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Levothyroxine in euthyroid thyroid peroxidase antibody positive women with recurrent pregnancy loss (T4LIFE trial): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Women positive for thyroid peroxidase antibodies (TPO-Ab) have a higher risk of recurrent pregnancy loss. Evidence on whether levothyroxine treatment improves pregnancy outcomes in women who are TPO-Ab positive women with recurrent pregnancy loss is scarce. The aim of this study was to determine if levothyroxine increases live birth rates in women who were TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

Methods The T4LIFE trial was an international, double-blind, placebo-controlled, phase 3 study done in 13 secondary and tertiary hospitals in the Netherlands, one tertiary hospital in Belgium, and one tertiary hospital in Denmark. Women (18–42 years) who were TPO-Ab positive, had two or more pregnancy losses, and had a thyroid stimulating hormone (TSH) concentration within the institutional reference range were eligible for inclusion. Women were excluded if they had antiphospholipid syndrome (lupus anticoagulant, anticardiolipin IgG or IgM antibodies, or β2-glycoprotein-I IgG or IgM antibodies), other autoimmune diseases, thyroid disease, previous enrolment in this trial, or contraindications for levothyroxine use. Before conception, women were randomly assigned (1:1) to receive either levothyroxine or placebo orally once daily. The daily dose of levothyroxine was based on preconception TSH concentration and ranged from 0·5–1·0 μg/kg bodyweight. Levothyroxine or placebo was continued until the end of pregnancy. The primary outcome was live birth, defined as the birth of a living child beyond 24 weeks of gestation measured in the intention-to-treat population. The trial was registered within the Netherlands Trial Register, NTR3364 and with EudraCT, 2011-001820-39.

Results Between Jan 1, 2013, and Sept 19, 2019, 187 women were included in the study: 94 (50%) were assigned to the levothyroxine group and 93 (50%) were assigned to the placebo group. The trial was prematurely stopped when 187 (78%) of the 240 predefined patients had been included because of slow recruitment. 47 (50%) women in the levothyroxine group and 45 (48%) women in the placebo group had live births (risk ratio 1·03 [95% CI 0·77 to 1·38]; absolute risk difference 1·6% [95% CI –12·7 to 15·9]). Seven (7%) women in the levothyroxine group and seven (8%) in the placebo group reported adverse events, none of them were directly related to the study procedure.

Interpretation Compared with placebo, levothyroxine treatment did not result in higher live birth rates in euthyroid women with recurrent pregnancy loss who were positive for TPO-Ab. On the basis of our findings, we do not advise routine use of levothyroxine in women who are TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

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Introduction

Recurrent pregnancy loss—defined as the loss of two or more pregnancies—is a significant health problem, affecting the physical and psychological wellbeing of prospective parents. It is a devastating experience for most couples and often leads to a long process of consulting multiple physicians and clinics in search for a cause and treatment.[1] Approximately 2% of women trying to conceive have recurrent pregnancy loss.[2]

Women positive for thyroid peroxidase antibodies (TPO-Ab) have a higher risk of single pregnancy loss and recurrent pregnancy loss.[3,4] TPO-Ab positivity is also associated with other pregnancy complications, including unexplained subfertility, preterm birth, and postpartum

Research in context

Evidence before this study

We searched PubMed for studies published between the inception of the database and Nov 1, 2021, using the search terms (" recurrent miscarriage" OR "recurrent pregnancy loss") AND ("thyroid peroxidase antibodies" OR "thyroid autoimmunity") to find randomised trials and meta-analyses of randomised trials, published in English, that evaluated the effectiveness of levothyroxine supplementation on live birth rates in women with thyroid peroxidase antibodies (TPO-Ab) and recurrent pregnancy loss. We did not find any randomised trials that included women with recurrent pregnancy loss, but we did find a meta-analysis of 2263 women who were TPO-Ab positive enrolled in six randomised trials. None of the included studies in this meta-analysis focused on women with recurrent pregnancy loss. No differences in pregnancy loss rates and live birth were found in women positive for TPO-Ab who received levothyroxine compared with control groups. The large randomised TABLET trial, included in the meta-analysis, did a subgroup analysis of women with recurrent pregnancy loss. No effect of levothyroxine was seen on live birth rates in women positive for TPO-Ab and recurrent pregnancy loss compared with placebo (RR 1·04 [95% CI 0·72–1·51). However, the TABLET trial did not exclude women with other risk factors for recurrent pregnancy loss besides TPO-Ab, which reduced the likelihood of a beneficial effect of levothyroxine for this subgroup. In the TABLET trial a fixed dose of levothyroxine was used, which did not reduce the number of abnormal thyroid function tests during pregnancy in comparison with placebo.

Added value of this study

Our international, double-blind randomised trial focussed on women with recurrent pregnancy loss who were positive for TPO-Ab. Levothyroxine was dosed depending on the participant's body weight and thyroid stimulating hormone concentration. There was no significant difference in live birth rate between the levothyroxine and placebo groups. There was also no evidence of a difference in any of the secondary outcomes, including pregnancy losses, ongoing pregnancy rates, and preterm birth.

Implications of all the available evidence

Routine use of levothyroxine in women with recurrent pregnancy loss, normal thyroid function, and positive for TPO-Ab is not recommended.

thyroiditis.[3,4] A leading hypothesis for this association is that women positive for TPO-Ab have a chronic lymphocytic thyroiditis that has not yet led to hypothyroidism. Subclinical or overt hypothyroidism can become apparent in early pregnancy because of the increased need for thyroid hormone.[5] Moreover, women positive for TPO-Ab have an impaired normal physiological thyroidal response to human chorionic gonadotropin in early pregnancy;[6] therefore, levothyroxine supplementation has been proposed to reduce the risk of pregnancy complications.

Starting levothyroxine preconceptionally would correct a possible thyroid hormone deficiency in the earliest phase of pregnancy. Previously published studies initiated levothyroxine during pregnancy.[7,8] The most recent developments in this area are two large randomised trials that investigated the effect of levothyroxine supplementation started before conception on live birth rates in euthyroid TPO-Ab positive women with a history of infertility or pregnancy loss[9] or undergoing in-vitro fertilisation (IVF).[10] Neither study found evidence that levothyroxine affected live birth rate.[5,6] A systematic review and meta-analysis including six trials found no difference in pregnancy loss rates (relative risk [RR] 0·93 [95% CI 0·76–1·14]) and live birth rates (RR 1·01 [0·89–1·16]) in women positive for TPO-Ab treated with levothyroxine compared with controls.[11] None of these studies focused on women with recurrent pregnancy loss.

Supplementation of levothyroxine in women who are TPO-Ab positive with normal thyroid function and recurrent pregnancy loss remains controversial due to a scarcity of evidence specific for this population. The European Society of Human Reproduction and Embryology Guideline on Recurrent Pregnancy Loss states that there is not enough evidence to support levothyroxine treatment outside of clinical trials.[12] The guidelines of the American Thyroid Association state that supplementation of levothyroxine in TPO-Ab positive women with recurrent pregnancy loss might be considered given its potential benefits in comparison with its minimal risk.[13] Neither the dated guidelines of the American Society for Reproductive Medicine nor the Royal College of Obstetricians and Gynaecologist recommend treatment of women who were TPO-Ab positive with a history of recurrent pregnancy loss.[14,15]

We are faced with conflicting recommendations from international guidelines due to a scarcity of high-quality evidence on the efficacy of levothyroxine treatment in euthyroid women who are TPO-Ab positive with recurrent pregnancy loss. We aimed to determine if levothyroxine increases live birth rates in women who were TPO-Ab positive with recurrent pregnancy loss and normal thyroid function.

Methods

Study design and participants

The T4LIFE trial was a multicentre, randomised, double-blind, placebo-controlled study done in 15 hospitals. 13 hospitals were in the Netherlands (four university hospitals and nine non-university hospitals)—all of which collaborated in the Dutch Consortium for Women's Health Research—one university hospital in Belgium, and one university hospital in Denmark.

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See Online for appendix

Women with two or more pregnancy losses were diagnostically tested for recurrent pregnancy loss in the participating centres, including assessment of thyroid-stimulating hormone (TSH) and TPO-Ab concentration. If women had TSH concentration within the centres' reference range (appendix pp 3–4) and were positive for TPO-Ab they were invited to participate in the study. Women aged 18–42 years at randomisation were eligible for the study.

Women were excluded if they had antiphospholipid syndrome (lupus anticoagulant, anticardiolipin IgG or IgM antibodies, or β2-Glycoprotein-I IgG or IgM antibodies), other autoimmune diseases, thyroid disease, previous enrolment in this trial, or contraindications for levothyroxine use.

Recurrent pregnancy loss was defined as two or more, not necessarily consecutive, pregnancy losses before 20 weeks of gestational age. The definition of previous pregnancy loss included documentation of pregnancy by a positive pregnancy test in combination with clinical manifestations of pregnancy loss (vaginal bleeding or cramping pain in the abdomen); it did not include the loss of a biochemical pregnancy (ie, pregnancy confirmed through elevated human chorionic gonadotropin concentrations, but not on ultrasound examination). Women trying to conceive both with and without the use of assisted reproductive technology (ART) were included. Women who were positive for TPO-Ab when the concentration of TPO-Ab exceeded the institutional reference range were included in the trial. The assays and reference ranges are listed in the appendix (pp 3–4). All participants provided written informed consent.

The trial protocol and all subsequent amendments were approved by the Central Committee on Research Involving Human Subjects, by the ethics committee of the Amsterdam University Medical Centre (MEC 2012_151), by the ethics committee on research of the Capital Region, Denmark (H-2-2013-070), by the medical ethics committee of Universitair Ziekenhuis Brussel, Belgium and Free University of Brussels, Brussels, Belgium (143), and by the boards of directors of all participating hospitals. The trial was registered within the Netherlands Trial Register, NTR3364, and with EudraCT, 2011-001820-39. Study medication was produced and packaged by Tiofarma BV, Tiofarma BV had no role in the trial design, data-analysis and interpretation. A centralised and independent Data and Safety Monitoring Board provided trial oversight and monitoring. The study protocol has been published previously.[16]

Randomisation and masking

Women were randomly assigned (1:1) to receive levothyroxine (levothyroxine group) or placebo (placebo group). Randomisation was done centrally with a web-based programme stratified by centre. Each participant was assigned a code through the programme. The research nurse or doctor ordered the study medication via this code at the pharmacy. The pharmacist checked the code on the randomisation list and provided tablets containing 25 µg levothyroxine or indistinguishable placebo tablets without levothyroxine. As a result, the participants, the research nurses, and the study team were masked to treatment.

Procedures

Participants in the levothyroxine group received once daily oral levothyroxine tablets; the placebo group received a corresponding placebo. An individual dosage for each participant was calculated based on body weight (kg) and TSH concentration (mU/L) at screening. If the TSH concentration was less than 1·0 mU/L the participants received 0·5 µg/kg levothyroxine, if the TSH concentration was 1·0–2·5 mU/L the participants received 0·75 µg/kg levothyroxine, and if the TSH concentration was more than 2·5 mU/L the participants received 1·0 µg/kg levothyroxine. Dosage was rounded in half tablets (12·5 µg). Study medication was initiated before conception and continued until the end of pregnancy in the same dosage (appendix p 2).

Participants received standard obstetrical care. In addition, TSH concentrations were assessed at three different time points: preconceptionally, in the first trimester (before the 12th week of gestation) and second trimester (before the 20th week of gestation). If the TSH concentration was outside the centres' reference range, women discontinued study medication and were referred to an endocrinologist to receive standard care. If the TSH concentration remained within the centres' reference range, the study medication was continued until the end of the pregnancy. For women with an ongoing pregnancy, an ultrasound measurement during the first trimester was done to determine gestational age. If a pregnancy was lost before the scheduled ultrasound, the first day of the last menstruation was used to calculate gestational age. For each individual patient, the trial was finished after the end of the first subsequent clinical pregnancy, whether it was a pregnancy loss, ectopic pregnancy, molar pregnancy, live birth, or after a 2-year period of preconception use of study medication, not resulting in a pregnancy (appendix p 2).

Outcomes

The primary outcome was live birth, defined as the birth of a living child after 24 weeks gestation. Prespecified secondary outcomes were ongoing pregnancy at 12 weeks, pregnancy loss (defined as pregnancy loss before 20 weeks gestation), preterm delivery (preterm birth defined as birth before 37 weeks gestation), adverse events (defined as any untoward medical occurrence in a participant or administration of a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment), serious adverse events (any untoward medical occurrence that at any dose results in death or is life-threatening that results in: requirement of inpatient hospitalisation or prolongation of existing hospitalisation,

persistent or significant disability or incapacity, or is a congenital anomaly or birth defect), time to pregnancy (defined as the interval between moment of randomisation and the date of positive pregnancy test), and survival at 28 days of neonatal life.

Statistical analysis

Previous data suggested that the live birth rate in women who were TPO-Ab positive with recurrent pregnancy loss but had not received levothyroxine was 55%, and levothyroxine has been shown to reduce risk of pregnancy loss by 52%.[17–19] We hypothesised that levothyroxine could increase the live birth rate by 20% by increasing the conception rate and decreasing pregnancy loss.

To detect an increase of 20% in live birth rate from 55% to 75%, 90 women per group were needed (alpha error rate of 5% and beta error rate of 20%). Anticipating a worst-case loss to follow-up rate of 10%, a total of 200 participants (100 in each group) would be required. We expected that 15% of women in the placebo group would have to discontinue the study medication because of the development of subclinical or clinical hypothyroidism. To make sure we could account for these dropouts we determined that 120 patients should be assigned to each group, 240 patients in total.

Statistical analyses were done as prespecified in our analysis plan. Baseline data and outcome data were summarised separately. For continuous variables, we examined the distribution of the observations. Normally distributed variables were summarised as means with SDs; if not normally distributed, medians and IQRs were reported. For dichotomous data, we provided proportions (or percentages). Dichotomous outcomes were analysed with either Fisher's Exact test or χ^2 test as appropriate. For continuous outcomes, we used t-test if the observations in each study group were normally distributed and Mann-Whitney U test if non-normally distributed.

Efficacy analyses was done according to the intention-to-treat principle and included all randomly assigned women. We compared the rate of the primary outcome (ie, live birth rate) between the intervention group and the control group. Differences in live birth rates were expressed as crude and centre adjusted risk ratio using log-linear binomial regression and as absolute risk difference, with associated 95% CI; the placebo group was the reference. For secondary outcomes, crude and adjusted risk ratios were calculated. Kaplan-Meier curves were used to estimate the cumulative probability of conception leading to live birth over time, and the log-rank test was used to assess differences. A preplanned per-protocol analysis of women that completed the study was done. Subsequently, two post-hoc subgroup analyses were done for the primary outcome: we assessed the effect of preconceptional TSH concentration at a cut-off of 2·5mU/L and the effect of two versus three or more previous pregnancy losses. The results of these analyses are shown in the appendix (p 7). All statistical analyses were done with SPSS (version 26.0).

	Levothyroxine group (n=94)	Placebo group (n=93)
General demographic characteristics		
Age	34·9 (4·2)	33·7 (4·7)
BMI	25·3 (5·5)	24·8 (4·3)
Current smoker	9 (10%)	12 (13%)
Race*		
White	72/90 (80%)	76 (82%)
Black	6/90 (7%)	9 (10%)
Asian	2/90 (2%)	2 (2%)
Other	10/90 (11%)	6 (6%)
Pregnancy history		
Nulliparous	53 (56%)	56 (60%)
Previous miscarriages	3 (2–7)	3 (2–9)
Previous miscarriages	2·8 (1·0)	2·9 (1·2)
Pre-randomisation thyroid hormone concentrations		
TSH concentration (mIU/L)	2·10 (1·40–3·11)	2·00 (1·36–2·70)
TPO-Ab (IU/mL)	225 (99–566)	178 (96–662)

Data are mean (SD), n (%), n/N (%), or median (IQR). BMI=body–mass index. TPO-Ab=thyroid peroxidase antibodies. TSH=thyroid stimulating hormone.
*Data on race or ethnicity were missing for four (4%) women in the levothyroxine group.

Table 1: **Baseline characteristics of the intention-to-treat population**

Role of the funding source

This trial was supported by a Dutch Organization for Health Research and Development grant (836011012) and a Fonds NutsOhra grant (1104-002). Grants were also provided by the Dutch Patient Organization of Thyroid Disorders, the Jan Dekkerstichting and Dr Ludgardine Bouwmanstichting, and through a personal donation via the Dutch Patient Organization of Thyroid Disorders. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 1, 2013, and Sept 19, 2019, 187 women consented to participate and were randomly assigned to the levothyroxine group (94 [50%] women) or the placebo group (93 [50%] women). The trial was prematurely stopped because of slow recruitment when 187 (78%) of the 240 predefined patients had been included.

Baseline characteristics were similar between the levothyroxine group and placebo group (table 1). Follow-up data were available for the primary outcome in 172 (92%) of the 187 women. Two (2%) of 94 women in the levothyroxine group withdrew consent; five (5%) women in this group were lost to follow-up. In the placebo group, one (1%) of 93 woman withdrew consent, and seven (8%) women were lost to follow-up. Two (2%) patients in the levothyroxine group did not meet the inclusion criteria in hindsight: one (1%) had a history of hyperthyroidism and one (1%) had a TSH concentration above the centre's

specific reference range. These women were included in the intention-to-treat analysis, but excluded from the per-protocol analysis.

In the placebo group, eight (9%) of the 93 women developed subclinical hypothyroidism during the study period and discontinued the trial medication. In the levothyroxine group, one (1%) of the 94 women developed subclinical hypothyroidism and three (3%) women developed subclinical hyperthyroidism. In two of these women low TSH concentrations could be ascribed to transient hyperthyroidism of early pregnancy (figure 1).

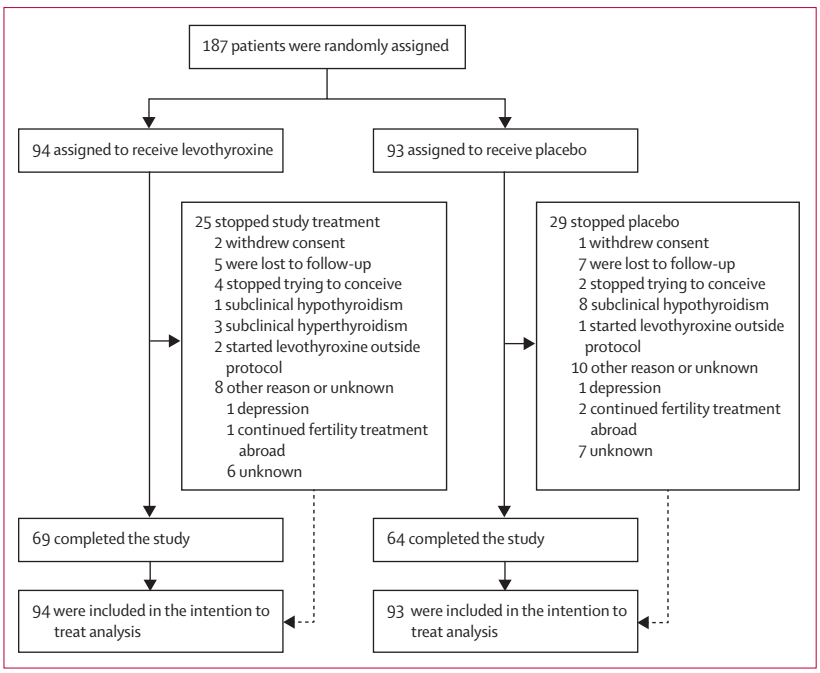

Figure 1: **Trial profile**

	Levothyroxine group (n=94)	Placebo group (n=93)	Adjusted risk ratio (95% CI)*	Risk Ratio (95% CI)
Primary outcome				
Live birth	47 (50%)	45 (48%)	1·03 (0·63–1·69)	1·03 (0·77–1·38)
Secondary outcome†				
Pregnancy at ≤24 months after enrolment	69/94 (73%)	73/93 (78%)	0·81 (0·42–1·57)	0·94 (0·81–1·12)
Pregnancy loss (at <20 weeks)	16/69 (23%)	24/73 (33%)	0·83 (0·56–1·25)	0·71 (0·41–1·21)
Ongoing pregnancy	47/69 (68%)	46/73 (63%)	1·11 (0·58–2·12)	1·08 (0·85–1·37)
Ectopic pregnancy	2/69 (3%)	3/73 (4%)	0·37 (0·17–4·54)	0·71 (0·12–4·09)
Pregnancy of unknown location	4/69 (6%)	1/73 (1%)	4·27 (0·46–39·60)	4·23 (0·48–36·93)
Preterm birth (at <37 weeks)	4/69 (6%)	3/73 (4%)	1·39 (0·30–6·49)	1·41 (0·33–6·08)
Survival 28 days of neonatal life	47/69 (68%)	45/73 (62%)	0·96 (0·64–1·45)	1·11 (0·87–1·41)
Serious adverse events	7/94 (7%)	7/93 (8%)	1·00 (0·35–2·85)	1·00 (0·92–1·09)

Data are n (%) or n/N (%), unless otherwise stated. *Adjusted for stratification per centre. †Patients could meet more than one secondary endpoint.

Table 2: **Primary outcome and secondary outcomes assessed in the intention-to-treat population**

47 (50%) of 94 women in the levothyroxine group had live births compared with 45 (48%) of 93 women in the placebo group (risk ratio 1·03 [95% CI 0·77 to 1·38; table 2). This corresponds to an absolute risk difference of 1·6% (–12·7 to 15·9). The time to conception leading to live birth was similar in both groups (log-rank score 0·004; p=0·95). Median time to conception leading to live birth was 9·1 months (95% CI 4·8 to 13·4) in the levothyroxine group and 9·8 months (5·4 to 14·2) in the placebo group (figure 2). There were no significant differences with respect to the secondary outcomes between the levothyroxine group and the placebo group (table 2). There were also no significant differences in results between groups in the per protocol analysis (appendix p 5).

69 (73%) of 94 women in the levothyroxine group and 73 (78%) of 93 women in the placebo group became pregnant (table 2). In the levothyroxine group, 50 (72%) of the 69 women conceived without the use of ART, three (4%) women conceived with ovulation induction, six (9%) with intrauterine insemination, and ten (14%) with IVF or intracytoplasmic sperm injection. In the placebo group 52 (71%) of 73 women conceived without ART, four (5%) women conceived with ovulation induction, four (5%) with intrauterine insemination, and 13 (18%) with IVF or intracytoplasmic sperm injection (appendix p 6).

There was one twin pregnancy in the placebo group which resulted in the birth of two healthy children.

As expected, TSH concentrations in the first trimester and second trimester were lower in the levothyroxine group compared with the placebo group. In the first trimester, median TSH concentration in the levothyroxine group was 1·37 mIU/L (IQR 0·65–2·16) compared with 1·79 mIU/L (1·30–2·68) in the placebo group. In the second trimester, the median TSH concentration was 1·52 mIU/L (0·92–1·93) in the levothyroxine group and 1·90 mIU/L (IQR 1·14–2·40) in the placebo group. We did two post-hoc subgroup analyses, one of which assessed a preconceptional TSH concentration at a cut-off 2·5mU/L and the other investigated the effects of levothyroxine in women with three or more previous pregnancy losses. Subgrouping women according to preconceptional TSH concentration and by number of pregnancy losses did not appear to affect live birth rates for levothyroxine versus placebo and there was no indication for interaction (appendix p 7).

Serious adverse events occurred in seven (7%) of 94 women in the levothyroxine group and in seven (8%) of 93 women in the placebo group (table 3). None of the adverse events were related to the study drug and no study related deaths were reported.

Discussion

Our international, double-blind, randomised trial showed no significant differences in live birth rate after

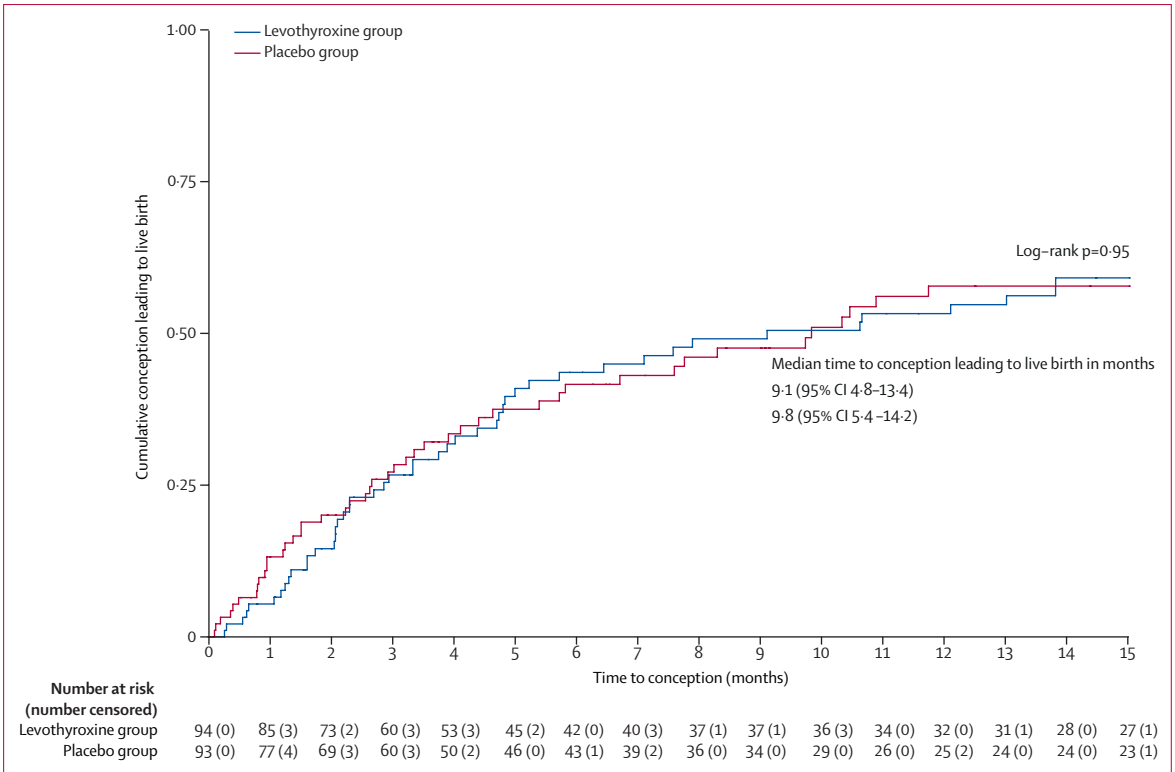

Figure 2: **Cumulative probability of conception leading to live birth**
Censoring occurred 13 times before 6 months of follow up in both groups.

levothyroxine treatment in women with recurrent pregnancy loss who were positive for TPO-Ab compared with placebo. There was also no evidence of a difference in any of the secondary outcomes, including pregnancy losses, ongoing pregnancy rates, and preterm birth.

Our study provides added value in the field of recurrent pregnancy loss research, in which large treatment trials to date are missing. Recruitment to this type of trial is extremely difficult due to the relative rarity of women with recurrent pregnancy loss who are TPO-Ab positive with normal thyroid function tests.

Because antiphospholipid syndrome has a strong association with recurrent pregnancy loss, we excluded women with antiphospholipid syndrome so no bias is to be expected from this association. Another strength of the study is that we used a pragmatic study design that reflects daily clinical practice and analysed the data according to the intention-to-treat principle. The generalisability of the findings are reasonable because we included women from multiple centres and from three high-income countries. Neither the intention-to-treat analysis nor the per-protocol analysis show any advantage of levothyroxine over placebo. Another strength of our trial is the individual adjustment of the study medication dose, depending on the participant's body weight and TSH concentration.

	Levothyroxine group (n=94)	Placebo group (n=93)
Total number of patients experiencing a serious adverse events	7 (7%)	7 (8%)
Obstetric or gyneacological		
Hospital admission for ectopic pregnancy	2/7 (29%)	3/7 (43%)
Hospital admission for vaginal bleeding in pregnancy	4/7 (57%)	0
Hospital admission for ovarian hyperstimulation syndrome	0	1/7 (14%)
Hospital admission for hyperemesis gravidarum	0	1/7 (14%)
Hospital admission for preterm premature rupture of membranes	0	1/7 (14%)
Thyroid or endocrine		
Hospital admission for operation (hemithyroidectomy)	1/7 (14%)	0
Psychological		
Admission to psychiatric hospital due to risk of suicide	0	1/7 (14%)

Data are n (%) or n/N (%)

Table 3: **Serious adverse events**

Including women with two or more pregnancy losses, compared with including those with three or more pregnancy losses might dilute the frequency of thyroid autoimmunity in couples with recurrent pregnancy loss or the treatment effect of levothyroxine. Our unplanned subgroup analysis of women with two pregnancy losses compared with those with three or more previous pregnancy losses did not suggest higher effectiveness of

levothyroxine in women with three or more previous pregnancy losses.

Our study has limitations. When designing the trial, the available literature on which we based our hypothesis for our power analysis and sample size was scarce and studies were of low quality. When setting up our trial, published data described varying prevalence of women who were TPO-Ab positive with recurrent pregnancy loss ranging from 20% to 36%.[20–22] During the trial, additional studies were published that suggest lower TPO-Ab positivity (15–17%) in women with recurrent pregnancy loss.[23,24] This expected lower prevalence made the recruitment of patients difficult, a problem that other similar studies have also faced.[9] We adhered to the predefined inclusion criteria because there was a high need for evidence in this specific patient group. The slow recruitment forced us to formally stop the trial once 187 women had been recruited. With this sample size we are not able to fully account for dropouts and the estimates have wide 95% CIs. Detection of a difference of 5% in live birth rate would require inclusion of more than 3000 women. Our results suggest levothyroxine treatment results in no or at most a very small increase in live birth rate. The Kaplan-Meyer curve shows an overlapping time to conception leading to live birth for the levothyroxine and placebo groups. Furthermore, our results are in line with previous trials in women who were TPO-Ab positive with a history of infertility or pregnancy loss[9] or undergoing IVF.[10]

The use of different assays for TPO-Ab and TSH concentrations in various centres is another potential limitation of our study. However, it can be regarded as a reflection of daily practice and the various measurements per individual patient were carried out in the same centre.

A considerable proportion of the women discontinued study medication. This can be partly explained by the study design and the study population. In total, 12 women discontinued the study medication because of abnormal TSH measurements. Other reasons mentioned for withdrawal from the study included no longer wanting to become pregnant, continuing fertility treatment abroad, and depressive symptoms.

On the basis of our findings, we do not advise routine use of levothyroxine in women with recurrent pregnancy loss who have normal thyroid function and are positive for TPO-Ab. Our results are in line with the findings from trials that studied the effect of levothyroxine on live birth rates in women who are TPO-Ab positive with a history of pregnancy loss or infertility,[9] and in those using IVF.[10] As expected, the live birth rate in women with recurrent pregnancy loss was higher than in women with a history of infertility, but both in our population and in randomised trials[9,10] of infertile women, levothyroxine did not appear to increase live birth rates. Women positive for TPO-Ab might, however, develop subclinical hypothyroidism during pregnancy. As such, measurement of TSH concentrations during pregnancy in women known to be TPO-Ab positive could be considered so that treatment can be started in case of abnormal TSH concentrations.

In conclusion, our trial suggests that 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.

Contributors

RV, MvW, PHB and MG designed the trial protocol and applied for the research grants. MMvD, PHB, and MG coordinated the trial. MMvD, RV, M-LPvdH, SdW, WKK, AH, JMS, HRV, KAB, CHdK, WV, OBC, CK, JPdB, DNMP, HT, PHB, and MG recruited participants. MMvD and MvW did the statistical analysis. MMvD and MG accessed and verified the data. MMvD, MvW, PHB, and MG interpreted the data and wrote the manuscript. All authors revised the manuscript and approved the final submitted version.

Declaration of interests

MG received research and educational grants from Guerbet, Merck, and Ferring, not related to the presented work, paid to their institution. AH reports an unrestricted educational grant from Ferring, not related to the presented work, paid to their institution. All other authors declare no competing interests.

Data sharing

Deidentified participant data, study protocol, and the statistical analysis plan will be made available with publication. The deidentified participant data can be requested by contacting the corresponding author after approval of a proposal and with a signed data access agreement.

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