

## CLINICAL DECISIONS

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### Thyroid Function and Conception

*This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.*

#### CASE VIGNETTE

### A Woman Trying to Conceive

Angela X. Chen, M.B., B.S., M.P.H.

Ms. Thompson is a 31-year-old woman who has been trying to conceive for the past 12 months and comes to see you, her primary care physician. One month ago, she had a miscarriage at 7 weeks of gestation. She has not had any other pregnancies.

Ms. Thompson has always been healthy; she has no significant medical history. Her only regular medication is a prenatal multivitamin, which she has been taking regularly for the past 12 months. Before that, she had used the combined estrogen–progesterone oral contraceptive pill for several years. Since she discontinued the contraceptive pill, her menses have been regular, with a 28-day cycle.

Her family history is significant for autoimmune disease. Her brother has type 1 diabetes mellitus, and a maternal uncle has Hashimoto's thyroiditis. Ms. Thompson has no personal history of thyroid disease and reports no symptoms suggestive of hyperthyroidism or hypothyroidism, nor does she have any localized neck discomfort or swelling.

Given the presentation and her family history, thyroid function tests and testing for thyroid peroxidase antibodies are performed. The thyrotropin concentration is 3.2 mIU per liter (normal range,

0.5 to 4.0) and the free thyroxine ( $T_4$ ) concentration is 1.1 ng per deciliter (14 pmol per liter; normal range, 0.86 to 1.9 ng per deciliter [11 to 24 pmol per liter]). However, the test for thyroid peroxidase antibodies is positive (78 IU per milliliter [normal range, <35]).

Ms. Thompson has read that changes in thyroid function can affect a woman's chances of having a successful pregnancy. Given the results of her tests, she is interested in your recommendation as to whether she should begin treatment with levothyroxine to increase her chances of conceiving.

#### TREATMENT OPTIONS

Which one of the following approaches would you take for this patient? Base your choice on the published literature, your own experience, published guidelines, and other information sources.

1. Recommend treatment with low-dose levothyroxine.
2. Do not recommend treatment with levothyroxine.

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which approach would you choose?

#### OPTION 1

### Recommend Treatment with Low-Dose Levothyroxine

Angela M. Leung, M.D.

This clinical scenario of a young, healthy woman who is found to have a serum thyrotropin concentration in the mid-to-upper reference range for nonpregnant women, a normal free  $T_4$  concentra-

tion, and a positive thyroid antibody titer is a common clinical entity. Whether a clinician initiates low-dose levothyroxine in this patient is based on current understanding of spontaneous loss of pregnancy<sup>1</sup> and its associations with thyroid dysfunction, thyroid antibody positivity, and these two factors in combination.

The prevalence of an elevated thyrotropin concentration among healthy nonpregnant women

is 2 to 3% and may be higher in regions where iodine deficiency is common.<sup>1</sup> Because iodine is an essential micronutrient for normal thyroid hormone production and severe iodine deficiency in pregnancy has been associated with miscarriage,<sup>2</sup> this patient should be counseled to ensure that her prenatal multivitamin contains 150  $\mu\text{g}$  of iodine per daily dose.<sup>1</sup> Thyroid hormone is crucial for early development, and overt hypothyroidism during pregnancy is associated with multiple adverse obstetrical and neonatal outcomes.<sup>1</sup> Trimester-specific goals for serum thyrotropin concentration during pregnancy vary, depending on whether concurrent tests for serum thyroid antibodies are positive.<sup>1</sup> However, among pregnant women who test negative for thyroid antibodies, those with even a slightly higher thyrotropin concentration (2.5 to 5.0 mIU per liter) in the first trimester have a significantly higher risk of pregnancy loss than those with thyrotropin concentrations of less than 2.5 mIU per liter.<sup>3</sup>

A positive thyroid antibody titer is an important separate consideration. Positive thyroid antibody (antithyroid peroxidase or antithyroglobulin) titers are found in up to 18% of all pregnant women and in up to 65% of those with an elevated thyrotropin concentration during pregnancy.<sup>4</sup> Thyroid autoimmunity confers a significant risk for the development of hypothyroidism but is also an independent risk factor for infertility, miscarriage, and other potential obstetrical and neonatal complications.<sup>4</sup> Proposed mechanisms for the association between thyroid autoimmunity and miscarriage include cross-reactivity between thyroid antibodies and oocyte human chorionic gonadotropin (hCG) receptors, the effect of other non-organ-specific autoimmunity, and increased levels of endometrial cytokines.<sup>1</sup>

In a longitudinal, randomized, controlled trial in pregnant women with normal thyroid function who tested positive for serum thyroid peroxidase antibodies, Negro and colleagues reported a significantly lower incidence of pregnancy loss among women who began receiving low-dose levothyroxine at a mean gestation of 10 weeks than among those who did not receive levothyroxine (3.5% vs. 13.8%),<sup>5</sup> findings that were in alignment with another recent small trial.<sup>6</sup> Furthermore, some studies have shown an association between thyroid antibody positivity and recurrent miscarriage, even when the serum thyrotropin concentration is in the reference range.<sup>1</sup> Given this evidence, the

American Thyroid Association recommends that women with normal thyroid function who test positive for thyroid antibodies be monitored just as rigorously as women with hypothyroidism during pregnancy and also suggests that treatment with levothyroxine should be initiated at a lower pregnancy-specific thyrotropin threshold in women with thyroid antibodies than in those without thyroid antibodies.<sup>1</sup>

However, most recently, a large double-blind, placebo-controlled trial (Thyroid Antibodies and Levothyroxine [TABLET]) in pregnant women with normal thyroid function showed that the use of levothyroxine at a dose of 50  $\mu\text{g}$  daily in women who tested positive for thyroid peroxidase antibodies did not result in a higher percentage of live births than placebo.<sup>7</sup> This robust trial adds important knowledge to the field, but unlike the study by Negro et al.,<sup>5</sup> this trial used fixed doses of levothyroxine that were not adjusted according to thyrotropin concentration or thyroid peroxidase antibody level; in addition, the baseline median serum thyroid peroxidase titer in this trial was lower in the intervention group than in the placebo group (baseline median serum thyroid peroxidase titers in the two groups were not reported in the study by Negro et al.)<sup>5</sup> In light of the overall safety of levothyroxine use, its relatively low cost, the patient's prolonged attempt to conceive, her history of miscarriage, and discrepant findings from the available trials on this topic, initiation of low-dose levothyroxine in anticipation of another pregnancy is reasonable.

Disclosure forms provided by the author are available with the full text of this article at [NEJM.org](http://NEJM.org).

From the UCLA David Geffen School of Medicine and the Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles.

## OPTION 2

### Do Not Recommend Treatment with Levothyroxine

Tim I.M. Korevaar, M.D., Ph.D.

Miscarriage occurs in 20 to 25% of pregnancies and has a considerable negative effect on psychological well-being. Whereas overt thyroid disease is a well-known risk factor and an indication for levothyroxine therapy, thyroid tests show that Ms. Thompson has thyroid peroxidase antibodies but otherwise normal thyroid function. Positivity for thyroid peroxidase antibodies reflects

thyroid autoimmunity, which is the most important risk factor for hypothyroidism in the developed world. The prevalence of positivity for thyroid peroxidase antibodies is approximately 10% among women of reproductive age. However, the majority of these women (75%) have normal thyroid function.<sup>7</sup> My advice regarding levothyroxine treatment in the current case is based on three main considerations.

First, there is no evidence that Ms. Thompson's thyroid profile would affect her chance of achieving clinical pregnancy. In observational studies involving women with a previous miscarriage or those undergoing fertility treatment, positivity for thyroid peroxidase antibodies has not been associated with the likelihood of clinical pregnancy or the time to pregnancy.<sup>8</sup> Furthermore, randomized, controlled trials have shown no benefit of levothyroxine supplementation for achieving a clinical pregnancy.<sup>6,7</sup>

Second, whether Ms. Thompson's thyroid profile is associated with adverse pregnancy outcomes should be considered. Positivity for thyroid peroxidase antibodies has been associated with a higher risk of miscarriage and preterm birth. There is some evidence that this association is mediated by decreased thyroid functional capacity, but positivity for thyroid peroxidase antibodies may merely reflect a higher susceptibility to autoimmunity. Three recent trials did not show a benefit of preconception or gestational levothyroxine treatment (or both) with respect to the risk of miscarriage or the likelihood of live birth in women with normal thyroid function who tested positive for thyroid peroxidase antibodies.<sup>7,9,10</sup> At best, subgroup analyses from two small trials suggest a possible reduction in preterm birth with levothyroxine supplementation among women with a thyrotropin concentration above 4.0 mIU per liter, but this finding requires further replication.<sup>9</sup>

Third, interpreting preconception thyroid function tests in anticipation of pregnancy is pivotal. If levothyroxine is indicated, treatment should be started as early as possible, because thyroid hormone regulates the increased metabolic demand of pregnancy. During gestation, levothyroxine treatment for women with thyroid peroxidase antibodies can be considered if the thyrotropin concentration is above 2.5 mIU per liter but is recommended if the thyrotropin concentration is greater than 4.0 mIU per liter.<sup>1</sup> Interpretation

of gestational thyrotropin and free T<sub>4</sub> concentrations is complicated by major changes in thyroid physiology during pregnancy. Most notably, high concentrations of hCG stimulate the thyroid gland, increasing free T<sub>4</sub> concentrations and decreasing thyrotropin concentrations from the 6th week of gestation onward. In women who test negative for thyroid peroxidase antibodies, a thyrotropin concentration of 3.2 mIU per liter before conception would be likely to fall below 2.5 mIU per liter during pregnancy. However, 40% of all women who test positive for thyroid peroxidase antibodies have an impaired thyroïdal response to hCG stimulation.<sup>11</sup> It is currently not possible to predict the course of thyrotropin concentrations in women with normal thyroid function who test positive for thyroid peroxidase antibodies during pregnancy.

Taken together, there is no compelling evidence that levothyroxine treatment before conception for women with normal thyroid function who test positive for thyroid peroxidase antibodies has a beneficial effect on achieving pregnancy or a live birth or on reducing the risk of pregnancy complications. Many doctors can provide anecdotal evidence of a beneficial effect of levothyroxine treatment in cases similar to that of Ms. Thompson. Although low-dose levothyroxine is safe, the risks of overtreating and of medicating unnecessarily are arguments against levothyroxine treatment. Instead, I would advise follow-up with thyroid function testing every 3 months before conception and every 4 weeks during pregnancy, starting at 6 to 8 weeks of gestation, to identify as soon as possible a potential lack of thyroïdal response to hCG.

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

From Erasmus University Medical Center, Rotterdam, the Netherlands.

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