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THYROID AND PREGNANCY

American Thyroid Association task force updates treatment guidelines for the diagnosis and management of thyroid disease during pregnancy and the postpartum

FULL JOURNAL TITLE

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American Thyroid Association Task Force Updates Guidelines on Thyroid Disease and Pregnancy

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If you are planning a pregnancy, currently pregnant, or in the postpartum period, it's important to stay up to date on the latest guidelines on thyroid disease and pregnancy. A task force from the American Thyroid Association (ATA) has reviewed the latest research and distilled it into a new publication: *"2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum."*
The task force was co-chaired by Dr. Erik K. Alexander (Brigham and Women's Hospital, Harvard Medical School) and Dr. Elizabeth N. Pearce (Boston University School of Medicine) and included Dr. Gregory A. Brent (VA Greater Los Angeles Healthcare System, David Geffen School of Medicine at UCLA), Dr. Rosalind S. Brown (Boston Children's Hospital, Harvard Medical School), Dr. Herbert Chen (University of Alabama at Birmingham), Dr. Chrysoula Dosiou (Stanford University School of Medicine), Dr. William A. Grobman (Northwestern University), Dr. Peter Laurberg (Aalborg University Hospital, Denmark), Dr. John H. Lazarus (Cardiff University, Cardiff, United Kingdom), Dr. Susan J. Mandel (Perelman School of Medicine, University of Pennsylvania), Dr. Robin P. Peeters (Rotterdam Thyroid Center, Erasmus Medical Center, The Netherlands) and Dr. Scott Sullivan (Medical University of South Carolina).

The new guidelines (updated from a prior edition from 2011) are available free on the website of Thyroid, the official peer-reviewed journal of the ATA, published by Mary Ann Liebert, Inc., publishers. "With an estimated 300,000 pregnancies impacted by thyroid disease in the United States annually, these guidelines coalesce the best available evidence into clear clinical recommendations, and will improve the health of many, many mothers and newborns alike," note Dr. Alexander and Dr. Pearce. The guidelines were reviewed in advance and endorsed by a number of medical associations as well as patient groups, including the Graves' Disease & Thyroid Foundation.

Pregnancy Planning

Thyroid dysfunction is a potential factor in infertility, possibly due to irregular menstrual cycles. The new guidelines recommend TSH testing for all women seeking treatment for infertility, with levothyroxine recommended for cases of overt hypothyroidism. For subclinical hypothyroidism (normal T3 and T4 values, with abnormally high TSH), the task force notes that there is insufficient evidence to determine whether levothyroxine can improve fertility, although states that treatment with a low dose of levothyroxine "may be considered in this setting given its ability to prevent progression to more significant hypothyroidism once pregnancy is achieved." Treatment of subclinical hypothyroidism is recommended for women who are undergoing IVF or ICSI fertility treatments, with a goal of reducing TSH to less than 2.5 mU/L. Low-dose levothyroxine therapy "may be considered" in women who are using assisted reproductive techniques and test positive for thyroid peroxidase antibodies (TPOAbs), which are often present in Hashimoto's thyroiditis.

The task force recommends that women who are currently being treated for hypothyroidism and are planning a pregnancy undergo TSH testing, with a goal of achieving

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a TSH between the lower end of the reference range and no more than 2.5 mU/L prior to conception.

For women with thyrotoxicosis due to an overactive thyroid nodule, balancing maternal and fetal thyroid function during pregnancy can be challenging; in these cases, ablative therapy (surgery or RAI) might be recommended prior to conception.

Women who are being treated for Graves' disease are advised to postpone pregnancy planning until thyroid function is stabilized, as indicated by two normal tests at least one month apart, with no change in medication dosing. The guidelines note that, *"Women with GD seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation, including the association of birth defects with antithyroid drug (ATD) use. Preconception counseling should review the risks and benefits of all treatment options and the patient's desired timeline to conception."* These treatment options include antithyroid medications, radioactive iodine, and thyroidectomy. Patients who choose radioactive iodine are advised to delay pregnancy by at least six months (and not attempt conception until thyroid levels are stable) and should be aware that increased antibody levels following treatment can potentially affect the fetus.

Thyroid Function Testing and Pregnancy

Trimester-specific ranges for thyroid function testing are recommended during pregnancy, due to typical increases of T4 and suppression of TSH in the first trimester. Variations that occur due to race, ethnicity, iodine intake, the presence or absence of thyroid antibodies, and even body mass index can make development of these ranges challenging. The guidelines note that ideally, the reference range should be tailored to a specific population as well as the specific process used by the test manufacturer.

Hypothyroidism and Pregnancy

Untreated hypothyroidism during pregnancy is associated with an increased risk of a number of adverse outcomes, including premature birth, low birth weight, lower offspring IQ, and even pregnancy loss.

Pregnant women who are euthyroid, but have positive TPOAbs, may develop hypothyroidism prior to delivery. To ensure timely treatment, the task force recommends TSH testing at the time pregnancy is confirmed and every four weeks until mid-pregnancy, when thyroid function tends to stabilize. Treatment of overt hypothyroidism is always recommended during pregnancy, and therapy is also recommended for subclinical hypothyroidism in TPOAb-positive women. The guidelines note that the recommended treatment is oral levothyroxine; combination therapy using T3 or desiccated thyroid is not recommended during pregnancy.

The task force also states that administration of 25-50 micrograms of levothyroxine "may be considered" in women who are TPOAb-positive, but euthyroid, and who have a prior history of pregnancy loss.

The guidelines recommend that women with overt or subclinical hypothyroidism, as well as those at risk for hypothyroidism, undergo TSH testing every four weeks until mid-pregnancy and at least once near 30 weeks gestation.

Women who are already taking thyroid hormone replacement at the time pregnancy is confirmed (or even suspected) should contact their provider immediately; the task force recommends independently increasing the dose of their replacement hormone by taking two additional tablets weekly of their current daily dose. Follow-up testing will determine if the dose needs to be further adjusted as pregnancy progresses.

Thyrotoxicosis and Pregnancy

Women can also experience thyrotoxicosis (excessive levels of thyroid hormone) during pregnancy. If left untreated, adverse affects noted in the new guidelines include "pregnancy loss, pregnancy-induced hypertension, prematurity, low birth weight, intrauterine growth restriction, stillbirth, thyroid storm, and maternal congestive heart failure."

Common causes of thyrotoxicosis during pregnancy are Graves' disease, an autoimmune condition, gestational transient thyrotoxicosis, and overactive thyroid nodules. Receiving a correct diagnosis is critical, as this will affect treatment options. Findings that point to gestational transient thyrotoxicosis include no prior history of thyroid disease, and absence of goiter or eye findings, mild symptoms of thyrotoxicosis, and vomiting. A blood

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test can confirm the presence of antibodies (TRAb) that cause Graves' disease, and an ultrasound can identify the presence of nodules. Although a radioactive iodine uptake & scan can distinguish between Graves' disease and other causes of thyrotoxicosis, this procedure is not recommended during pregnancy.

Gestational transient thyrotoxicosis often resolves itself after the first half of pregnancy, although management of dehydration is needed, and hospitalization may be required. Beta blockers may be considered for relief of symptoms, but ATD are not needed.

Dealing with overactive nodules during pregnancy is challenging, as treatment with ATDs in the mother can potentially cause hypothyroidism in the fetus. Therefore, the task force recommends using a low dose of ATDs, with the goal of keeping the mother's Free T4 at or slightly above the reference range.

The standard treatment options for Graves' disease come with special considerations during pregnancy. Radioactive iodine is never an option for pregnant women. Thyroid surgery is only recommended during the second trimester and for specific situations, particularly women who are unable to take antithyroid medications.

Antithyroid medications come with an increased risk of birth defects, although PTU generally has a lower risk than methimazole, and is the recommended medication during the first trimester. (The task force did not make a recommendation on switching back to methimazole after the first trimester. Although MMI comes with a reduced risk of liver issues, the medications are not dose-equivalent, so finding the "sweet spot" dose with the new medication could take some time).

Within the first days of an absent or weak menstrual period, women who are taking ATDs are advised to contact their provider to discuss thyroid function testing and potential dose adjustments.

Block-replace therapy, which involves giving large doses of ATDs in conjunction with replacement hormone, is not recommended during pregnancy, due to the risk of fetal hypothyroidism. However, this approach may be used in rare cases where the mother is hypothyroid after RAI or surgery, but maternal antibodies are causing hyperthyroidism in the fetus. The ATDs will pass through the placenta to calm the fetal hyperthyroidism, while the replacement hormone will keep the mother's thyroid levels stable.

As autoimmunity tends to lessen during pregnancy, Graves' patients might find that they are able to reduce or discontinue ATDs as pregnancy progresses. For some women, discontinuing antithyroid medications after confirmation of pregnancy is an option, but is not recommended for women who have a high risk of relapse of hyperthyroidism. The guidelines note that women considered high risk include "patients who have been treated for a short period (<6 months), who have suppressed or low serum TSH while on medication pre-pregnancy, who require >5-10 mg of MMI per day to stay euthyroid, who have active orbitopathy or large goiter, and those who have high levels of TRAb." If ATDs are discontinued, the guidelines state that thyroid function tests should be performed every 1-2 weeks during the first trimester and every 2-4 weeks thereafter if levels are stable.

Thyroid Dysfunction and the Fetus

Because antithyroid medications may affect the fetal thyroid, the guidelines recommend that the lowest possible dose in the mother should be used to prevent fetal hypothyroidism; reference targets for Free T4 in the mother should be at or just above the upper limit of normal.

Thyroid stimulating antibodies (TRAb) in the mother can also cross the placenta and cause hyperthyroidism in the fetus. This is a rare but serious occurrence that can result in complications, and even death, if not diagnosed and treated. The task force has significantly updated the ATA's 2011 recommendations on antibody testing, now calling for earlier, and in some cases, more frequent testing:

For women with a history of Graves' who were treated with surgery or RAI, antibody testing is recommended at the time pregnancy is confirmed. If antibodies are elevated, the test should be repeated at weeks 18-22.

For women who are currently taking ATDs, antibody testing is recommended at the time pregnancy is confirmed, with a second test at weeks 18-22, and then a third test in weeks 30-34 if the second test was elevated.

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Fetal surveillance – as well as consultation with a maternal-fetal medicine specialist – is recommended for women with uncontrolled hyperthyroidism during the second half of pregnancy and for women whose TRAb levels are three times the upper cutoff limit. Fetal ultrasound can be used to identify signs of potential hyperthyroidism. More rarely, if the fetus has a goiter, umbilical cord sampling might be recommended if it is unclear whether the fetus is hyperthyroid or hypothyroid. For women with severe thyroid illness during pregnancy, the task force recommends establishing a relationship with a neonatologist or pediatrician prior to delivery to ensure seamless care for the newborn.

The Postpartum Period

The guidelines note that women who were diagnosed with hypothyroidism prior to pregnancy and increased their dose of thyroid hormone replacement should resume their pre-pregnancy dose following delivery, with follow-up testing recommended six weeks later. Women who began taking levothyroxine during pregnancy might find that they no longer need the medication; this is a decision that should be made by the patient and the physician, with follow-up testing completed in six weeks if the medication is discontinued.

The most common cause of thyrotoxicosis during the postpartum period is postpartum thyroiditis (PPT), an autoimmune inflammatory condition in which excessive levels of stored thyroid hormone are released. PPT occurs in approximately 5% of pregnancies and usually resolves itself without treatment. More severe symptoms may occur in women with elevated TPOAbs; in these cases, a course of beta blockers may be used. The task force recommends that TSH testing should be completed 4-8 weeks after resolution of the hyperthyroid symptoms to screen for the development of hypothyroidism. For patients who do become hypothyroid, treatment with levothyroxine is recommended, particularly if the patient is symptomatic or planning another pregnancy. After one year, the levothyroxine dose may be slowly tapered to see if the hypothyroidism has resolved. If the medication is successfully withdrawn, annual TSH testing is recommended "to evaluate for the development of permanent hypothyroidism."

Although studies linking depression with PPT have yielded inconsistent results, the task force recommends that "all patients with depression, including postpartum depression, should be screened for thyroid dysfunction."

For women with a history of Graves' disease, the postpartum period comes with a high risk of relapse or of increasing severity of disease. A study out of Japan has indicated that low-dose ATD therapy following delivery might reduce the risk of relapse, although further studies are needed in this area. The postpartum period is also a high risk time for new development of Graves' disease.

Distinguishing between Graves' disease and PPT is critical, as the treatment options are different. The guidelines note that factors pointing to PPT include development within the first three months after delivery, negative TRAb testing, an elevated T4:T3 ratio, and the absence of eye involvement. A radioactive uptake can provide a differential diagnosis, but is not recommended for breastfeeding women.

Thyroid Dysfunction and Newborns

The good news is that the vast majority of women with thyroid dysfunction give birth to healthy infants – and all newborns in the U.S.A. are automatically screened for thyroid dysfunction, so that any potential issues can be identified quickly.

For infants with congenital hypothyroidism, thyroid hormone replacement is required. For babies born with hypothyroidism due to the mother taking ATDs during pregnancy, the drugs typically clear the infant's system quickly, with thyroid function being restored to normal.

Hyperthyroidism in newborns is often caused by TRAb from the mother crossing the placenta during pregnancy. This issue is treated with ATDs and usually resolves within 1-3 months. Due to the increased risk of liver issues with PTU (a rare, but very serious occurrence), methimazole is the preferred drug.

Thyroid Dysfunction and Breastfeeding

Both hyperthyroidism and hyperthyroidism can affect lactation, so proper control of thyroid levels is critical for women who are breastfeeding. Any testing or therapeutic treatments with radioactive iodine are generally not recommended while breastfeeding. However, if necessary, I^{123} can be used if the mother waits several days for the

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radioactive iodine to clear her system before resuming breastfeeding.

For women taking ATDs while breastfeeding, the guidelines note that low to moderate doses (up to 20 mg/day of methimazole or 450 mg/day of PTU) are considered safe. However, the task force recommends that "breastfed children of women who are treated with ATDs should be monitored for appropriate growth and development during routine pediatric health and wellness evaluations."

Thyroid Cancer and Pregnancy

If a thyroid nodule in the mother is detected during pregnancy, follow-up will include a detailed family history, ultrasound, and thyroid function testing. A procedure called a fine needle aspiration may be recommended to assess potential malignancy. The timing of this procedure (during pregnancy or after delivery) can be influenced by the risk of malignancy as well as patient preference.

If a malignancy is identified, surgery will be recommended, although the timing can be affected by the type of cancer. For papillary thyroid cancer in a woman with stable disease or a diagnosis during the second half of pregnancy, surgery may be delayed until after delivery. For women with more aggressive forms of cancer, such as medullary carcinoma or anaplastic cancer, the task force notes that surgery should be "strongly considered" during pregnancy.

Iodine — A Necessary Nutrient

Although the guidelines state that iodine deficiency is generally not a concern in the U.S., "U.S. women of reproductive age are the most likely group to have low urinary iodine values." One challenge to research on iodine is the ethical consideration of conducting randomized clinical trials – which would require not giving supplementation to one of the groups. The guidelines note that women who are pregnant or breastfeeding should ingest 250 micrograms of iodine daily. In order to achieve this, the task force recommends a daily oral supplement with 150 micrograms of iodine in the form of potassium iodide for women who are planning a pregnancy, pregnant, or breastfeeding; for women planning a pregnancy, the task force recommends starting supplementation three months in advance. (One exception is that women currently being treated with thyroid hormone replacement do not require supplemental iodine).

The task force cautions against the use of excessive iodine (from sources such as seaweed snacks or high-dose supplements) during pregnancy and while breastfeeding, as this can lead to hypothyroidism in the fetus or infant.

Areas for future study

Many areas remain where research has yielded conflicting results, including whether subclinical hypothyroidism should be treated during pregnancy and whether there is a benefit to universal screening for thyroid dysfunction in pregnant women. The task force noted that there was insufficient evidence to recommend for or against universal screening, although one member dissented with this opinion. All agreed that women who are newly pregnant and are at increased risk for thyroid disease should undergo TSH testing. (Risk factors include a history of diabetes mellitus type I or other autoimmune diseases, symptoms of thyroid dysfunction, goiter, family history of thyroid dysfunction, and "a history of pregnancy loss, preterm delivery, or infertility.")

Although the task force notes that "all care must be individualized", these new guidelines are a great starting point for discussions with your doctor to ensure optimal care for both you and your baby. And if you have a family member who is planning a pregnancy, don't forget to share these guidelines with her as well, as family history is a risk factor for thyroid dysfunction in pregnancy – even for women with no previous thyroid issues. A timely diagnosis and appropriate treatment will go a long way towards keeping both mother and baby healthy and happy!

The guidelines were dedicated to Dr. Peter Laurberg, an internationally recognized thyroidologist and a member of the task force, who sadly passed away in 2016.

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