



Euthyroid Thyroperoxidase Antibody Positivity during Pregnancy, to Treat or Not to Treat?

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Thyroperoxidase antibody (TPOAb) positivity is a well-known risk factor for thyroid dysfunction during pregnancy and is associated with a suboptimal response to thyroidal stimulation by human chorionic gonadotropin. About 75% of TPOAb positive women are euthyroid and there seems to be a higher risk of predominantly miscarriage and preterm birth in this subgroup. Nonetheless, clinical decision making with regards to gestational levothyroxine treatment remains difficult due to a lack of large randomized trials. Future studies assessing dose-dependent associations and additional biomarkers that can distinguish low-risk from high-risk individuals will be key in disentangling the crude clinical data.

Keywords: Pregnancy; Thyroid gland; Thyroperoxidase antibodies

INTRODUCTION

Thyroperoxidase antibodies (TPOAbs) are a reflection of thyroid autoimmunity. While TPOAb positivity is pathognomic for the diagnosis of Hashimoto's hypothyroidism, the production of TPOAbs are a consequence of thyroid autoimmunity rather than the (sole) cause. This distinction is important to make in order to interpret the relevance of certain findings. For example, similar to any immunoglobulin G antibodies, TPOAbs are known to pass the placental barrier, but their placental passage has no meaningful effects on thyroid function of the newborn. During pregnancy, TPOAb positivity can be identified in about 8% (range, 5.0% to 13.8%) of all otherwise healthy pregnant women [1-3]. Roughly one-third of women with subclinical hypothyroidism (high thyroid stimulating hormone [TSH] with a normal free throxine [FT4]) are TPOAb positive and oppositely, about 25% of women with TPOAb positivity present with sub-

clinical hypothyroidism [1-3]. Risk factors for TPOAb positivity are similar to those outside of pregnancy and include a higher age, iodine deficiency or excess and a family or personal history of autoimmune disease, while the link with multiparity remains controversial [4-7]. The familial risk component seems particularly relevant in case of maternal TPOAb positivity, as children from TPOAb positive mothers are at higher risk of TPOAb positive at 16 years of age (9.0% vs. 3.7% in boys; 22.7% vs. 7.5% for girls) [8]. Paradoxically, smoking seems to be associated with a lower risk of TPOAb positivity, also in pregnancy [7,9, 10]. TPOAb positivity is much more often identified in euthyroid pregnant women than in those with a thyroid function test abnormality simply because the majority of women are euthyroid. However, it remains unknown what the clinical relevance is of euthyroid TPOAb positivity. This short review will focus on the (patho)physiology, clinical risks and treatment indications of euthyroid TPOAb positivity. Thyroglobulin antibodies

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are not associated with thyroid function or adverse outcomes during pregnancy independently from TPOAbs [2].

Although TPOAbs are normally dichotomized into negative or positive for interpretation in clinical practice, it is important to realize that the actual TPOAb concentration is a reflection of the continuous spectrum of the gradual thyroid autoimmunity process. In fact, there is a dose-dependent association of the TPOAb concentrations with TSH (positive) and FT4 (negative) concentrations in pregnant women [2,11], but no such association has yet been shown for adverse pregnancy outcomes to date. The association of TPOAbs with a lower thyroid function during pregnancy is probably mediated via two main mechanisms. First of all, thyroid autoimmunity mediated thyrocyte destruction decreases the functional capacity of the thyroid gland. Second, pregnancy is a state of increased demand for thyroid hormone that is mediated via increased TSH receptor stimulation by human chorionic gonadotropin (hCG). In TPOAb positive women, the reduced thyroid functional capacity leads to an impaired thyroidal response to stimulation by hCG (Fig. 1) [12-14].

Also the definition of TPOAb positivity may change during pregnancy. Due to immunotolerance, TPOAb concentrations considerably decline during pregnancy so that about 16% of women who were TPOAb positive during the first trimester are no longer TPOAb positive during the third trimester [12,15]. Furthermore, TPOAb concentrations are already associated with

an increase in TSH concentrations during pregnancy well below the cut-off that is used to define positivity [11]. Therefore, for cases in which concomitant TPOAb positivity would affect the decision to start levothyroxine treatment (for example those with gestational subclinical hypothyroidism) or to intensify clinical follow-up (for example screening for postpartum thyroiditis), a gestational TPOAb concentrations just below the cut-off for positivity could still be considered as TPOAb positivity. This is another example of how understanding of the (patho) physiology can affect the clinical interpretation of TPOAb concentrations.

RISK OF ADVERSE OUTCOMES

TPOAb positivity in itself has been associated with a higher risk of adverse pregnancy outcomes, predominantly miscarriage and preterm birth [3,4,16,17]. In unselected populations, the risk of miscarriage was 7.1% in TPOAb negative women compared to 26.7% in TPOAb positive women in a large meta-analysis [16]. Furthermore, the risk of preterm birth and very preterm birth was 4.9% and 0.7% in TPOAb negative women compared to 6.6% and 1.7% for TPOAb positive women in a large recent individual participant data meta-analysis, respectively [3]. It is important to communicate these risks in absolute numbers rather than a relative form and highlight that it remains more likely for the outcome to not occur, because the psychological stress

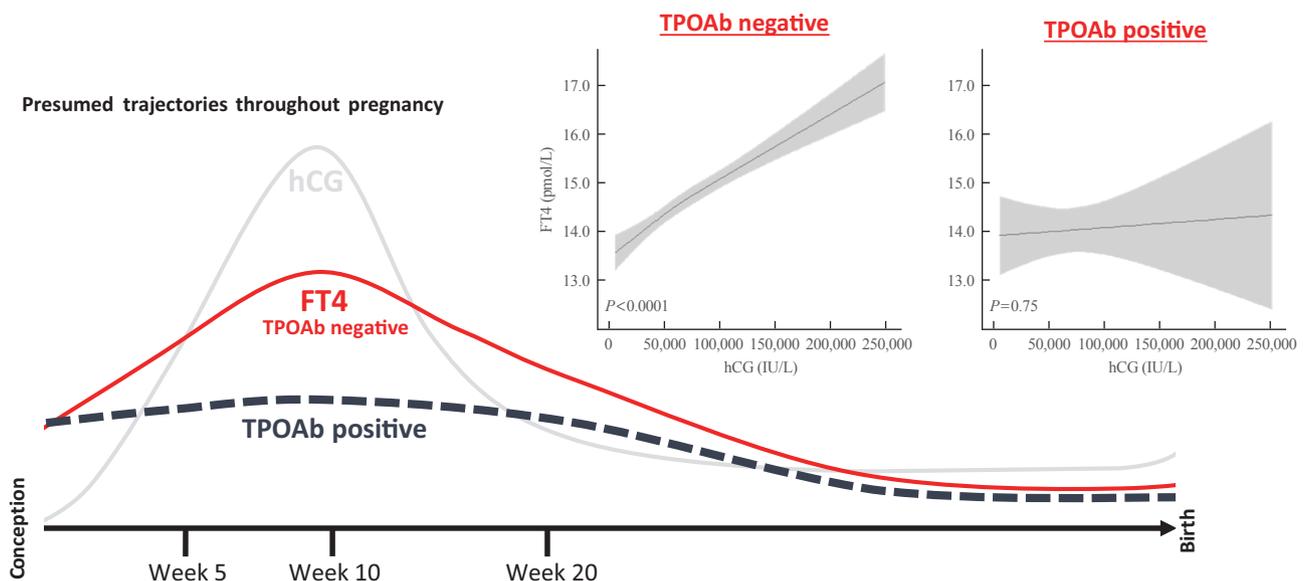


Fig. 1. Thyroid stimulation by human chorionic gonadotropin (hCG) according to thyroperoxidase antibody (TPOAb) status (top right) and presumed physiological changes throughout pregnancy with TPOAb negative women in red and TPOAb positive women in black. Adapted from Korevaar et al. [13], with permission from Oxford University Press. FT4, free thyroxine.

from a 'thyroid diagnosis' can sometimes outweigh any risks related to the underlying lab abnormality. Moreover, there is no data to suggest that TPOAb positivity is associated with other adverse pregnancy outcomes such as pre-eclampsia or (abnormal) birth weight [18,19]. There are some positive and some negative studies on the association of maternal TPOAb positivity and child IQ [20,21], but those data are too sparse and heterogeneous to draw any conclusions from at this time.

In TPOAb positive women, a higher TPOAb concentration is not associated with a higher risk of adverse pregnancy outcomes; however, there is a considerable difference in the risk of these adverse outcomes dependent on the TSH concentration. For example, in a Chinese study [17], TPOAb and/or TgAb positivity in women with a TSH <2.5 mU/L was associated with a 6% risk of miscarriage (odds ratio [OR] compared to TPOAb negative women with a TSH <2.5 mU/L, 2.71; 95% confidence interval [CI], 1.43 to 5.12) while a TSH above 2.5 mU/L was associated with a 10% risk of miscarriage (OR, 4.96; 95% CI, 2.76 to 8.90) and a TSH above the upper reference interval limit was 18% (OR, 9.56; 95% CI, 3.76 to 24.3). A similar pattern, although with smaller effect estimate differences, was shown for preterm birth and the risk of gestational diabetes mellitus (GDM) [3,22,23]. The association for GDM is interesting because thyroid hormone concentrations are associated with various components of glucose homeostasis including insulin production, insulin resistance and gluconeogenesis, but there also is an immunological link [24]. In a recent meta-analysis, risk estimates for the association of subclinical hypothyroidism with GDM were compared for a TSH cut-off used to diagnose subclinical hypothyroidism. When studying the relevance of a TSH cut-off of >4.0 mU/L (as advocated for the first time in the 2017 American Thyroid Association Guidelines), women with a TSH concentration >4.0 mU/L had a 60% higher relative risk of GDM, whereas those classified as having subclinical hypothyroidism according to a lower cut-off only had a higher risk of GDM if they were also TPOAb positive [23].

LEVOTHYROXINE TREATMENT

It remains difficult to determine whether levothyroxine treatment is of benefit in TPOAb positive women during pregnancy. We have now learned from three well-performed randomized trial that there is no benefit of preconception levothyroxine treatment for euthyroid TPOAb positive women [25-27]. However, the randomized trial data for gestational levothyroxine treatment of euthyroid TPOAb positivity are poor since there

are no randomized trials focusing primarily on euthyroid TPOAb positivity but only subanalyses can be identified. The two largest available randomized trials either did not measure TPOAbs or did not perform the relevant sensitivity analyses stratifying for example TPOAb positive from TPOAb negative subclinical hypothyroidism [28,29]. One interesting analyses (albeit an underpowered one) can be found in the supplemental data of the latest trial, indicating that in fact levothyroxine treatment may have a larger effect on child IQ comparing TPOAb positive to TPOAb negative women with either subclinical hypothyroidism (1.5-point difference vs. 4-point difference) or isolated hypothyroxinemia (3-point difference vs. 4.5-point difference)—but this remains speculative. The two trials that were able to focus on euthyroid TPOAb positivity were both small but were positive owing to the large effect size. A small Italian randomized trial showed that levothyroxine treatment started at median 10 weeks for euthyroid TPOAb positivity was associated with a lower risk of miscarriage and preterm birth. one small randomized trial from Iran has shown that gestational levothyroxine treatment started at approximately 12 weeks pregnancy for TPOAb positive women does reduce the risk of preterm birth, but subanalyses showed this is driven only by the women with a TSH concentration >4.0 mU/L [30]. Although it seems preliminary to advise for levothyroxine treatment for all euthyroid TPOAb positive pregnant women, these data do seem to suggest that any possible advantageous effects of treatment are to be expected when treatment is started during or before the early second trimester.

ROLE OF hCG

Another factor that seems to distinguish TPOAb positive women with a high-risk of adverse outcomes is the hCG concentration. In a study by our group, we assessed if the extent of impairment of the thyroidal response to hCG stimulation (defined as the distance from the expected FT4 concentration in TPOAb negative women with the same hCG concentrations) was associated with the risk of preterm birth in TPOAb positive women. We identified out of the TPOAb positive women with a good or above average thyroidal response to hCG stimulation respectively 0.0% and 3.7% had a preterm birth, while those with a response below what was expected had a risk of 7.6% to 10.7% [13]. In a Chinese study, an impaired thyroidal response to hCG stimulation in early pregnancy was associated with a lower crown rump length, as a marker of early fetal growth [31]. More studies are needed to replicate these findings and to investigate

to what extent the TSH concentrations and/or additional measurement of the hCG concentration can help to identify high-risk TPOAb positive women.

CONCLUSIONS

TPOAb positivity has considerable impact on thyroid physiology during pregnancy and is a major risk factor for gestational thyroid dysfunction. Still, the majority of TPOAb positive women remain euthyroid. While we can learn from the published work so far that euthyroid TPOAb positive women likely have a higher risk of miscarriage and preterm birth, it remains unknown whether this is through a thyroidal mechanism or related to a higher general susceptibility for autoimmune disease. Moreover, currently available data does not allow for recommendation for or against gestational levothyroxine treatment of euthyroid TPOAb positivity. As with any grey area in medicine, the key lies within patient-doctor communication and weighing the potential harms (levothyroxine overtreatment) and benefits during clinical decision making.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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