ORIGINAL ARTICLE

Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception

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ABSTRACT

BACKGROUND

Thyroid peroxidase antibodies are associated with an increased risk of miscarriage and preterm birth, even when thyroid function is normal. Small trials indicate that the use of levothyroxine could reduce the incidence of such adverse outcomes.

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.

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.)

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Miscarriage, which occurs in one of five women who conceive, is one of the most common complications of pregnancy.[1] Preterm birth, which occurs in approximately 7% of live births, is the single largest cause of neonatal complications and death.[2] Both miscarriage and preterm birth substantially affect the physical and psychological well-being of prospective parents and have major cost implications for patients and health institutions.

A systematic review of 31 studies involving euthyroid women showed a strong association between the presence of thyroid peroxidase antibodies and miscarriage (odds ratio, 3.90; 95% confidence interval [CI], 2.48 to 6.12; P<0.001) and preterm birth (odds ratio, 2.07; 95% CI, 1.17 to 3.68; P=0.01). Studies included in the systematic review involved women with recurrent miscarriage, infertile women, and unselected populations.[3]

Three randomized trials have examined the use of levothyroxine in women with thyroid peroxidase antibodies and normal thyroid function. The pooled results of the first two trials, one involving an unselected population of 115 women[4] and the other involving 72 women undergoing assisted conception,[5] showed a substantially lower incidence of miscarriage among women taking levothyroxine than among those who received placebo or no treatment (relative risk, 0.48; 95% CI, 0.25 to 0.92; P=0.03).[3] A third trial, the results of which were published after our trial began, was limited to women undergoing in vitro fertilization. It showed that the use of levothyroxine did not reduce the incidence of miscarriage or preterm birth.[6] That trial involved 600 women, among whom there was a total of 220 pregnancies and 23 miscarriages. Evidence to support the use of levothyroxine has therefore remained inconclusive.

The 2017 guidelines of the American Thyroid Association stated that "insufficient evidence exists to conclusively determine whether LT4 [levothyroxine] therapy decreases pregnancy loss risk in TPOAb-positive [thyroid peroxidase antibody–positive] euthyroid women who are newly pregnant" and recommended that "administration of LT4 to TPOAb-positive euthyroid pregnant women with a…history of loss may be considered given its potential benefits in comparison with its minimal risk."[7] The guideline task force drew attention to our ongoing trial.[7] We designed the multicenter, randomized, placebo-controlled Thyroid Antibodies and Levothyroxine (TABLET) trial to investigate whether the use of levothyroxine would increase the rates of live births after at least 34 weeks of gestation among euthyroid women with thyroid peroxidase antibodies.

METHODS

TRIAL OVERSIGHT

Our trial was approved by the United Kingdom Medicines and Healthcare Products Regulatory Authority, the National Research Ethics Service, and the research department at each participating hospital. Generic levothyroxine and placebo were packaged and supplied by Sharp HealthCare (formerly Bilcare United Kingdom), which had no role in the design of the trial; the collection, analysis, or interpretation of the data; or the writing of the manuscript. Trial oversight and monitoring were provided by a trial steering committee and by an independent data and safety monitoring committee. The first, second, and last authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol (available with the full text of this article at NEJM.org).

TRIAL PARTICIPANTS

The participants were recruited from 49 hospitals across the United Kingdom. We originally restricted the trial population to women who had had one or more miscarriages. However, owing to the lower-than-expected prevalence of thyroid peroxidase antibodies, which became evident within the first 6 months after the beginning of trial recruitment, we expanded the recruitment to include women who were receiving treatment for infertility, since data from cohort studies had shown an association between miscarriage and thyroid autoantibodies in the population with infertility.[3] This also allowed our results to be generalizable to both populations. Women were eligible for enrollment in the trial if they were 16 to 40 years of age, had a history of miscarriage or infertility, and were trying to conceive in the subsequent 12 months (either naturally or through assisted conception). Women were excluded if they were receiving treatment for a thyroid disorder, had cardiac disease, or were receiving amiodarone or lithium.

The screening stage involved tests to detect thyroid peroxidase antibodies and thyroid-function tests. Euthyroidism was defined as a thyro-

tropin level of 0.44 to 3.63 mIU per liter and a free thyroxine (T_4) level of 10.0 to 21.0 pmol per liter as measured with one of these specified analyzers: Abbott ARCHITECT (Fisher Scientific); Elecsys, Modular, or Cobas (Roche); and ADVIA Centaur (Siemens [Bayer]). The euthyroid reference range covered the second and third quartiles of all accepted assays. Thyroid peroxidase antibody positivity was defined according to individual hospital laboratory thresholds, which are known to produce results with greater than 99% concordance in the U.K. Immunology, Immunochemistry, and Allergy National External Quality Assurance Service (NEQAS IIA) analysis.[8] A list of the analyzers and corresponding thresholds is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. Women who were found to have normal thyroid function and thyroid peroxidase antibody positivity were then invited to take part in the trial. All participants provided written informed consent for both the screening tests and trial participation.

TRIAL DESIGN AND DRUG REGIMEN

Participants were randomly assigned in a 1:1 ratio to receive oral capsules containing either 50 μg of levothyroxine or matched placebo once a day. Administration of the trial agents began immediately after randomization. The appearance, route, and timing of the administration of the trial agents were identical in the two groups. Throughout the duration of the trial, the participants, clinicians, and trial nurses were unaware of the trial-group assignments.

Computerized randomization was performed centrally through a secure Internet application. Minimization was used to balance the trial-group assignments according to age (<35 or ≥35 years), the number of previous miscarriages (0, 1, 2, or ≥3), infertility treatment (yes or no), and the baseline thyrotropin concentration (≤2.5 or >2.5 mIU per liter).

The use of the trial agent was initiated before conception and continued until the end of pregnancy. After randomization, women underwent a 12-month evaluation. Participants were instructed to contact their local trial team as soon as they had a positive urinary pregnancy test. During the 12-month period when the women were trying to conceive, they returned to the hospital every 3 months to undergo thyroid-function testing, report adverse events, and obtain a new supply of the trial agent. Once pregnant, the women had three trial visits, including thyroid-function testing, at 6 to 8 weeks, 16 to 18 weeks, and 28 weeks. Test results outside of assay-specific limits were managed locally by the relevant clinicians, and the trial agent was discontinued. Outcomes in all women who underwent randomization (pregnant and nonpregnant) were included in the trial intention-to-treat analysis.

Adherence to the trial agent was primarily ascertained by pill counting at the scheduled trial visits; trial participants were also asked questions about adherence. The pharmacokinetic properties of levothyroxine suggest that missing tablets intermittently is unlikely to substantively affect thyroxine bioavailability.[9] Therefore, good adherence was defined a priori by pill counts or verbal confirmation (in cases in which pill counts were not available) indicating that at least 75% of the pills were taken.

OUTCOME MEASURES

The primary outcome was the percentage of women who underwent randomization and had a live birth after at least 34 completed weeks of gestation. Prespecified secondary outcomes included the following: clinical pregnancy at 7 weeks; ongoing pregnancy at 12 weeks; miscarriage before 24 weeks; stillbirth (intrauterine death at ≥24 weeks); ectopic pregnancy; termination of pregnancy; live birth before 28 weeks, before 34 weeks, and before 37 weeks; the week of gestation at delivery; birth weight (in grams); and Apgar scores at 1 and 5 minutes. Maternal antenatal, intrapartum, and postnatal complications and neonatal complications were also included in the prespecified secondary outcomes. Table S2 in the Supplementary Appendix provides a complete list of prespecified trial outcomes.

Gestational age was determined with the use of crown–rump length from ultrasonographic measurement in the first trimester when available. Otherwise, it was based on the date of the last menstrual period.

STATISTICAL ANALYSIS

We calculated that we would need to assign 760 women (380 in each group) for the trial to have 80% power to detect a minimally important difference of 10 percentage points between the levothyroxine group and the placebo group with respect to the rate of live births (65% vs. 55%)

after at least 34 weeks of gestation at a two-sided P value of 0.05. The minimally important difference was estimated on the basis of consultations among health care practitioners, patients, and representatives of patient organizations. The baseline live-birth rate of 55% in the control group was based on the assumption that 10% of unselected women would not conceive within 1 year[10] and a further 35% would either miscarry or have a preterm birth.[1] We planned to include 900 participants in the trial to account for a 15% loss to follow-up.

Analyses were conducted as prespecified in our statistical analysis plan. Estimates of differences between the groups for the primary outcome are presented with 95% confidence intervals and P values from two-sided tests at the 5% significance level. The statistical analysis plan did not include a provision for correction for multiple comparisons when tests were conducted for secondary or other outcomes. Therefore, the results for these outcomes are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals were not adjusted for multiple comparisons, so the intervals should not be used to infer definitive treatment effects.

For the primary outcome (live birth at ≥34 weeks of gestation), the trial population consisted of all participants who underwent randomization (intention-to-treat population). For maternal pregnancy outcomes (e.g., miscarriage and stillbirth), the analysis population consisted of all women who had a confirmed pregnancy. Confirmation of pregnancy was initially by a positive urinary pregnancy test, followed by an ultrasonographic examination at 6 to 8 weeks. Women who had an empty uterus at the follow-up ultrasonographic examination or who reported a negative pregnancy test subsequent to a positive test were classified as having had a miscarriage. Log-binomial regression was used to generate relative risks, with adjustment for the minimization variable for all binary outcomes. A Cox proportional-hazards model was used for the time from conception to the end of pregnancy and the time from conception to birth. A linear regression model was used for continuous outcomes.

Sensitivity analyses were performed for the primary outcome and the outcome of miscarriage at less than 24 weeks, under the assumption that all patients who withdrew from the trial or were lost to follow-up did not have a live birth at or after 34 weeks. Prespecified subgroup analyses were completed for the primary outcome according to maternal age (<35 or ≥35 years), the number of previous miscarriages (0, 1 or 2, or ≥3), the initial thyrotropin concentration (≤2.5 mIU per liter or >2.5 mIU per liter), and infertility treatment (yes or no). Further exploratory subgroup analyses were also prespecified: race or ethnic group (black, white, Chinese, South Asian, or other), baseline level of thyroid peroxidase antibodies (≥50th percentile [very high] or <50th percentile [high]), and body-mass index (the weight in kilograms divided by the square of the height in meters; <25 or ≥25). The effects of these subgroups were examined by adding the subgroup according to trial-group interaction variables to the log-binomial model.

Interim analyses of effectiveness and safety end points were performed on behalf of the data and safety monitoring committee at approximately 6-month intervals during the recruitment period. Because these analyses were performed with the use of the Haybittle–Peto principle,[11] no adjustment was made in the final P values to determine significance. All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

A total of 19,556 women underwent tests to detect thyroid peroxidase antibodies and thyroid-function tests between December 2011 and January 2016. Of these women, 1420 were eligible for enrollment in the trial, of whom 952 consented to participate and were randomly assigned to receive either levothyroxine (476 women) or placebo (476 women). The follow-up rate for the primary outcome was 98.7% (940 of 952 women); 6 women from each group were lost to follow-up or withdrew consent. 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 (Fig. 1). The baseline characteristics were similar in the two groups (Table 1, and Table S3 in the Supplementary Appendix).

OUTCOMES

Among all women who underwent randomization, the live-birth rate after at least 34 weeks of gestation was 37.4% (176 of 470 women) in the levothyroxine group, as compared with 37.9%

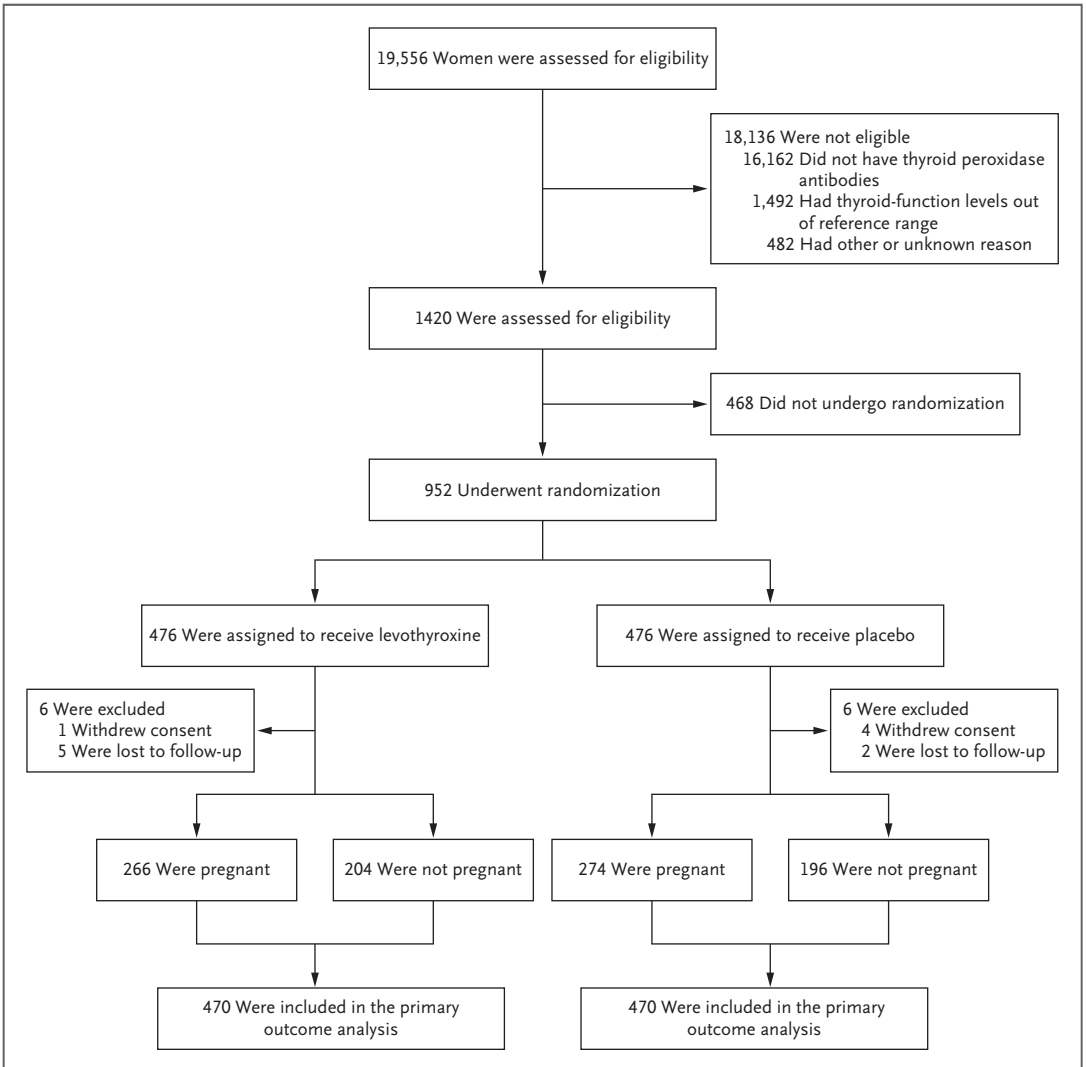

Figure 1. Enrollment, Randomization, Follow-up, and Analysis.

(178 of 470 women) in the placebo group (relative risk, 0.97; 95% CI, 0.83 to 1.14; P=0.74; absolute risk difference, 0.4 percentage points; 95% CI, −6.6 to 5.8) (Table 2). There was no significant between-group difference in the results in sensitivity analyses (Table S4 in the Supplementary Appendix) nor in any of the preplanned subgroup analyses (Fig. 2).

There were no significant between-group differences with respect to any of the secondary outcomes (Table 2, and Table S5 in the Supplementary Appendix). The distributions of gestational age at the time of live-birth delivery were similar in the two trial groups (Fig. S1 in the Supplementary Appendix). No significant differences were noted in the incidence of maternal or neonatal complications (Table S6 in the Supplementary Appendix).

As expected, at every time point, the serum thyrotropin concentrations were lower and the free T_4 concentrations were higher in the levothyroxine group than in the placebo group (Table S7 and Figs. S2 and S3 in the Supplementary Appendix); this indicates a biologic effect of levothyroxine. The percentages of women who discontinued the trial agent because of abnormal results on thyroid-function tests were similar in the levothyroxine and placebo groups (9.8% and 9.6%, respectively) (Table S8 in the Supplementary Appendix). In women for whom adherence data were reported, adherence was good, ranging from 81% to 94%

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Levothyroxine Group (N=476)	Placebo Group (N=476)
General demographic characteristics		
Maternal age†		
<35 yr — no. (%)	306 (64.3)	306 (64.3)
Mean age — yr	32.5±4.9	32.7±4.9
BMI		
BMI ≥25 — no./total no. (%)	240/462 (51.9)	240/464 (51.7)
Mean BMI	26.4±5.6	26.5±5.5
Race or ethnic group — no. (%)‡		
White	328 (68.9)	337 (70.8)
Chinese	4 (0.8)	4 (0.8)
South Asian	110 (23.1)	94 (19.7)
Black	16 (3.4)	23 (4.8)
Other	18 (3.8)	18 (3.8)
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)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. There were no significant differences between the groups in the listed characteristics at baseline. To convert the values for free thyroxine to nanograms per deciliter, divide by 12.87. BMI denotes body-mass index, and IQR interquartile range.
† This variable was a minimization variable.
‡ Race or ethnic group was reported by the participants.
§ Data were missing for six women in the levothyroxine group and four women in the placebo group.

across all time points (Table S8 in the Supplementary Appendix).

Serious adverse events occurred in 28 women in the levothyroxine group (5.9%) and in 18 in the placebo group (3.8%) (P=0.14) (Table S9 in the Supplementary Appendix). The reported symptoms at each follow-up visit are listed in Table S10 in the Supplementary Appendix.

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 at ≥24 wk			
Gestational age at delivery			
Wk of gestation	38 wk 6 days±2 wk 3 days	39 wk±2 wk 4 days	1 day (–0 wk 4 days to 0 wk 3 days)
No. of women	186	188	
Birth weight			
Mean weight — g‖	3226±660	3262±668	–35 (–168 to 97)
No. of infants	187	188	
Apgar score			
At 1 min			
Median (IQR)	9 (9–9)	9 (8–9)	0.1 (–0.2 to 0.4)
No. of infants	179	178	
At 5 min			
Median (IQR)	9 (9–10)	9 (9–10)	0.0 (–0.2 to 0.2)
No. of infants	178	178	

* Plus–minus values are means ±SD. There were no significant differences between the groups.
† Relative risks are shown for the primary outcome and all pregnancy outcomes listed as secondary outcomes. The mean difference is shown for all neonatal outcomes listed as secondary outcomes. For binary outcomes, a relative risk of less than 1 favors the levothyroxine group, except for live birth after at least 34 weeks of gestation, clinical pregnancy at 7 weeks, and ongoing pregnancy at 12 weeks, for which a relative risk greater than 1 would favor levothyroxine. For continuous outcomes, mean differences greater than 1 favor the levothyroxine group. The widths of the confidence intervals have not been adjusted for multiple comparisons.
‡ Nine ectopic pregnancies were considered to be unviable and so were assumed to have ended on day 0. One pregnancy was terminated at 12 weeks, so it was counted as survival to this time. One missing date of miscarriage was assumed in this analysis to be between 7 and 12 weeks (the period during which miscarriage typically occurs).
§ The median gestational age in the levothyroxine group was 8 weeks (IQR, 6 to 10), and the median gestational age in the placebo group was 9 weeks (IQR, 7 to 10). One woman in the placebo group who was pregnant with twins and who had both a live birth at less than 34 weeks of gestation and a miscarriage was counted in both categories.
¶ The reason for termination of pregnancy was fetal abnormality (anencephaly).
‖ Eight birth weights were unknown in the levothyroxine group, and seven birth weights were unknown in the placebo group.

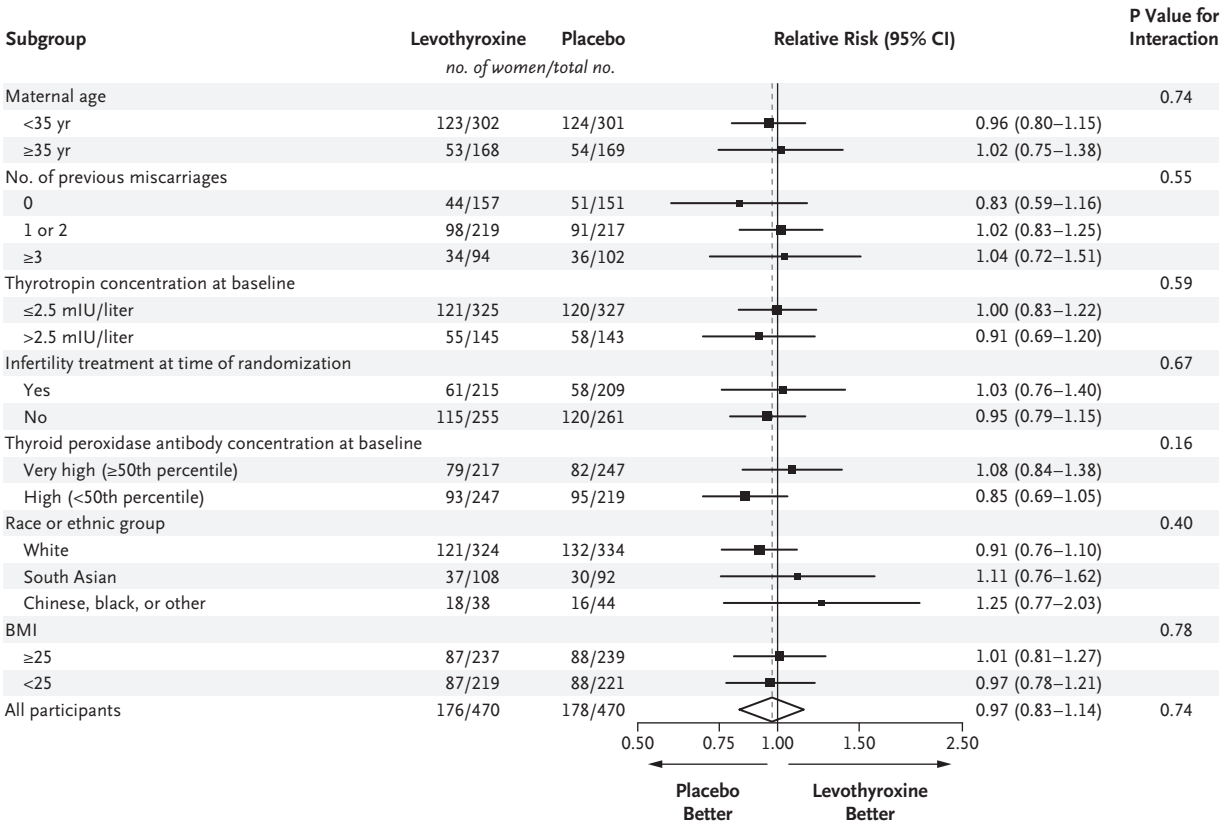

Figure 2. Prespecified Subgroup Analyses in Women Who Had a Live Birth after at Least 34 Weeks of Gestation.

The widths of the confidence intervals were not adjusted for multiple comparisons. The size of the black squares corresponds to the total number of women in the subgroup. Prespecified subgroup analyses included maternal age, the number of previous miscarriages, the thyrotropin concentration at baseline, and infertility treatment at the time of randomization. Prespecified "exploratory" subgroup analyses included the thyroid peroxidase antibody concentration at baseline, race and ethnic group, and the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters).

DISCUSSION

In our multicenter, randomized, placebo-controlled trial, the use of levothyroxine, initiated before conception and continued throughout pregnancy, did not result in a higher rate of live births after at least 34 weeks of gestation than placebo among thyroid peroxidase antibody–positive euthyroid women who had a history of miscarriage or infertility. There was also no significant effect on other pregnancy or neonatal outcomes, including the incidence of miscarriage and preterm birth.

Our trial was larger than previous studies, which were inadequately powered[4,5] or restricted to a single population.[5,6] Our inclusion of multiple centers and multiple clinical populations improved the generalizability of the findings.

One limitation of our trial is that we studied levothyroxine at a dose of 50 μg once daily. It is possible that the dose may need to be adjusted depending on the participant's body weight, thyroid peroxidase antibody level, or thyrotropin concentration. The thyroid-function test thresholds in our trial, which were used to assess the continuation of the trial agent at each time point, were within the limits that are considered to be safe during pregnancy. The frequency of withdrawal from the trial agents was similar in the levothyroxine and placebo groups. Although women who received levothyroxine had significantly lower mean thyrotropin levels and higher free T_4

concentrations than those who received placebo, this did not have a clinically relevant effect on the rates of thyroid dysfunction or clinical outcomes.

Another potential limitation of our trial is the use of various assays for thyroid peroxidase antibodies, each with different detection limits and thresholds for test positivity, that were predetermined by the assay manufacturer. However, these variations are an accepted part of normal practice. Quality assurance for assays in the laboratories for all the participating centers is provided by U.K. NEQAS IIA (a national quality-assurance scheme), which shows greater than 99% concordance in the classification of samples as either positive or negative for thyroid peroxidase antibodies across all assays.[8] With this assurance, the TABLET protocol did not define a single threshold for thyroid peroxidase antibody positivity but accepted the classification of abnormality provided by the laboratories servicing the participating centers.

It was anticipated that broadening of the inclusion criteria to women with infertility might result in a decreased rate of live births and affect the power of the trial. However, the 95% confidence interval for the primary outcome rules out a clinically meaningful benefit, and therefore a potential reduction in power does not affect our inferences.

In conclusion, our trial showed no significant difference in rates of live births after at least 34 weeks of gestation with the use of 50 μg of levothyroxine once daily, started before conception and continued throughout pregnancy, among euthyroid women with thyroid peroxidase antibodies.

This report presents independent research commissioned by the National Institute for Health Research (NIHR). A monograph reporting the data collected in this trial will be published in the NIHR Journals Library. Further information is available at www.journalslibrary.nihr.ac.uk/programmes/eme/0910010/#/. The views and opinions expressed in this article are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the Medical Research Council, the Central Commissioning Facility, the NIHR Evaluation, Trials, and Studies Coordinating Centre, the efficacy and mechanism evaluation program, or the Department of Health.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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