The potential benefit of levothyroxine treatment during pregnancy: another step forward

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Thyroid hypofunction during pregnancy is associated with a wide range of adverse pregnancy and child outcomes such as miscarriage, premature delivery, abnormal birth weight and suboptimal offspring neurodevelopment. Thyroid autoimmunity, reflected by thyroperoxidase antibody (TPOAb) positivity, is the most important risk factor for thyroid hypofunction. During pregnancy, TPOAb-positive women have higher TSH and lower FT4 concentrations and a higher risk of overt and subclinical hypothyroidism than TPOAb-negative women (1, 2). Intriguingly, TPOAb positivity is associated in several observational studies with a higher risk of adverse outcomes including miscarriage, premature delivery and gestational diabetes, even in euthyroid women (2, 3, 4, 5, 6, 7). Such studies suggest potential adverse effects of thyroid autoimmunity on pregnancy outcome. However, the mechanisms underlying these associations, as well as causality of the associations, remain to be elucidated. In this context, the study by Nazarpour *et al.* in the current issue of the European Journal of Endocrinology is a very valuable contribution.

Two main hypotheses have been proposed regarding the underlying mechanism: the first being that TPOAb positivity is more likely to occur in women with a higher susceptibility to autoimmune disease in general. A higher prevalence of (mild) autoimmune disease would cause the higher risk of adverse outcomes via non-thyroidal pathways. In other words, autoimmune disease is a confounder in the association of TPOAb positivity with adverse pregnancy outcomes. In this case, levothyroxine will not be a plausible treatment. The second hypothesis is that TPOAb positivity leads to (mild) thyroid hypofunction and that suboptimal thyroid hormone availability would subsequently increase the risk of adverse outcomes. In that case, restoring thyroid hormone availability may overcome the negative effects on pregnancy outcome.

During pregnancy, high concentrations of hCG stimulate the thyroid leading to a higher FT4 and a lower TSH (8). Recently, our group showed that in TPOAb-positive women, higher hCG concentrations are not associated with higher FT4 or lower TSH (9). This indicates that TPOAb-positive women have an impaired thyroidal response to hCG stimulation. We subsequently showed that out of all TPOAb-positive women, those with the lowest thyroidal response to hCG stimulation have an up to 2.8-fold higher risk of premature delivery, whereas women with a relatively normal hCG response do not have a higher risk (9, 10). This implies that TPOAb positivity is associated with adverse pregnancy outcomes via changes in thyroid function (or more specifically via the thyroidal response to hCG stimulation) instead of via other autoimmune processes. Still, it should be noted that these data come from observational studies and thus cannot infer causality. The only study design that can truly answer the question of causality is a study that includes (1) randomization: to overcome any confounding and (2) thyroid hormone supplementation: to restore the potential lack of thyroid hormone availability and confirm a thyroid hormone pathway.

In the current study by Nazarpour *et al.* (10), 1734 pregnant women (a necessary extension from the 1600 initially planned to adhere to their power calculation) were screened for thyroid dysfunction (measuring TSH and the FT4 index (FT4I)) and TPOAb positivity. This yielded 131 TPOAb-positive women without (subclinical) hypothyroidism or hyperthyroidism eligible for randomization. Four to eight days after randomization, women in the treatment group received levothyroxine based on their TSH at baseline (<1 U/L: 0.5 µg/kg/day; 1–2 U/L: 0.75 µg/kg/day; >2 U/L and/or TPOAbs >1500 IU/mL: 1 µg/kg/day). Although both the patient and the treating physicians were aware of what group the patient was randomized to, the physicians that

Commentary	T I M Korevaar and R P Peeters	Levothyroxine treatment during pregnancy	176:4	C4
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determined the pregnancy outcome were blinded, making this a single-blinded randomized controlled trial.

In the treatment group, median TSH concentrations decreased from 3.7 to 1.5 and 1.0 U/L, whereas TSH remained stable in the non-treated group at 3.2, 3.9 and 3.4 U/L during the first, second and third trimester respectively. Levothyroxine treatment reduced the risk of premature delivery by 70% (7.1% vs 23.7%; RR: 0.30 (95% CI: 0.1–0.85)). Levothyroxine treatment did not change the percentage of miscarriage (3.6% vs 3.4%) but due to the low number of cases (4/114 that completed follow-up) analyses on this outcome were considered to be underpowered.

The current study was a replication of a study published by Negro *et al.* in 2006 (11), in which 115 TPOAb-positive women were randomized to receive levothyroxine treatment using the same dosing regimen or remain untreated. The effect of levothyroxine treatment on the risk of premature delivery in TPOAb-positive women in the study by Nazarpour *et al.* (7.1% vs 23.7%) was almost an exact replication of the study by Negro *et al.* (22.4% vs 7.0%) (11). Interestingly, the authors of the current study also stratified the analyses according to the TSH concentration at baseline, demonstrating that the main reduction in premature delivery was achieved in women with an initial TSH concentration of ≥ 4 U/L (<4 U/L: 5.6% reduction ($P=0.69$), vs a 24.1% reduction for ≥ 4 U/L ($P=0.01$)). Even though this trial was not designed to detect such differences, these results are very much in line with recent observational studies that indicate that the risk of adverse pregnancy outcomes in TPOAb-positive women is dependent on their TSH concentration. Recent studies show that TPOAb-positive women with a high-normal TSH have a higher risk of miscarriage, premature delivery and gestational diabetes than TPOAb-positive women with low (normal) TSH concentrations. In addition, a recent randomized controlled trial has indicated that levothyroxine treatment in TPOAb-positive women with a TSH: 0.5–2.5 U/L did not lower the risk of miscarriage or premature delivery, although some important methodological issues hamper the interpretation of these results (12). Taken together, these data suggest that a higher TSH in TPOAb-positive women is likely to indicate a more severe form of autoimmunity, having more impact on thyroid functional capacity and the overall thyroid hormone availability during pregnancy.

In contrast to premature delivery, miscarriage is notoriously difficult to study given that roughly 80% of all miscarriages occur in the first trimester, and many women miscarry before they know that they are pregnant. In contrary to the current study, Negro *et al.* found that

levothyroxine treatment reduced the rate of miscarriage (3.5% vs 13.8%) (11). This could be because Negro *et al.* included women at an earlier gestational age than the current study (10.4 ± 3 weeks vs 11.4 ± 4 weeks). In the study by Negro *et al.*, the vast majority of miscarriages occurred during the first trimester, and the time between treatment initiation and miscarriage was very short (11). Interestingly, to overcome potential bias due to very early miscarriages or late inclusions, randomized controlled trials that include TPOAb-positive women before pregnancy are currently ongoing (TABLET trial, ISRCTN: 15948785 and T4LIFE trial, NTR3364).

In the current study, overt and subclinical hypothyroidism was defined by a normal FT4 with a TSH above 2.5 U/L. Although it has become apparent that this cut-off is too low to define an abnormal TSH (13, 14, 15, 16), the use of this cut-off in the current study leads to a sensible control group of women with a very low risk of having or developing an abnormal thyroid function (e.g. TPOAb-negative women with a TSH of 0.1–2.5 U/L). Another strength of this study is the fact that FT4 was estimated by calculating a free thyroxine index, which is a more robust way of measuring FT4 concentrations given that FT4 assays may be flawed due to thyroid-binding protein interference, especially during late pregnancy.

The levothyroxine dosing strategy based on weight and TSH concentration at presentation mimics clinical practice and is also a strength of the current study. On the other hand, it may be that the lack of treatment effect in the women with a TSH <4.0 U/L was because they were treated with a lower dose. In the face of two randomized controlled trials showing a benefit of levothyroxine in TPOAb-positive women, the next step could be to further study what the optimal dosage would be. Importantly, recent studies, as well as preliminary results of unpublished studies, have suggested that high-normal maternal thyroid function during pregnancy may be harmful for the fetus. Especially during early pregnancy, it would be a safe alternative to start with a low and fixed dose at presentation and titrate the dose, if necessary, after 4–6 weeks. We look forward to future trials that may incorporate risk stratification markers such as TSH, TPOAbs and/or hCG at presentation to further improve clinical treatment regimens of thyroid disease during pregnancy.

Declaration of interest

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