THYROID AND FERTILITY

Clin Thyroidol 2019;31:189–194.

Preconception Levothyroxine Treatment in Euthyroid TPOAb-Positive Women Does Not Affect Miscarriage or Preterm Birth Rates

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Review of: Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, Bender-Atik R, Agrawal R, Bhatia K, Edi-Osagie E, Ghobara T, Gupta P, Jurkovic D, Khalaf Y, MacLean M, McCabe C, Mulbagal K, Nunes N, Overton C, Quenby S, Rai R, Raine-Fenning N, Robinson L, Ross J, Sizer A, Small R, Tan A, Underwood M, Kilby MD, Boelaert K, Daniels J, Thangaratinam S, Chan SY, Coomarasamy A 2019 Levothyroxine in women with thyroid peroxidase antibodies before conception. *N Engl J Med* **380**:1316–1325. Epub 2019 Mar 23. PMID: 30907987.

SUMMARY

Background

Miscarriage and preterm birth are common pregnancy complications; they occur in 5 to 10% and 20 to 25% of pregnancies, respectively. These complications have a considerable negative impact on physical and psychosocial well-being. Untreated hyperthyroidism (e.g., Graves' hyperthyroidism or toxic nodular disease) as well as autoimmune hypothyroidism are well-known risk factors for miscarriage and preterm birth. When taking together the results of observational studies on mild forms of thyroid-function test abnormalities, these show that TPOAb positivity, but not subclinical hypothyroidism or subclinical hyperthyroidism, is associated with a higher risk of miscarriage and preterm birth. Although TPOAb-positive subclinical hypothyroidism is a widely accepted indication for levothyroxine treatment, the decision whether or not to start levothyroxine treatment for euthyroid TPOAb-positive women remains difficult. A recent randomized trial performed in China showed no benefit of levothyroxine treatment in euthyroid TPOAb-positive women undergoing assisted conception (1). The current study (2) investigated the effects of levothyroxine treatment in euthyroid TPOAb-positive women with a history of miscarriage or infertility.

Methods

Participants were recruited from 49 UK hospitals between December 2011 and January 2016. Eligible for inclusion were women 16 to 40 years of age with a prior miscarriage or infertility who were trying to conceive in the subsequent 12 months (either naturally or through assisted conception). Exclusion criteria were a treated thyroid disorder, cardiac disease and lithium or amiodarone treatment. Participants were randomly assigned (1:1) to receive either 50 µg of levothyroxine or matched placebo once daily, after which women were followed for 12 months. The primary outcome was live birth after 34 weeks' gestation; secondary outcomes included clinical pregnancy at 7 weeks and miscarriage before 24 weeks. The study was powered to detect an increase in live births after 34 weeks' gestation of 55 to 65% (with a power of 80% and an alpha of 5%).

Results

A total of 19,556 women underwent screening; 1420 of them were eligible for enrollment. and 952 who consented were randomly assigned to receive either levothyroxine or placebo (both n = 476). The follow-up rate for the primary outcome was 98.7%.

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Of the women included in the study, 43.7% were above 35 years of age, roughly half were obese (BMI [the weight in kilograms divided by the square of the height in meters], >25 in 51.8%), 65.2% had a history of miscarriage, 45.1% were undergoing fertility treatment, and 30.8% had a TSH above 2.5 mU/L.

Clinical pregnancy occurred in 56.6% of women in the levothyroxine group and in 58.3% in the placebo group (RR, 0.97; 95% CI, 0.88–1.07). Rates of live births after 34 weeks' gestation did not differ between the groups (levothyroxine, 37.4%, vs. placebo, 37.9%; RR, 0.97; 95% CI, 0.83–1.14). Sensitivity analyses showed no difference between the groups for the primary outcome when comparing women below or above 35 years of age, number of

previous miscarriages, or TSH above 2.5 mU/L. Miscarriage occurred in 28.2% of women in the levothyroxine group and in 29.6% of women in the placebo group (RR, 0.95; 95% CI, 0.73–1.23). Preterm birth before 34 weeks' gestation occurred in 3.8% of women in the levothyroxine group and 3.6% in the placebo group (RR, 1.02; 95% CI, 0.43–2.42). There were no differences between the levothyroxine group and the placebo group for other outcomes, including birth weight, stillbirth, or Apgar scores.

Conclusions

Preconception levothyroxine did not affect the risk of miscarriage or preterm birth in euthyroid TPOAb-positive women who had had a miscarriage or who had undergone fertility treatment.

COMMENTARY

In this seminal study, Dhillon-Smith et al. investigate the effects of 50 μ g of levothyroxine supplementation started before conception in euthyroid TPOAb-positive women on the rate of clinical pregnancy, miscarriage, and live birth (1). The main result is that levothyroxine treatment does not lower the rate of miscarriage in TPOAb-positive women. The results of this study are important because observational studies show that TPOAb positivity—even in euthyroid women—is a risk factor for miscarriage and preterm birth. Although the ATA guidelines advocate preconception levothyroxine treatment in TPOAb-positive women with subclinical hypothyroidism, it was unknown whether TPOAb-positive women with normal thyroid function could benefit from levothyroxine therapy. The current study provides long-awaited evidence suggesting that there is no benefit.

Euthyroid TPOAb positivity is a difficult combination because the thyroid function is still normal, so everything seems okay, but the main risk factor for

thyroid dysfunction (i.e., in the developed world) is present. However, are all euthyroid TPOAb-positive women similar? It is likely that this is a very heterogeneous group defined by basic biochemistry, but it includes large within-group differences in thyroid autoimmunity and/or thyroid functional capacity. For example, it remains unknown why hypothyroidism never develops in some TPOAb-positive individuals, but it does in others, and why some women have an impaired thyroidal response to hCG stimulation (2–6). Further subspecification of TPOAb-positive women could be the key to unraveling the risk of miscarriage and to identify which, if any, women could benefit from levothyroxine.

Interestingly, the current study was powered to detect an increase in the rate of live births (which is mostly affected by miscarriage without differences in clinical pregnancy rates) of 55 to 65%. In the trial protocol, the authors mention that they would have more than enough statistical power if they took into account

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the results of previous trials (combined meta-analysis of two studies by Negro et al. (8,9): RR, 0.48; 95% CI, 0.25–0.92) and the same goes for the meta-analysis by Thangaratinam et al. (10) (see Table 1). Based on the association of TPOAbs in previous observational studies and small RCTs (Table 1), the results of the current study indicate that previous studies have grossly overstated the extent by which TPOAb positivity is a risk factor for miscarriage (e.g., in observational studies, due to selection bias of the control group or publication bias) or the effects of levothyroxine. From that point of view, it would be important to know whether TPOAb positivity was a risk factor for miscarriage as compared to TPOAb negativity in the TABLET trial (2, 12). Alternatively, TPOAbs could be a risk factor for miscarriage, but levothyroxine therapy is not beneficial because either there is a nonthyroidal pathway via, for example, autoimmunity itself or immune dysregulation, or levothyroxine therapy cannot fully restore thyroid function.

A widely discussed potential explanation for this lack of effect is the dosage—some endocrinologists argue that a dosage of 50 µg is too low. An alternative approach would have been to base the levothyroxine dosage on the TSH, the TPOAb titer, the patient's weight or to use dose adjustment striving for a treatment aim of a TSH <2.5 mU/L. However, the authors show a substantial decline in mean TSH concentrations in the levothyroxine group after 3 months (from roughly 2.0 mU/L to 0.9 mU/L) and a long-term increase in FT₄ (increase of roughly 2.5 pmol/L [0.2 ng/dl])—a biochemical change that suggests that a dosage is high enough. What is interesting though, is that after 3 months the mean TSH starts to increase until it reaches concentrations at 12 months that are similar to those at baseline. A steady FT₄ with an increasing TSH could reflect differences in compliance that increased throughout the first 12 months (increase per 3 months from baseline: 11%-14%-19%-18%; self-reported; pill

counting not stratified in supplemental data). Alternatively, the rise in mean TSH could reflect a physiologic response to a relatively hyperthyroid state—for example, reflecting changes in peripheral thyroid hormone metabolism or sensitivity. This raises the question of whether perhaps (local) thyroid hormone insensitivity could play a role in the pathophysiology of miscarriage in TPOAb-positive women.

Interestingly, Dhillon-Smith and colleagues in this study replicate two other reports (7, 8) with regard to low compliance with levothyroxine therapy during pregnancy, with only 55% verified use at weeks 6 to 8 (pill-counting overall, but 7–10% based on self-reporting) and 65 to 69% thereafter. Since TPOAb positivity is mainly associated with miscarriage (and most likely, therefore, with lower live birth rates) and preterm birth, the low compliance particularly during weeks 6 to 8 weeks could affect the results of this study. However, the similar rates of miscarriage and preterm birth suggest that compliance likely was not a relevant issue, unless, of course, if women with previous high odds of miscarriage would be more likely to be noncompliant. This raises the question: What are the characteristics of women who do not (regularly) take their levothyroxine before or during pregnancy, and is the noncompliance out of self-protection for overmedicalization or fear of adverse effects? Future studies are needed to address this.

In conclusion, this very important study has certainly provided very important arguments against preconception levothyroxine treatment in euthyroid TPOAb-positive women. Although it is in a typical thyroidologist's nature to cross-reference these findings with their own anecdotal evidence and raise more new questions than the current trial can answer, it is important to take into account the potential risks for overtreatment and overmedicalization of otherwise healthy women. I look forward to new insights that elucidate the heterogeneity of TPOAb positivity.

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Table 1. An overview of the major studies on the effect of levothyroxine use on miscarriage rates.

	TPOAb-negative	TPOAb-positive	OR (95% CI)
Thangaratinam et al. 2011 (10)—meta-analysis observational data			
Recurrent miscarriages	22.9%	47.1%	4.22 (0.97–18.4)
Subfertility	11.0%	29.6%	3.15 (2.23–4.44)
Unselected/other populations	5.4%	24.3%	4.28 (2.06–8.92)
<i>Total</i>	7.1%	26.7%	3.90 (2.48–6.12)
Negro et al. 2006 (8)—euthyroid women, L-T₄ started during pregnancy	2.4%		
Placebo		13.8%	
Levothyroxine		3.5%	0.20 (0.11–0.38)
Negro et al. 2016 (9)—TSH <2.5 mU/L	8.1%		
Placebo		14.9%	
Levothyroxine		11.6%	0.77 (0.47–1.30)
Nazarpour et al. 2017 (11)—L-T₄ started during pregnancy	4.3%		
Placebo		3.4%	
Levothyroxine		3.6%	
Wang et al. (1)—preconception L-T₄, normal TSH, assisted reproductive technology (ART) only			
Placebo		10.6%	
Levothyroxine		10.3%	0.97 (0.45–2.10)
Dhillon Smith et al. (2)—euthyroid women, preconception L-T₄, ART or history of miscarriage			
Placebo		29.6%	
Levothyroxine		28.2%	0.95 (0.73–1.23)

*Empty cells indicate no data available from original publication.

For comparison: miscarriage occurs in 20% to 25% of the general population, and in 30% to 33% in women who had a previous miscarriage.

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REFERENCES

1. Wang H, Gao H, Chi H, et al. 2017 Effect of levothyroxine on miscarriage among women with normal thyroid function and thyroid autoimmunity undergoing in vitro fertilization and embryo transfer: a randomized clinical trial. *JAMA* **318**:2190–2198.
2. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, Bender-Atik R, Agrawal R, Bhatia K, Edi-Osagie E, et al. 2019 Levothyroxine in women with thyroid peroxidase antibodies before conception. *N Engl J Med* **380**:1316–1325. Epub 2019 Mar 23.
3. Korevaar TI, Steegers EA, Pop VJ, Broeren MA, Chaker L, de Rijke YB, Jaddoe VW, Medici M, Visser TJ, Tiemeier H, Peeters RP 2017 Thyroid autoimmunity impairs the thyroidal response to human chorionic gonadotropin: two population-based prospective cohort studies. *J Clin Endocrinol Metab* **102**:69–77.
4. Bjoro T, Holmen J, Kruger O, Midthjell K, Hunstad K, Schreiner T, Sandnes L, Brochmann H 2000 Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trøndelag (HUNT). *Eur J Endocrinol* **143**:639–647.
5. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P 2010 Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. *J Clin Endocrinol Metab* **95**:1095–1104. Epub 2010 Jan 22.
6. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, et al. 1995 The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)* **43**:55–68.
7. Amouzegar A, Gharibzadeh S, Kazemian E, Mehran L, Tohidi M, Azizi F 2017 The prevalence, incidence and natural course of positive antithyroperoxidase antibodies in a population-based study: Tehran Thyroid Study. *PLoS One* **12**:e0169283.
8. Negro R, Formoso G, Mangieri T, Pezzarossa A, Hassan H 2006 Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. *J Clin Endocrinol Metab* **91**:2587–2591. Epub 2006 Apr 18.
9. Negro R, Schwartz A, Stagnaro-Green A 2016 Impact of levothyroxine in miscarriage and preterm delivery rates in first trimester thyroid antibody-positive women with TSH less than 2.5 mIU/L. *J Clin Endocrinol Metab* **101**:3685–3690. Epub 2016 Jul 26.
10. Thangaratnam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A 2011 Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. *BMJ* **342**:d2616.
11. Nazarpour S, Ramezani Tehrani F, Simbar M, Tohidi M, Alavi Majd H, Aziz F 2017 Effects of levothyroxine treatment on pregnancy outcomes in pregnant women with autoimmune thyroid disease. *Eur J Endocrinol* **176**:253–265. Epub 2016 Nov 22.

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12. Boelaert K 2018 TABLET trial—implications for targeted levothyroxine in pregnancy. *Endocr Abstr* **59**:S8.
13. Frank AS, Lupattelli A, Matteson DS, Nordeng H 2018 Maternal use of thyroid hormone replacement therapy before, during, and after pregnancy: agreement between self-report and prescription records and group-based trajectory modeling of prescription patterns. *Clin Epidemiol* **10**:1801–1816.
14. Turunen S, Vaarasmaki M, Mannisto T, Hartikainen AL, Lahesmaa-Korpinen AM, Gissler M, Suvanto E 2019 Pregnancy and perinatal outcome among hypothyroid mothers: a population-based cohort study. *Thyroid* **29**:135–141. Epub 2018 Dec 20.