 9)
No. of previous miscarriages - mean ($\pm$ SD)	2.8 $\pm$ 1.0	2.9 $\pm$ 1.2
Prerandomisation thyroid hormone concentrations		
TSH level (mIU/liter) – median (IQR)	2.10 (1.40 – 3.11)	2.00 (1.36 – 2.70)
TPO-Ab (IU/ml) – median (IQR)	225 (99 – 566)	178 (96 – 662)



Outcomes

Outcome	Levothyroxine N = 94	Placebo N = 93	Adjusted risk ratio (95% CI) *	Risk Ratio (95% CI)
Primary outcome				
Live birth - no. (%)	47 / 94 (50.0)	45 / 93 (48.3)	1.03 (0.63 - 1.69)	1.03 (0.77 - 1.38)
Secondary outcomes				
Pregnancy at $\leq$ 24 months after enrolment	69 / 94 (73.4)	73 / 93 (78.5)	0.81 (0.42 - 1.57)	0.94 (0.81 - 1.12)
Pregnancy loss (at < 20 weeks) - no. (%)	16 / 69 (23.2)	24 / 73 (32.9)	0.83 (0.56 - 1.25)	0.71 (0.41 - 1.21)
Ongoing pregnancy - no. (%)	47 / 69 (68.1)	46 / 73 (63.0)	1.11 (0.58 - 2.12)	1.08 (0.85 - 1.37)
Ectopic pregnancy - no. (%)	2 / 69 (2.9)	3 / 73 (4.1)	0.37 (0.17 - 4.54)	0.71 (0.12 - 4.09)
Pregnancy of unknown location - no. (%)	4 / 69 (5.8)	1 / 73 (1.4)	4.27 (0.46 - 39.60)	4.23 (0.48 - 36.93)
Preterm birth (at < 37 weeks) - no. (%)	4 / 69 (5.8)	3 / 73 (4.1)	1.39 (0.30 - 6.49)	1.41 (0.33 - 6.08)
Serious adverse events - no. (%)	7 / 94 (7.4)	7 / 93 (7.5)	1.00 (0.35 - 2.85)	1.00 (0.92 - 1.09)



Lessons learned

- Budget too low
- Slow recruitment
- Regulations
- Persistence paid off!





Conclusion

- Levothyroxine treatment does not increase live birth rates in women with normal thyroid function who have a history of recurrent pregnancy loss and are TPO-Ab positive