american thyroid association

Clinical Thyroidology for the Public

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CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**
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EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We will be providing summaries of research studies that were discussed in a recent issue of *Clinical Thyroidology*, a publication of the American Thyroid Association for physicians. These summaries are present in lay language to allow the rapid dissemination of thyroid research to the widest possible audience. This means that you are getting the latest information on thyroid research and treatment almost as soon as your physicians. As always, we are happy to entertain any suggestions to improve *Clinical Thyroidology for the Public* so let us know what you want to see.

We also provide even faster updates of late-breaking thyroid news through Twitter at @thyroidfriends and on Facebook. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room.

Also check out our friends in the Alliance for Thyroid Patient Education. The Alliance member groups consist of: the *American Thyroid Association*, *Bite Me Cancer*, the *Graves' Disease and Thyroid Foundation*, the *Light of Life Foundation*, *ThyCa: Thyroid Cancer Survivors Association*, *Thyroid Cancer Canada and Thyroid Federation International*.

May is International Thyroid Awareness Month.

World Thyroid Day is May 25, 2017.

In honor of this topic, our lead summary in this issue is a review of the recent ATA Thyroid Disease in Pregnancy and the Postpartum Guidelines provided by Kimberly Dorris, Executive Director/CEO of the Graves' Disease and Thyroid Foundation

In this issue, the studies ask the following questions:

1. What do the new American Thyroid Association Thyroid Disease in Pregnancy and the Postpartum guidelines mean for patients?
2. Should subclinical hypothyroidism during pregnancy be treated?
3. Does pregnancy affect the progression of thyroid cancer?
4. Can a new clinical scoring system predict the outcome of antithyroid treatment in Graves' disease?
5. What is the efficacy and safety of the three treatment options for Graves' disease?
6. What are the treatment options for anaplastic thyroid cancer?

We welcome your feedback and suggestions. Let us know what you want to see in this publication. I hope you find these summaries interesting and informative.

— Alan P. Farwell, MD, FACE

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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

Alexander, Pearce, et al., 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum. Thyroid. DOI: 10.1089/thy.2016.0457

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

Kimberly Dorris, Executive Director/CEO
Graves' Disease and Thyroid Foundation

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

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

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

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

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.

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

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

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

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.

2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Alexander, Pearce, et al., DOI: 10.1089/thy.2016.0457

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HYPOTHYROIDISM

Subclinical hypothyroidism and pregnancy outcomes

BACKGROUND

Overt hypothyroidism occurs when the TSH in increased and the T_4 level is low. Subclinical hypothyroidism is defined by an increased TSH but a normal T_4. It is clear that overt hypothyroidism should be treated, especially when diagnosed during pregnancy in the mother. Failure to do so results in problems during pregnancy and interferes with normal development of the baby. It is less clear of the benefits of treating subclinical hypothyroidism, just as it is controversial whether there are any problems with the pregnancy if the mother is not treated. However, treatment of subclinical hypothyroidism in the mother during pregnancy has been recommended in the recently published guidelines of the American Thyroid Association as well as in prior guidelines from the Endocrine Society and the European Thyroid Association. The current study investigated the harms and benefits associated with the treatment of subclinical hypothyroidism during pregnancy.

THE FULL ARTICLE TITLE

Maraka S et al, Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ 2017;356:i6865.

SUMMARY OF THE STUDY

Data was collected in this study from a database of privately insured and Medicare advantage enrollees throughout the United States. The study included women in the age group of 18 to 55 years with a TSH level between 2.5 to 10 Mu/L. All women had normal T_4 levels. Treatment was associated with a reduced risk of pregnancy loss in women with a TSH level between 4.1 to 10 but not for a TSH of 2.5 to 4. A total of 5405 women with subclinical hypothyroidism were identified; 843 (15.6%) started levothyroxine treatment with an average dose of 50 µg, 7 (0.8%) with thyroid extract formulation and 4 (0.5%) with a combination of levothyroxine and liothyronine. The remaining 4562 women (84.4%) were not treated with thyroid hormone. The percentage of women treated increased from 12% in 2010 to 19% in 2014. Of the 843 women who were treated, 719 (85.3%) had at least one follow up TSH test and 130 (18.0%) had a TSH concentration above 3 mU/L.

Treatment was associated with a lower risk of pregnancy loss but a higher risk of premature delivery, diabetes and high blood pressure during pregnancy and in high heart rates.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that treatment of subclinical hypothyroidism was associated with a lower risk of pregnancy loss, especially in women with TSH concentrations of 4.1 to 10 mU/L prior to treatment. Mild increases in blood pressure, heart rate and diabetes during pregnancy were also seen. This study provides additional information to help determine to need to treat women diagnosed with subclinical hypothyroidism during pregnancy.

—Vibhavasu Sharma, MD

ATA THYROID BROCHURE LINKS

Thyroid Disease and Pregnancy: http://www.thyroid.org/thyroid-disease-pregnancy/

Thyroid Function Tests: http://www.thyroid.org/thyroid-function-tests/

ABBREVIATIONS & DEFINITIONS

Subclinical Hypothyroidism: a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated

TPO antibodies: these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

Thyroxine (T4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body. Free T_4 is the proportion of this hormone not bound to a protein in the blood.

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THYROID CANCER

Pregnancy does not affect progression of thyroid cancer

BACKGROUND

The rate of thyroid cancer is increasing in women of childbearing age, so it is not surprising that thyroid cancer is occasionally diagnosed during pregnancy. It is unclear whether pregnancy affects the response of thyroid cancer to treatment or the risk of recurrence of thyroid cancer. The risk assessments for thyroid cancer have changed over the past few years and the risk for recurrence is now reassessed two years after the initial surgery based on how they responded to their initial therapy. However, the initial risk assessment guidelines did not address pregnant women since no studies had evaluated this particular group of patients. Therefore, this study wanted to see if the risk assessment classifications, both initial and two years later, were the same for pregnant women.

THE FULL ARTICLE TITLE

Rakhlin L et al Response to therapy status is an excellent predictor of pregnancy-associated structural disease progression in patients previously treated for differentiated thyroid cancer. Thyroid. January 19, 2017 [Epub ahead of print].

SUMMARY OF THE STUDY

A total of 235 women with a history of thyroid cancer and pregnancy treated at Memorial Sloan Kettering in New York were evaluated. Of these, 90% had a total thyroidectomy and 61% received radioactive iodine therapy. Patients were assigned risk categories based on blood tests for thyroglobulin and evidence of cancer in the neck by some form of imaging (usually ultrasound). Abnormal lymph nodes in the neck was the evidence for cancer in the neck. All patients had levels determined within 1 year prior to pregnancy and within 1 year after delivery.

At evaluation after delivery, no woman without abnormal lymph nodes after initial therapy developed abnormal lymph nodes after pregnancy. In increase of abnormal lymph nodes occurred in about 30% of women that still had abnormal lymph nodes after initial treatment. Additionally, 52% of women where it was unclear if there were abnormal lymph nodes before pregnancy had no evidence of thyroid cancer recurrence after pregnancy.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggests that development of abnormal lymph nodes during pregnancy is rare and happens in less than 5% of women. Young women with a history of thyroid cancer do not need to worry that pregnancy will cause their thyroid cancer to grow to anything that changes their risk status. However, studies with longer term follow-up are needed.

— Melanie Goldfarb, MD

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): http://www.thyroid.org/thyroid-cancer/

Thyroid Disease and Pregnancy: http://www.thyroid.org/thyroid-disease-pregnancy/

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer: the most common type of thyroid cancer. There are 4 variants of papillary thyroid cancer: classic, follicular, tall-cell and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).

Total thyroidectomy: surgery to remove the entire thyroid gland.

Thyroglobulin antibodies: these are antibodies that attack the thyroid instead of bacteria and viruses, they are a marker for autoimmune thyroid disease, which is the main underlying cause for hypothyroidism and hyperthyroidism in the United States.

Thyroglobulin: a protein made only by thyroid cells, both normal and cancerous. When all normal thyroid tissue is destroyed after radioactive iodine therapy in patients with thyroid cancer, thyroglobulin can be used as a thyroid cancer marker in patients that do not have thyroglobulin antibodies.

THYROID CANCER, continued

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and with an overactive thyroid. I-123 is the non-destructive form that does not damage the thyroid and is used in scans to take pictures of the thyroid (Thyroid Scan) or to take pictures of the whole body to look for thyroid cancer (Whole Body Scan).

Cancer recurrence: this occurs when the cancer comes back after an initial treatment that was successful in destroying all detectable cancer at some point.

Thyroid Awareness Monthly Campaigns

The ATA will be highlighting a distinct thyroid disorder each month and a portion of the sales for Bravelets™ will be donated to the ATA. The month of **May** is **International Thyroid Awareness Month** and a bracelet is available through the ATA Marketplace to support thyroid cancer awareness and education related to thyroid disease.

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GRAVES' DISEASE

The "GREAT" score, a clinical tool that predicts the success of antithyroid drug therapy for Graves' disease

BACKGROUND

Graves' disease is an autoimmune condition that affects the thyroid and is the most common cause of hyperthyroidism. There are three main treatment options for Graves' disease: a) oral antithyroid drugs (ATDs) such as methimazole and propylthiouracil, b) radioactive iodine therapy, and c) surgical removal of the thyroid gland (thyroidectomy). ATDs are often prescribed because they are easy to administer and effectively treat the hyperthyroidism from Graves' disease. However, 50-75% of patients will experience a recurrence of their hyperthyroidism after stopping their ATD. When this happens patients may need to continue taking ATDs indefinitely, or they will need to pursue another treatment such as radioactive iodine therapy or surgery.

Many studies have tried to identify factors which can predict the success of ATD therapy to determine whether or not a given patient treated with ATDs will have a recurrence of their hyperthyroidism after stopping their medication. Those at high risk of having a recurrence could then choose another treatment option at the time of diagnosis. A recent study from the Netherlands established a prediction tool called the "Graves Recurrent Events After Therapy (GREAT)" score. The GREAT score uses 4 variables (age, goiter size, Free T_4 level and level of thyrotropin binding inhibitory immunoglobulin (TBII)) that can easily be assessed at the time a patient is diagnosed with Graves' disease to calculate a six point score which is then classified into three categories. Each category is associated with a higher risk of recurrence of Graves' disease after starting ATDs.

The present study seeks to validate the GREAT score and to predict the outcome of ATD treatment in large group of patients with Graves' disease.

THE FULL ARTICLE TITLE

Struja T et al, External validation of the GREAT score to predict relapse risk in Graves' disease: results from a multicenter, retrospective study with 741 patients. Eur J Endocrinol. 2017;176:413-9.

SUMMARY OF THE STUDY

The authors reviewed the rate of relapse of Graves' disease in 741 patients (79.9% female; mean age 49 years) who attended one of four endocrinology clinics in Switzerland between 2004-2014. Only patients presenting with their first episode of Graves' disease, who did not have radioactive iodine treatment and who took ATDs for more than 12 months before stopping were included in the study. Calculation of the GREAT 6-point score is as follows: age (<40 or ≥40 years: 1 or 0 point, respectively), goiter (not visible to slightly visible or clearly visible: 0 or 2 points), FT_4 (<3.1 or ≥3.1 ng/dl: 0 or 1 point), and TBII (<6; 6–19.9; >19.9 U/L: 0, 1, or 2 points) resulting in the GREAT score classes of I (0–1 point), II (2–3 points), and III (4–6 points).

Of the 741 patients with Graves' disease, 371 (50.1%) experienced a relapse after stopping their ATDs. When the GREAT score was calculated for each patient they found a relapse rate of 33.8% for class I patients and 59.4% and 73.6% for Class II and III patients respectively. Thus a higher GREAT score predicted a higher risk of relapse after stopping ATDs

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The current study supports using the GREAT score, which can be easily calculated at the time of diagnosis, to predict the success of ATD therapy to treat Graves' disease. Those classified in GREAT score class II and III have a higher chance of relapse following a 12-18 months course of treatment with ATDs. Consequently, they may decide to pursue other treatment options from the outset.

— Philip Segal, MD

ATA THYROID BROCHURE LINKS

Graves' Disease: http://www.thyroid.org/graves-disease/

GRAVES' DISEASE, continued

ABBREVIATIONS & DEFINITIONS

Goiter: a thyroid gland that is enlarged for any reason is called a goiter. A goiter can be seen when the thyroid is overactive, underactive or functioning normally. If there are nodules in the goiter it is called a nodular goiter; if there is more than one nodule it is called a multinodular goiter.

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Thyrotropin-binding inhibitory immunoglobulin (TBII): A measure of the amount of antibodies directed against the TSH receptor on the surface of thyroid cells. These antibodies are detected primarily in patients with Graves' disease.

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HYPERTHYROIDISM

Radioactive iodine therapy has the most favorable profile for the treatment of Graves' disease at the Mayo Clinic

BACKGROUND:

Graves' disease is an autoimmune condition that affects the thyroid and is the most common cause of hyperthyroidism. There are three main treatment options for Graves' disease: a) oral antithyroid drugs (ATDs) such as methimazole and propylthiouracil, b) radioactive iodine therapy and c) surgical removal of the thyroid gland (thyroidectomy). The treatment needs to be individualized based on the unique risks and benefits of each treatment option as well as the patients' preferences. The goal of this study is to compare the efficacy and safety of the three treatment options for Graves' disease in a large single-center group of patients.

THE FULL ARTICLE TITLE:

Sundaresh V et al. Comparative effectiveness of treatment choices for Graves' hyperthyroidism—a historical cohort study. Thyroid. Apr 2017, 27(4): 497-505.

SUMMARY OF THE STUDY

The study included 720 adult patients diagnosed and treated for Graves' disease at the Mayo Clinic in Rochester, MN, from 2002 to 2008. A total of 77% of patients were women, the average age was 49 years and the average follow-up duration was 3.3 years. The most commonly used therapy was radioactive iodine therapy (75%), followed by ATDs (16%) and thyroid surgery (3%). Interestingly, 6% of patients (40 patients)were initially monitored without treatment. Among ATD users, methimazole was preferred over propylthiouracil use after 2003. No gender-specific differences were noted.

In 80% of the 40 patients with mild hyperthyroidism who were initially observed, the disease progressed requiring treatment later. Among the 118 patients treated with ATDs, 39 (33%) changed therapy because of personal preferences or minor side effects. Of the remaining 89 patients, 25 (28%) had persistent hyperthyroidism on a high doses of ATD or significant adverse effects and required a change in treatment. A total of 17 out of 64 (27%) patients who completed the first ATD treatment had a relapse. The overall treatment failure rate for ATDs was 48% as compared to 8% for radioactive iodine therapy treatment. The radioactive iodine therapy treatment was the most common treatment choice for patients who failed ATDs. None of the 35 patients who underwent thyroidectomy had recurrent hyperthyroidism.

Adverse effects were reported in 17% of the patients treated with ATDs. Minor side effects included altered taste sensation (4%), rash (3%), and nausea (2%), while major adverse reactions included elevated liver enzymes (2%), bile duct inflamation (0.8%), and low white blood cell count (agranulocytosis) (0.8%). After radioactive iodine therapy, 1% of patients developed radiation thyroiditis and 6% developed new thyroid eye disease. After surgery, 29% of patients developed low calcium levels, 3% developed a bleeding problem after surgery and 3% developed permanent hoarseness due to recurrent laryngeal nerve injury.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Radioactive iodine therapy was the most commonly used treatment and had the most favorable efficacy and safety profile for Graves' disease. Although surgery was performed rarely, it was successful in all cases and had a low complication rate with experienced surgeons. ATD use resulted in frequent adverse effects and relapse. A detailed discussion with the patients is recommended before initiating treatment for Graves' disease.

— Alina Gavrila, MD, MMSC

ATA THYROID BROCHURE LINKS

Graves' Disease: http://www.thyroid.org/graves-disease/

Hyperthyroidism (Overactive): http://www.thyroid.org/hyperthyroidism/

Radioactive Iodine: http://www.thyroid.org/radioactive-iodine/

Thyroid Surgery: http://www.thyroid.org/thyroid-surgery/

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HYPERTHYROIDISM, continued

ABBREVIATIONS & DEFINITIONS

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid medications, radioactive iodine, or surgery.

Thyroid eye disease (TED): also known as Graves' ophthalmopathy. TED includes inflammation of the eyes, eye muscles and the surrounding tissues. Symptoms include dry eyes, red eyes, bulging of the eyes and double vision.

Antithyroid drugs (ATDs): medications that block the thyroid from making thyroid hormone. Methimazole, carbimazole and propylthiouracil (PTU) are used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Radioactive iodine (RAI): this plays a valuable role in diagnosing and treating thyroid problems since it is taken up only by the thyroid gland. I-131 is the destructive form used to destroy thyroid tissue in the treatment of thyroid cancer and hyperthyroidism.

Thyroidectomy: surgery to remove the entire thyroid gland.

Cholestasis: a condition where the bile cannot flow from the liver to the intestine.

Agranulocytosis: a marked decrease in the neutrophil count, the most abundant type of white blood cells that causes a patient to be more likely to develop an infection. This is commonly associated with a fever and/or a sore throat.

Radiation thyroiditis: painful inflammation of the thyroid gland caused by the RAI therapy used to treat hyperthyroidism.

Hypocalcemia: low calcium levels in the blood, a complication from thyroid surgery that is usually short-term and relatively easily treated with calcium pills. If left untreated, low calcium may be associated with muscle twitching or cramping and, if severe, can cause seizures and/or heart problems.

Recurrent laryngeal nerve: a branch of the vagus nerve located close to the thyroid gland that regulate the muscles that move the vocal cords.

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THYROID CANCER

Treatment with surgery, external-beam radiation, and chemotherapy improves survival for selected patients with anaplastic thyroid cancer

BACKGROUND

Anaplastic thyroid cancer comprises less than 2% of all thyroid cancers. While the other 98% of thyroid cancer types have an excellent prognosis, anaplastic thyroid cancer is extremely aggressive, with an average overall survival of less than 6 months. In up to half of cases, anaplastic thyroid cancer may arise from preexisting differentiated thyroid cancer.

Because of their poor prognosis, all anaplastic thyroid cancers are considered stage IV. Surgical treatment is performed when possible in patients with cancer confined to the thyroid, followed by external-beam radiation with or without chemotherapy. Patients with cancer that cannot be surgically removed and those with distant spread are usually treated non-surgically with palliative radiation and chemotherapy. The current study evaluated the effectiveness of different treatment methods for anaplastic thyroid cancer. It also examined the association between the genetic profile of the cancer and clinical outcomes.

THE FULL ARTICLE TITLES:

Rao SN et al. Patterns of treatment failure in anaplastic thyroid carcinoma. Thyroid. January 9, 2017 [Epub ahead of print].

SUMMARY OF THE STUDY

This was a review of 54 patients treated at the University of Texas MD Anderson Cancer Center between January 2013 and October 2015. Staging was used: stage IVA, limited to thyroid gland; stage IVB, gross local invasion; and stage IVC, distant spread at the time of diagnosis. Cancers were analyzed for genetic mutations. The primary outcomes were time to treatment failure and site of cancer progression (local vs. distant). Overall survival was also assessed.

Half of the patients presented with stage IVC disease (the majority with spread to the lung), while 19% were stage IVA and 32% were stage IVB. In 10 patients (19%) who had a history of differentiated thyroid cancer, anaplastic thyroid cancer subsequently developed. An additional 31 patients (57%) had differentiated thyroid cancer detected at the time of anaplastic thyroid cancer diagnosis.

Surgery, consisting of thyroidectomy with or without lymph node removal, was performed in 23 patients. Importantly, in 21 of the 23 surgically treated patients, anaplastic thyroid cancer was diagnosed only with surgical pathologic results. In other words, surgery was undertaken with a needle biopsy diagnosis of a more differentiated thyroid cancer. External beam radiation therapy was given to 22 patients following surgery and to an additional 27 patients as first-line treatment. Almost all patients underwent chemotherapy at the time of radiation therapy. An additional 18 patients were treated with chemotherapy as treatment for disease progression.

The average time to treatment failure was 3.8 months, and the average overall survival was 11.9 months. Cancer progression most commonly occurred in distant spread sites. Predictors of treatment failure and overall survival included advanced stage at presentation, male sex, and specific pathologic findings. Patients who were treated with surgery, radiation, and chemotherapy had improved median survival as compared with those treated with radiation and chemotherapy alone, leading the authors to conclude that complete surgical resection was the most important determinant of survival.

In genetic testing, there was no significant association found between the presence or number of mutations and clinical outcomes.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Anaplastic thyroid cancer has a very poor prognosis both because it is locally aggressive and because of its early spread to distant sites. Despite multiple treatment methods, the average survival in the current study was less than 2 years for patients who underwent surgical excision and only 6 months for those who underwent radiation and chemotherapy alone. Surgery for anaplastic thyroid cancer may extend survival and

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THYROID CANCER, continued

should be considered for patients in whom complete surgical removal may be possible. Though surgery may be helpful, it is also possible that this study is looking at a specially selected patients. More studies are needed to develop improved treatments.

— Ronald B. Kuppersmith, MD, FACS

ATA THYROID BROCHURE LINKS

Thyroid Surgery: http://www.thyroid.org/thyroid-surgery/

Thyroid cancer: http://www.thyroid.org/cancer-of-the-thyroid-gland

DEFINITIONS

Anaplastic thyroid cancer: a very rare (<2%) but very aggressive type of thyroid cancer. In contrast to all other types of thyroid cancer, most patients with anaplastic thyroid cancer die of their cancer and do so within a few years.

Differentiated thyroid cancer: the most common type of thyroid cancer. The two main subtype are papillary and follicular thyroid cancer.

Cancer metastasis: spread of the cancer from the initial organ where it developed to other organs, such as the lungs and bone.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

Mutation: A permanent change in one of the genes.

ATA Alliance for Thyroid Patient Education

GOAL

The goal of our organizations is to provide accurate and reliable information for patients about the diagnosis, evaluation and treatment of thyroid diseases.

We look forward to future collaborations and continuing to work together toward the improvement of thyroid education and resources for patients.

WHO WE ARE (in alphabetical order)

AMERICAN THYROID ASSOCIATION
www.thyroid.org
ATA Patient Resources:
http://www.thyroid.org/thyroid-information/
Find a Thyroid Specialist: www.thyroid.org
(Toll-free): 1-800-THYROID
thyroid@thyroid.org

BITE ME CANCER
http://www.bitemecancer.org
info@bitemecancer.org

GRAVES' DISEASE AND THYROID FOUNDATION
www.gdatf.org
(Toll-free): 877-643-3123
info@ngdf.org

LIGHT OF LIFE FOUNDATION
www.checkyourneck.com
info@checkyourneck.com

THYCA: THYROID CANCER SURVIVORS' ASSOCIATION, INC.
www.thyca.org
(Toll-free): 877-588-7904
thyca@thyca.org

THYROID CANCER CANADA
www.thyroidcancercanada.org
416-487-8267
info@thyroidcancercanada.org

THYROID FEDERATION INTERNATIONAL
www.thyroid-fed.org
tfi@thyroid-fed.org

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www.thyca.org

Thyroid Cancer Canada
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