EDITORIAL

Subclinical hypothyroidism and pregnancy: Public health problem or lab finding with minimal clinical significance?

There is no clear evidence that thyroxine can improve pregnancy outcomes in women with subclinical hypothyroidism

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In a US study of more than 17,000 people, overt hypothyroidism and hyperthyroidism were detected in about 4.6% and 1.3% of adults, respectively.[1] In this population-based study, thyroid disease was 5 times more prevalent among women than among men. In our ObGyn practices, there are many women of reproductive age with thyroid disease who are considering pregnancy. Treatment of active hyperthyroidism in a woman planning pregnancy is complex and best managed by endocrinologists. Treatment of hypothyroidism is more straightforward, however, and typically managed by internists, family medicine clinicians, and obstetrician-gynecologists.

Clinical management of hypothyroidism and pregnancy

Pregnancy results in a doubling of thyroxine-binding globulin (TBG) levels and a 40% increase in plasma volume, resulting in a need for more thyroxine production.[2] Of note, from conception to approximately 13 weeks' gestation, the sole source of embryonic and fetal thyroid hormones is from the mother.[2] Women who have been taking chronic thyroxine treatment may have suppressed thyroid gland activity and be unable to increase thyroxine production in response to pregnancy, necessitating a 30% to 50% increase in their thyroxine dose to maintain TSH levels in the normal range.

For hypothyroid women on long-term thyroxine treatment, recommend increasing the thyroxine dose when pregnancy is recognized. For your patients on chronic thyroxine treatment who are planning a pregnancy, a multiprong approach is helpful in preparing the patient for the increased thyroxine requirements of early pregnancy. First, it is important to counsel the woman that she should not stop the thyroxine medication because it may adversely affect the pregnancy. In my experience, most cases of overt hypothyroidism during pregnancy occur because the patient stopped taking her thyroxine therapy. Second, for hypothyroid women who are considering conception it is reasonable to adjust the thyroxine dose to keep the TSH concentration in the lower range of normal (0.5 to 2.5 mU/L). This will give the woman a "buffer," reducing the risk that in early pregnancy she and her fetus will have a thyroxine deficit. Third, in early pregnancy, following detection of a positive pregnancy test, your patient can start to increase her thyroxine dose by about two tablets weekly (a 28% increase in the dose). Fourth, TSH levels can be measured every 4 weeks during the first trimester, with appropriate adjustment of the thyroxine dose to keep the TSH concentration below the trimester-specific upper limit of normal (< 4 mU/L).[2]

TSH and free thyroxine measurements identify women with overt hypothyroidism who need thyroxine treatment. Overt hypothyroidism is associated with adverse reproductive outcomes, including decreased fertility, increased spontaneous abortion, increased fetal loss, and preterm birth.[2,3] Hence it is important to immediately initiate thyroxine treatment in pregnant

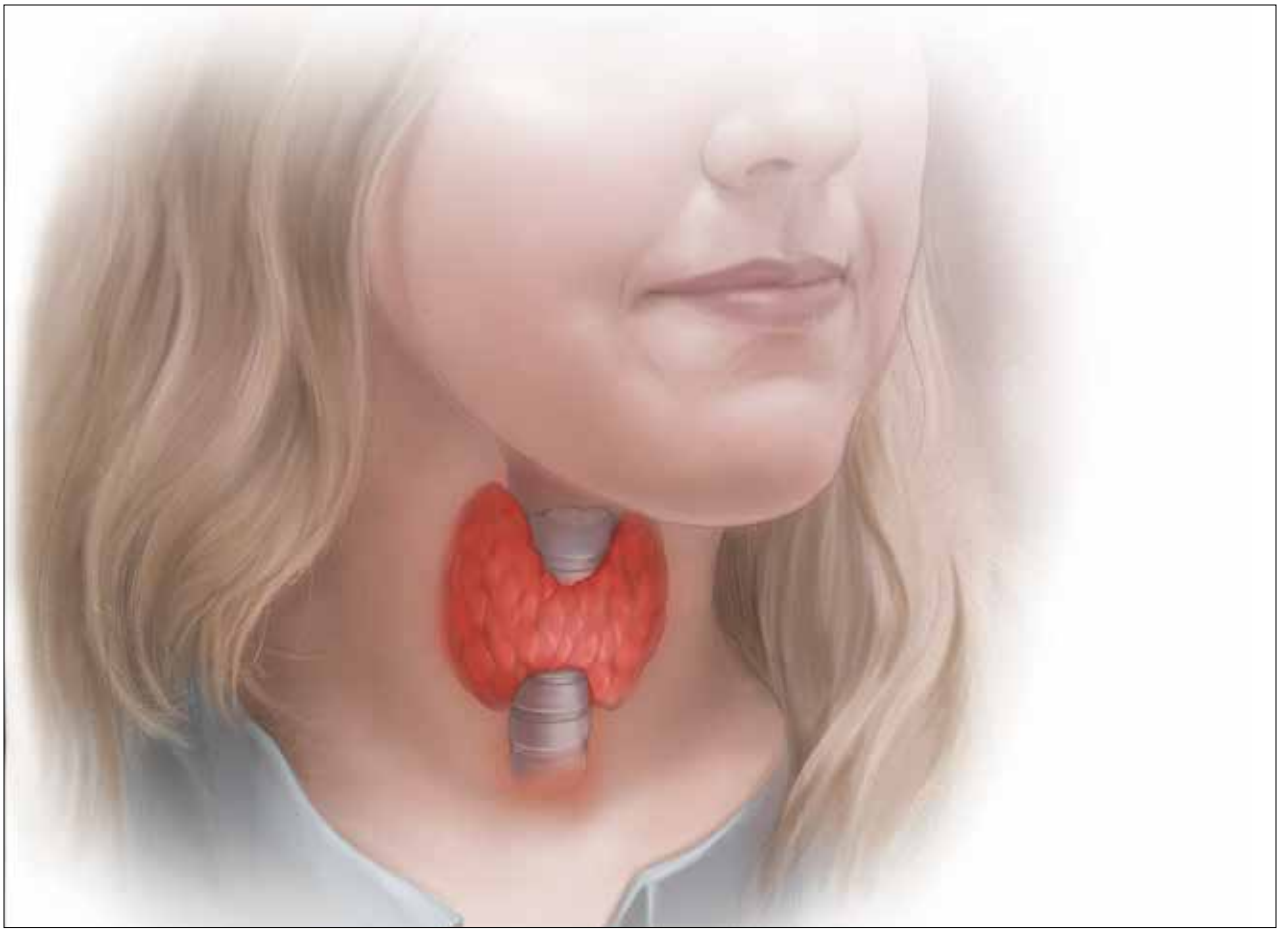

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MAMAGEMENT

women who have overt hypothyroidism. A diagnosis of overt hypothyroidism is indicated in women with an intact hypothalamic-pituitary axis and a TSH level ≥10 mU/L plus a low free thyroxine concentration. A TSH level of >4 to 10 mU/L, with normal free thyroxine concentration, is evidence of subclinical hypothyroidism (SCH). Among women, there are about 5 times more cases of SCH than overt hypothyroidism.

The literature concerning SCH and pregnancy is vast, and often contradictory, leading to confusion among clinicians. Contributing to the confusion is that some observational studies report a modest association between SCH and adverse pregnancy outcomes. To date, however, randomized clinical trials show no benefit of thyroxine treatment in these cases. I explore these contradictory pieces of evidence below.

Is SCH associated with adverse pregnancy outcomes due to low thyroxine levels?

There is conflicting literature about the association of SCH and adverse reproductive outcomes. A meta-analysis of 47,045 pregnant women reported that the preterm birth rate for women with SCH and euthyroid women (normal TSH and normal free thyroxine levels) was 6.1% and 5.0%, respectively (odds ratio [OR], 1.29; 95% CI, 1.01–1.64).[4] Interestingly, pregnant women with normal TSH levels but a low free thyroxine level also had an increased rate of preterm birth (7.1% vs 5.0%; OR, 1.46; 95% CI, 1.12–1.90).

Although observational studies report an association between SCH and adverse reproductive outcomes, multiple randomized clinical trials conducted in women with SCH or hypothyroxinemia have failed to demonstrate that thyroxine replacement improves reproductive outcomes. For example, in a study of 794 pregnant women with elevated TSH and/or low free thyroxine levels randomly assigned to thyroxine treatment (0.15 mg daily) or no treatment, there was no difference in preterm birth rate (5.6% vs 7.9%, $P = .2$), mean birth weight (3.5 kg vs 3.3 kg, $P = .15$), gestational age at delivery (40.1 vs 40.2 weeks, $P = .10$), or the

intelligence quotient of children at 3 years (99 vs 100, $P = .40$).[5]

In another study, 674 pregnant women with mild SCH (mean TSH, 4.4 mU/L) were randomly assigned to receive thyroxine (0.1 mg daily and dose adjusted to achieve a normal TSH level) or placebo. In this study there was no difference between the thyroxine treatment or placebo groups in preterm birth rate (9% vs 11%, $P = .44$), gestational age at delivery (39.1 vs 38.9 weeks, $P = .57$) or intelligence quotient of children at 5 years (97 and 94, $P = .71$).[6]

The same investigators also randomized 524 pregnant women with isolated hypothyroxinema (mean free thyroxine level, 0.83 ng/dL) and normal TSH level (mean, 1.5 mU/L) to thyroxine (0.05 mg daily and dose adjusted to achieve a normal free thyroxine level) or placebo.[6] In this study there was no difference in preterm birth rate (12% vs 8%, $P = .11$), gestational age at delivery (39.0 vs 38.8 weeks, $P = .46$) or intelligence quotient of children at 5 years (94 and 91, $P = .31$).[6]

When large randomized clinical trials and observational studies report discrepant results, many authorities prioritize the findings from the randomized clinical trials because those results are less prone to being confounded by unrecognized factors. Randomized trials do not demonstrate that mild SCH or isolated hypothyroxinemia have a major impact on pregnancy outcomes.

Thyroid antibodies, fertility, miscarriage, and preterm birth

Some observational studies report that the presence of thyroid antibodies in a euthyroid woman reduces fecundity and increases the risk for miscarriage and preterm birth. For example, a meta-analysis of 47,045 pregnant women reported that the preterm birth rate for women with and without antithyroid antibodies was 6.9% and 4.9%, respectively (OR, 1.33; 95% CI, 1.15–1.56). However, in euthyroid women with antithyroid antibodies, low-dose thyroxine therapy has not been shown to improve fertility, or reduce miscarriages or preterm birth rate.

In a large randomized clinical trial, 952 euthyroid women (normal TSH level; range, 0.44 to 3.63 mIU/L and free thyroxine level; range, 10 to 21 pmol/L) who were planning on conceiving and had elevated thyroid peroxidase antibodies were randomized prior to conception to receive either thyroxine (50 µg) or placebo.[7] After 12 months, outcomes were similar for women treated with thyroxine or placebo, including live birth rate (37.4% vs 37.9%), miscarriage rate for those who became pregnant (28.2% vs 29.6%), and preterm birth ≤ 34 weeks of gestation (3.8% vs 3.6%, respectively).[7] The investigators concluded that the use of low-dose thyroxine in euthyroid women with thyroid peroxidase antibodies was not effective for increasing the rate of live birth or reducing the rate of miscarriage or early preterm birth.

Thyroid antibodies and the rate of IVF pregnancy and miscarriage

Some observational studies suggest that the presence of antithyroid antibodies may be associated with an increased rate of miscarriage.[8] To test the effects of thyroxine treatment on the rate of miscarriage in euthyroid women with antithyroid antibodies, 600 euthyroid infertile women with antithyroid antibodies (antithyroid peroxidase levels ≥ 60 IU/mL) scheduled to have in vitro fertilization (IVF) were randomly assigned to receive thyroxine (dose adjustment to keep TSH levels in the range of 0.1 to 2.5 mIU/L) or no treatment.[9] The thyroxine treatment was initiated 2 to 4 weeks before initiation of ovarian stimulation. In this study, treatment with thyroxine or no treatment resulted in similar rates of clinical pregnancy (35.7% vs 37.7%) and live birth (31.7% vs 32.3%).[9] Among the women who achieved a clinical pregnancy, miscarriage rates were similar in the thyroxine and no treatment groups (10.3% vs 10.6%).[9]

Let's focus on more serious problems that affect pregnancy

There is a clear consensus that women with overt hypothyroidism should be treated with thyroxine prior to attempting pregnancy.[2,6] There is no clear consensus about how to treat women considering pregnancy who have one isolated laboratory finding, such as mild subclinical hypothyroidism, mild isolated hypothyroxinemia, or antithyroid antibodies. Given the lack of evidence from randomized trials that thyroxine improves pregnancy outcomes in these cases, obstetrician-gynecologists may want to either refer women with these problems to an endocrinologist for consultation or sequentially measure laboratory values to assess whether the patient's laboratory abnormality is transient, stable, or worsening.

Obstetrician-gynecologists and their patients are confronted by many serious problems that adversely affect pregnancy and deserve priority attention, including iron deficiency anemia, excess gestational weight gain, peripartum depression, intimate partner

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violence, housing insecurity, cigarette smoking, substance misuse, chronic hypertension, morbid obesity, diabetes, gestational diabetes, preeclampsia, venous thromboembolism, obstetrical hemorrhage, sepsis, and infectious diseases. Given limited resources our expertise should be focused on these major obstetric public health problems rather than screening for mild subclinical hypothyroidism. ●

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Correction

Per the article authors, in the following article, The case for outpatient cervical ripening for IOL at term for low-risk pregnancies. *OBG Manag.* 2019;31(9):41-48, 52., box 5 of Figure 3 should have read, "50 µg of oral misoprostol administered if nonstress test appropriate." The article has been corrected online.

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