Volume 13 | Issue 10 | October 2020

Clinical Thyroidology® for the Public

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

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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 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, MCT8 – AHDS Foundation, ThyCa: Thyroid Cancer Survivors' Association, Thyroid Cancer Canada, Thyroid Cancer Alliance* and *Thyroid Federation International*.

We invite all of you to join our **Friends of the ATA** community. It is for you that the American Thyroid Association (ATA) is dedicated to carrying out our mission of providing reliable thyroid information and resources, clinical practice guidelines for thyroid detection and treatments, resources for connecting you with other patients affected by thyroid conditions, and cutting edge thyroid research as we search for better diagnoses and treatment outcomes for thyroid disease and thyroid cancer. We thank all of the *Friends of the ATA* who support our mission and work throughout the year to support us. We invite you to help keep the ATA mission strong by choosing to make a donation that suits you — it takes just one moment to give online at: www.thyroid.org/donate and all donations are put to good work. The ATA is a 501(c)3 nonprofit organization and your gift is tax deductible.

The Covid-19 pandemic has caused an unprecedented upheaval in our daily lives and presented extremely difficult challenges to our healthcare system. There is a lot of information circulating around. We at the American Thyroid Association would like to make sure that you all have access to most accurate, reliable, fact-based and updated information. (https://www.thyroid.org/covid-19/)

October is Thyroid Nodule Awareness Month.

In this issue, the studies ask the following questions:

- Does COVID-19 infection affect the thyroid?
- Are there options besides anti-thyroid medications for treating Graves' disease during pregnancy?
- Is the use of thyroid hormone increasing in the United States?
- Are women with a history of miscarriage or infertility have a high risk of hypothyroidism?
- Does increasing the levothyroxine dose affect mood in older hypothyroid patients?
- Is the rate of surgery decreasing in patients that had been undergoing active surveillance for papillary microcarcinoma?

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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COVID-19 AND THYROID DISEASE

COVID-19 infection and thyroid function

BACKGROUND

A novel coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-COV-2) is responsible for the coronavirus 19 (COVID-19) global pandemic that began in late 2019. COVID-19 infection can range from a very mild or asymptomatic presentation to critical illness and death. Along with multiple organ systems that may be affected by COVID-19 is the thyroid gland. In some patients, infection with COVID-19 may cause a hypersensitive immune reaction and widespread inflammation known as a "cytokine storm". Since the most common causes of thyroid problems result from antibodies attacking the thyroid (autoimmune thyroid disease), this immune system activation may also cause inflammation and dysfunction of the thyroid. The thyroid also can be affected indirectly as a result of the overall severity of the infection. These 2 studies report changes in thyroid function in patients with COVID-19 infection.

Lania et al sought to characterize thyroid function in patients hospitalized with COVID-19 infection. The goal of the study was to assess thyroid function in all patients admitted to the hospital with confirmed COVID-19 to determine if this infection was associated with abnormalities in thyroid function.

Muller et al report the association of subacute thyroiditis and COVID-19. The aim of this study was to evaluate the frequency subacute thyroiditis in COVID-19 patients as compared to non-COVID patients admitted to the intensive care unit in Italy.

THE FULL ARTICLE TITLE

Lania A et al on behalf of Humanitas COVID-19 Task Force. Thyrotoxicosis in patients with COIVD-19: the THYRCOV study. Eur J Endocrinol. 2020. doi: 10.1530/EJE-20-0335.PMID: 32698147

SUMMARY OF THE STUDY

This study is a medical record review that examines thyroid function in patients hospitalized in one center in Italy with COVID-19 infection. They excluded all patients who were on treatment for either hyperthyroidism or hypothyroidism. Additionally, patients were not included if they were taking drugs known to alter thyroid function or if they were critically ill requiring ventilator support. TSH was measured routinely and Free T_4 and Free T_3 levels were assessed if the TSH was abnormal. A marker of inflammation (Interleukin- 6 (IL-6)) was also measured.

A total of 287 patients were included in the study, of which 214 (74.6%) demonstrated normal thyroid function. Of those with abnormal thyroid tests, 58 (20.2%) showed lab tests consistent with hyperthyroidism (low TSH) and 15 (5.2%) with hypothyroidism (high TSH). Of those with a low TSH, most were mildly low, but 31 of 58 patients (53%) had elevated FreeT_4 levels indicating overt hyperthyroidism. In addition, 10 patients with overt hyperthyroidism had atrial fibrillation, a known heart complication of hyperthyroidism. TSH was lower with increasing age and higher IL-6 levels. Lower death rates were seen in patients with normal TSH levels.

Overall, the results of this study indicated that abnormal thyroid function is common in patients with COVID-19, particularly hyperthyroidism, and that TSH suppression appears to be associated with higher levels of the inflammatory cytokine IL-6. Although more research is needed, these investigators suggest that COVID-19 associated with systemic immune activation may possibly cause thyroid inflammation and result in hyperthyroidism.

THE FULL ARTICLE TITLE

Muller I et al 2020 SARS-CoV-2-related atypical thyroiditis. Lancet Diabetes Endocrinol. Epub 2020 Jul 30. PMID: 32738929.

SUMMARY OF THE STUDY

The study evaluated 93 consecutive patients admitted for COVID-19 infection to the ICU at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy, in 2020. The non-COVID group included 101 consecutive ICU patients with thyroid function test

COVID-19 AND THYROID DISEASE, continued

results available admitted at the same institution in 2019. Patients with pre-existing thyroid disorders were excluded, therefore, data from 78 patients in the COVID-19 group and 85 in the control group was analyzed. Of note, pre-existing thyroid disease was not more frequent in the COVID-19 group, suggesting that thyroid disease does not predispose to COVID-19 infection.

The patients had serum thyroid function tests measured within the first 2 days after their ICU admission. Serum thyroid stimulating hormone (TSH) was measured in all patients, while free thyroxine (FT_4) and free triiodothyronine (FT_3) levels were measured if the TSH was abnormal. Serum C-reactive protein (CRP) was also measured; this is a general marker of inflammation, which increases in subacute thyroiditis. A subset of the COVID-19–infected patients had follow-up tests 1.5 to 2 months after the initial infection when they were COVID-negative, including serum thyroid function tests and thyroid imaging.

The COVID-19 group was younger and included more males than females as compared to the control, non-COVID group (average age, 65 vs. 73 years; males, 69% vs. 56%). In the COVID-19 group, 13 of 85 (15%) patients had thyroid function tests showing hyperthyroidism, as compared with 1 of 78 (1%) in the control group. More men than women had abnormal thyroid function tests (64% vs. 36%). The hyperthyroid patients had low serum TSH levels, while serum free T_4 levels remained within normal range and were similar in both groups. Serum free T_3 levels were low and similar in both groups. Serum CRP levels were higher in the COVID-19 group than in the controls. No patient reported neck pain, which is usually associated with an episode of subacute thyroiditis.

Among the patients from the COVID-19 group who were followed-up after discharge, 6 patients with initial thyroid tests showing hyperthyroidism had normal thyroid function tests 1.5 to 2 months later. Some of these patients had a thyroid ultrasound and scan, which showed clear evidence of thyroiditis. This supports the idea that the abnormal thyroid function tests noted in COVID-19 patients could be secondary to subacute thyroiditis.

WHAT ARE THE IMPLICATIONS OF THESE STUDIES?

The results of this study indicated that abnormal thyroid function is common in patients with COVID-19, with the most common finding a low TSH. The low TSH levels appear to be associated with higher levels of the inflammatory cytokine IL-6 in the Lania study while the Muller study observed that a substantial proportion of COVID-19 patients requiring intensive care have low TSH levels initially, possibly suggestive of the hyperthyroid phase of subacute thyroiditis. Although more research is needed, these studies suggest that COVID-19 associated with systemic immune activation may possibly cause thyroid inflammation and result in hyperthyroidism or thyroiditis.

— Alina Gavrila, MD, MMSc, and Whitney W. Woodmansee MD

ATA THYROID BROCHURE AND WEBSITE LINKS

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

Thyroiditis: https://www.thyroid.org/thyroiditis/

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

Novel Coronavirus (COVID-19) and the Thyroid: https://www.thyroid.org/covid-19/coronavirus-frequently-asked-questions/

COVID-19 AND THYROID DISEASE, continued

ABBREVIATIONS & DEFINITIONS

Autoimmune thyroid disease: a group of disorders that are caused by antibodies that get confused and attack the thyroid. These antibodies can either turn on the thyroid (Graves' disease, hyperthyroidism) or turn it off (Hashimoto's thyroiditis, hypothyroidism).

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

Subclinical Hyperthyroidism: a mild form of hyperthyroidism where the only abnormal hormone level is a decreased TSH.

Subacute thyroiditis: acute inflammation of the thyroid gland probably caused by a virus that usually follows an upper respiratory infection. Symptoms include fever and thyroid tenderness. This is a self-limited condition with three clinical phases: hyperthyroidism, hypothyroidism and then return to normal function. Alternative Names: deQuervain's thyroiditis; granulomatous giant cell thyroiditis.

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.

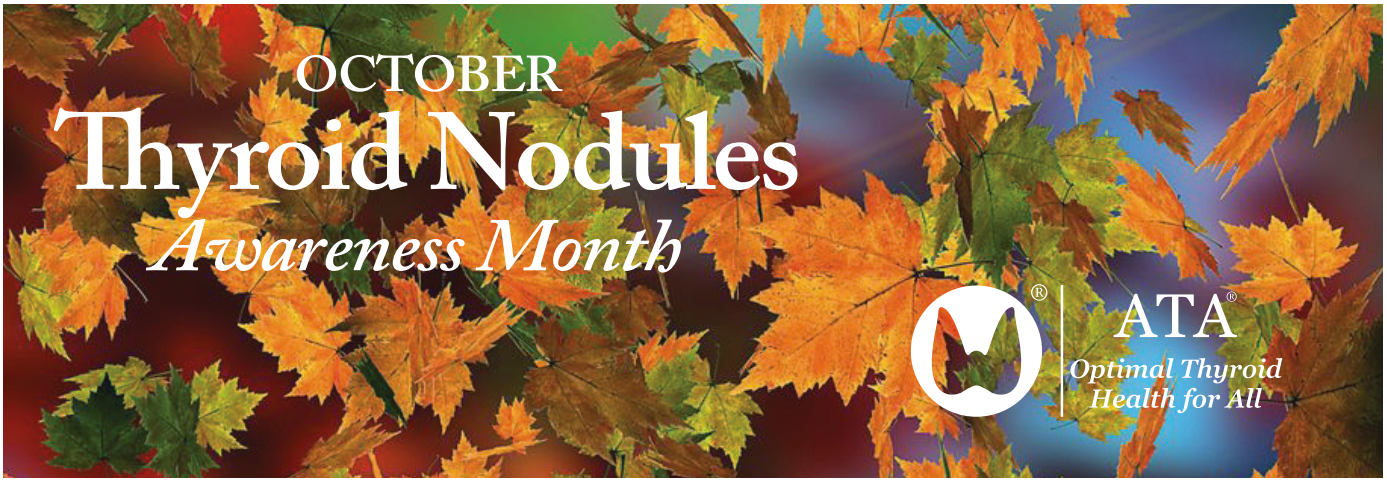
Thyroxine (T_4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

Triiodothyronine (T_3): the active thyroid hormone, usually produced from thyroxine.

Antibodies: proteins that are produced by the body's immune cells that attack and destroy bacteria and viruses that cause infections. Occasionally the antibodies get confused and attack the body's own tissues, causing autoimmune disease.

Thyroid ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize abnormal areas within the thyroid.

Thyroid scan: this imaging test uses a small amount of a radioactive substance, radioactive iodine or technetium-99m, to obtain a picture of the thyroid gland.



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HYPERTHYROIDISM

Substituting potassium iodide for methimazole in first-trimester pregnant women with Graves' disease may unpredictably worsen hyperthyroidism

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism (overactive thyroid) in the United States. Women are affected 7-8 times more frequently than men and many are in the pre-menopausal age group. This results in Graves' disease being the most common cause of hyperthyroidism during pregnancy. Treatment of Graves' disease includes anti-thyroid medications, surgery and radioactive iodine therapy. During pregnancy, radioactive iodine therapy is contraindicated and surgery is only safe to be performed during the second trimester. This leaves anti-thyroid medications as the main treatment option for Graves' disease during pregnancy. Both of the available anti-thyroid medications, propylthiouracil (PTU) and methimazole, can affect the baby, although the risk is very low. Methimazole is the safer medication during pregnancy, since the risk is less than PTU and can be limited by maintaining the lowest possible dose during pregnancy. However, the possibility of identifying an alternative medical therapy for Graves' disease in early pregnancy without side effects in the baby is highly appealing.

Potassium iodide (KI) has been used to prepare patients with Graves' disease for surgery and has occasionally been used to control hyperthyroidism by itself. The major drawback to KI as a treatment option is that it can occasionally make the hyperthyroidism worse and more difficult to treat. A prior study by the current research group suggests that the risk of side effects on the baby is less with KI than with methimazole. However, in some patients, the switch from methimazole to KI did indeed make the hyperthyroidism worse. This study aimed to identify predictors of both clinical improvement and worsening hyperthyroidism following the switch from methimazole to KI treatment in hyperthyroid pregnant women.

THE FULL ARTICLE TITLE

Yoshihara A et al 2020 The characteristics of patients with Graves' disease whose thyroid hormone level increases after substituting potassium iodide for methimazole in the first trimester of pregnancy. Thyroid. Epub 2020 Jan 13. PMID: 31928169.

SUMMARY OF THE STUDY

This study was conducted at Ito Hospital in Tokyo. Pregnant women with Graves' disease whose treatment was switched from methimazole to KI during the first trimester and who gave birth between 2005 and 2018 were included. The switch from methimazole to KI was made at the first visit following confirmation of the pregnancy. KI was given from 10 to 30 mg/day in a solution or in the form of 38-mg tablets.

Level of serum TSH, free T_3, free T_4 levels and TSH receptor antibodies (the cause of Graves' disease) were measured during the first trimester both before and then 2 to 4 weeks after changing from methimazole to KI treatment. After the change of therapy, the KI dose was decreased if the free T_4 was low or increased if the free T_4 was elevated. If hyperthyroidism persisted in the second trimester of pregnancy, an anti-thyroid drug was either added to the KI or substituted for it.

The average age of the 240 women at the time of delivery was 33 years. The switch from methimazole to KI treatment occurred at an average of 6 weeks of pregnancy. Of the 133 (55%) patients who were able to taper off of all medication during pregnancy, 4 became hypothyroid and needed levothyroxine by the time of delivery. Women who were able to discontinue therapy required lower methimazole doses prior to the switch to KI, had lower antibody and higher serum TSH levels and were on lower KI doses as compared with women who needed treatment for hyperthyroidism throughout the pregnancy. The only significant predictor of the ability to discontinue therapy was the level of the TSH receptor antibody. A continued high level of thyroid receptor antibody predicted a need to continue medication. Worsened hyperthyroidism

HYPERTHYROIDISM, continued

occurred in 22 patients (9.2%) following the switch to KI, requiring higher methimazole doses by the third trimester than before the medication switch. There was no clinical sign or level of thyroid hormone or antibody level that predicted which patient would get worse with KI therapy.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that ~9% of pregnant women with Graves' disease who were switched from methimazole to KI in the first trimester of pregnancy are at risk for worsening hyperthyroidism during the pregnancy. No clear predictors for this observation could be identified. Thus, while KI may have a lower risk of developing rare side effects in the baby, the increased risk of worsening hyperthyroidism supports the current American Thyroid Association guideline that recommends that KI treatment for Graves' disease in pregnancy is not recommended outside Japan until more evidence on safety and efficacy is available. Therefore, staying with methimazole in pregnant women with Graves' disease continues to be the safer option for both the mother and the developing baby.

— Alan P. Farwell, MD, FACE

ATA THYROID BROCHURE LINKS

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

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

Thyroid Disease in Pregnancy: https://www.thyroid.org/thyroid-disease-pregnancy/

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

ABBREVIATIONS & DEFINITIONS

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

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.

Methimazole: an antithyroid medication that blocks the thyroid from making thyroid hormone. Methimazole is used to treat hyperthyroidism, especially when it is caused by Graves' disease.

Propylthiouracil (PTU): an antithyroid medication that blocks the thyroid from making thyroid hormone. Propylthiouracil is used to treat hyperthyroidism, especially in women during pregnancy.

TSH receptor antibodies: antibodies often present in the serum of patients with Graves disease that are directed against the TSH receptor, often causing stimulation of this receptor with resulting hyperthyroidism.

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 (T_4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

Triiodothyronine (T_3): the active thyroid hormone, usually produced from thyroxine.

Levothyroxine (T_4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tirosint™ and generic preparations.

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HYPOTHYROIDISM

Thyroid hormone use doubled in the United States from 1997 to 2016

BACKGROUND

Thyroid hormone, usually in the form of levothyroxine, is primarily used to treat hypothyroidism. In the National Health and Nutrition Examination Survey III, which was conducted from 1988 to 1994, 4.6% of the U.S population was found to have some degree of hypothyroidism: 0.3% overt and 4.3% subclinical. However, thyroid hormone is the most frequently prescribed medication in the United States, and the proportion of adults who report taking thyroid hormone has increased in recent years.

The authors of this study sought to understand the proportion of adult individuals using thyroid hormone by age, sex, race/ethnicity from 1996 though 2016. They also aimed to study the costs associated with all thyroid hormone prescriptions during that time.

THE FULL ARTICLE

Johansen ME, Marcinek JP, Doo Young Yun J 2020 Thyroid hormone use in the United States, 1997–2016. J Am Board Fam Med 33:284–288. PMID: 32179

SUMMARY OF THE STUDY

This study was done using data from the 1997 to 2016 Medical Expenditure Panel Survey (MEPS). This survey is funded by the Agency of Health Care Research and Quality and is representative of the population of the United States who do not reside in institutions. For this analysis, all participants in MEPS from 1997-2016 who were older than age 17 were included. They provided information regarding demographics, medical conditions and prescription information, which was then verified by pharmacies.

Thyroid hormone was described as brand (Synthroid, Levoxyl, Tirosint) or generic (Levothyroixine); also included were T_4 and T_3 formulations. The expenses were calculated including both insurance and out-of-pocket payments. The differences in thyroid medication cost and use over time were then assessed using statistical tests.

A total of 470,067 participants were included in the study. The proportion of the U.S population reporting taking thyroid hormone increased from 4.1% in 1997 to 8.0% in 2016. Thyroid hormone use was higher in women than in men at all times. It was also higher in non-hispanic whites than in black or hispanic participants, however the rate of increase in thyroid hormone use did not differ by race/ethnicity. Use increased with increasing age, especially among individuals older than 65.

The annual expenditures associated with taking thyroid hormone increased from 1.1 billion in 1997 to 3.2 billion in 2016. The proportion of patients taking generic thyroid hormone increased from 18.1% in 2004 to 80% in 2016, and the average annual expense per individual for a generic preparation increased from $64.60 in 2010 to $123 in 2016.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that thyroid hormone use doubled in the United States between 1997 and 2016, and expenditures tripled during that time period. Thyroid hormone use was highest in women, older individuals and in non-hispanic whites. Importantly, the percent of individuals on thyroid hormone was ~2x greater than the frequency of hypothyroidism in the population. While there has been an increase in thyroid surgery for thyroid cancer and an increased in obesity, which has been linked to an increase in hypothyroidism, it is unlikely the main reason for the increased use of thyroid hormone. This suggests that a large number of patients are being treated with thyroid hormone for reasons other than hypothyroidism. This study reinforces the importance of appropriate thyroid hormone prescribing.

— Jessie Block-Galarza, MD

HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/

Thyroid Hormone Treatment: https://www.thyroid.org/thyroid-hormone-treatment/

ABBREVIATIONS & DEFINITIONS

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

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 or not.

Overt Hypothyroidism: clear hypothyroidism an increased TSH and a decreased T_4 level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

Thyroid hormone therapy: patients with hypothyroidism are most often treated with Levothyroxine in order to return their thyroid hormone levels to normal. *Replacement therapy* means the goal is a TSH in the normal range and is the usual therapy. *Suppressive therapy* means that the goal is a TSH below the normal range and is used in thyroid cancer patients to prevent growth of any remaining cancer cells.

Levothyroxine (T_4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tirosint™ and generic preparations.

Thyroxine (T_4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

Triiodothyronine (T_3): the active thyroid hormone, usually produced from thyroxine.

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THYROID AND PREGNANCY

A high proportion of women with history of miscarriage or infertility may have mild hypothyroidism or positive thyroid antibody status

BACKGROUND

Uncontrolled severe overt thyroid disease can cause infertility, miscarriage, or preterm delivery. Subclinical hypothyroidism, a mild form of hypothyroidism where only thyroid stimulating hormone (TSH) is slightly high, also appears to be associated with higher risks of miscarriage and preterm delivery. The most common cause of hypothyroidism in the United States is autoimmune thyroiditis where the thyroid is attacked by antibodies and destroyed. The marker for autoimmune thyroid disease is the thyroid peroxidase antibody (TPOAb). Several studies also suggested that a high TPOAb level may be associated with infertility or miscarriage.

Currently, the American Thyroid Association recommends checking TSH levels in high-risk women with a history of miscarriage or infertility. Treatment with levothyroxine is recommended for women who have TSH >2.5mIU/L and is receiving infertility treatment, such as *in-vitro* fertilization. In addition, treatment with levothyroxine can be considered in any woman with a positive TPOAb level and TSH >2.5mIU/L. However, testing and treatment for subclinical hypothyroidism in pregnancy is still debated because clinical trials have not shown improvement in miscarriage or infertility rates when women with subclinical hypothyroidism or positive TPOAb levels were treated with levothyroxine. This study was done to determine how frequent subclinical hypothyroidism or a positive TPOAb level is seen among high-risk women with a history of miscarriage or infertility.

THE FULL ARTICLE TITLE

Dhillon-Smith RK et al 2020 The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility. J Clin Endocrinol Metab 105:dgaa302. PMID: 32593174.

SUMMARY OF THE STUDY

A total of 19,350 non-pregnant women with history of miscarriage or infertility and no history of thyroid disease were recruited from specialty miscarriage or fertility clinics across the United Kingdom from November 2011 to January 2016. Thyroid hormone levels and TPOAb titers were measured. Subclinical hypothyroidism was defined as having high TSH and normal free T_4 levels. Two cutoff levels for TSH was used; >2.5mIU/L or >4.5mIU/L.

However, when a cutoff TSH >4.5mIU/L was used, subclinical hypothyroidism was diagnosed in 2.4% of women. However, a cutoff TSH >2.5mIU/L was used, subclinical hypothyroidism was diagnosed in 19.9% of women. Subclinical hypothyroidism with TSH >2.5mIU/L was diagnosed in 16.1% of women with a history of ≥3 miscarriages and in 20.1% of women with a history of infertility. Overall, 9.5% of women had positive TPOAb levels. Women with high TSH levels were more likely to have positive TPOAb levels. Women with body mass index (BMI) ≥35 kg/m^2 were 1.7 times more likely to have subclinical hypothyroidism compared to women with normal BMI. Asian women were 1.8 times more likely to have subclinical hypothyroidism compared to white women. Women with a history of infertility were 1.16 times more likely to have subclinical hypothyroidism compared to women with history of one or two miscarriages. Women with BMI ≥35 kg/m^2 were 1.5 times more likely to have positive TPOAb levels.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that subclinical hypothyroidism and a positive TPOAb is common in women in the United Kingdom with a history of miscarriage or infertility. This suggests a high number of women with history of miscarriage or infertility may benefit from treatment with levothyroxine. However, previous clinical trials have failed

THYROID AND PREGNANCY, continued

to show clear improvement in miscarriage or infertility rates when women with subclinical hypothyroidism or positive TPOAb levels were treated with levothyroxine, but all of these studies have flaws. A large, randomized clinical trial would be helpful to determine the need for testing and treatment of subclinical hypothyroidism in high-risk women with history of miscarriage or infertility before they become pregnant. Until this is known, the decision to treat with levothyroxine should be individualized.

— Sun Lee, MD

ATA THYROID BROCHURE LINKS

Thyroid Disease in Pregnancy: https://www.thyroid.org/thyroid-disease-pregnancy/
Thyroid Function Tests: https://www.thyroid.org/thyroid-function-tests/
Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/

ABBREVIATIONS & DEFINITIONS

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills.

Overt Hypothyroidism: clear hypothyroidism an increased TSH and a decreased T_4 level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

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 or not.

Autoimmune thyroid disease: a group of disorders that are caused by antibodies that get confused and attack the thyroid. These antibodies can either turn on the thyroid (Graves' disease, hyperthyroidism) or turn it off (Hashimoto's thyroiditis, hypothyroidism).

Hashimotos thyroiditis or autoimmune thyroiditis: the most common cause of hypothyroidism in the United States. It is caused by antibodies that attack the thyroid and destroy it.

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.

TPO antibodies (TPOAb): 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.

Levothyroxine (LT_4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tyrosint™ and generic preparations.

Miscarriage: this occurs when a baby dies in the first few months of a pregnancy, usually before 22 weeks of pregnancy.

In-vitro fertilization: a procedure when an egg is fertilized outside of the body and then implanted in a woman to achieve a pregnancy

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HYPOTHYROIDISM

Effects of increasing levothyroxine doses on mood in older patients with hypothyroidism

BACKGROUND

Many symptoms of hypothyroidism can occur with disorders of other conditions – few symptoms are specific solely to the thyroid. This can make it challenging when treating hypothyroidism and can also give patients unrealistic expectations to the treatment of hypothyroidism. Levothyroxine is the main treatment for hypothyroidism and, indeed, most symptoms that are caused by hypothyroidism resolve once the thyroid hormone levels return to the normal range on levothyroxine. However, there are patients who still complain of some residual hypothyroid symptoms even after achieving normal thyroid hormone levels.

One such symptom is depression, as it is well known that some patients with hypothyroidism may experience depressive symptoms. Depression is more common in older adults in general and they are more prone to develop depression as the result of hypothyroidism. Prior studies have not shown a beneficial effect on mood after starting levothyroxine in depressed older individuals with subclinical hypothyroidism. The current study examined older hypothyroid patients with depressive symptoms who were already on levothyroxine. They examined the effect of increasing the levothyroxine dose on their depressed mood.

THE FULL ARTICLE TITLE

Moon JH et al 2020 Effect of increased levothyroxine dose on depressive mood in older adults undergoing thyroid hormone replacement therapy. Clin Endocrinol. Epub 2020 Apr 13. PMID: 32282957.

SUMMARY OF THE STUDY

This study was conducted in South Korea. A total of 30 hypothyroid patients (21 women and 9 men) were included in the study. Their average age was 74 year old. Their daily dose of levothyroxine ranged from 25 to 100 mcg (average 59 mcg). All patients had normal TSH and T_4 levels before entering the study. The authors assessed the patients for depression and for symptoms of excess thyroid hormone by two questionnaires; one validated for detecting geriatric depression in the Korean population and the other for hyperthyroid symptoms in Korean population. Then all the patients received an extra 12.5 mcg daily dose of levothyroxine for 3 months followed by their baseline levothyroxine dose for another 3 months. The two questionnaires were completed *first* at the beginning of the study, for the *second time* after taking the higher dose of levothyroxine for 3 months and for the *third time* after taking their baseline levothyroxine dose for 3 months.

Overall 24 patients were able to complete this study. The TSH level remained within the normal range during the study period but was lower after taking the higher dose of levothyroxine for 3 months. The number of study subjects who had depression scores based on Questionnaire at the beginning of the study was significantly higher than general population. The depression scores improved after 3 months of taking the higher levothyroxine dose and remained higher even after returning to the lower baseline dose.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors suggest that increasing levothyroxine dose in older hypothyroid adults who were already on levothyroxine might improve depressive symptoms. Importantly, the TSH remained in the normal range on the increased levothyroxine dose. However, this is a very small study and did not have a control group that was not given increased levothyroxine. This study needs to be repeated with much more patients and with a control group before these results can be validated.

— Shirin Haddady, MD, MPH

HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Thyroid Hormone Treatment: https://www.thyroid.org/thyroid-hormone-treatment/
Thyroid Function Tests: https://www.thyroid.org/thyroid-function-tests/

ABBREVIATIONS & DEFINITIONS

Hypothyroidism: a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone. Treatment requires taking thyroid hormone pills

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 or not

Levothyroxine (T_4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tirosint™ and generic preparations.

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 (T_4): the major hormone produced by the thyroid gland. T_4 gets converted to the active hormone T_3 in various tissues in the body.

AMERICAN THYROID ASSOCIATION
Optimal Thyroid Health for All

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Clinical Thyroidology® for the Public

THYROID CANCER

Patients with papillary microcarcinoma under active surveillance are proceeding to have surgery less frequently.

BACKGROUND

Detection of thyroid cancer has been increasing in recent years. A big part of this is a marked increase in the number of small thyroid cancers (<1 cm, papillary microcarcinomas), which have been more frequently detected due to a large number of imaging tests done on patients, like CT scans, MRIs and ultrasounds that image the neck region. This detection occurs long before patients experience any symptoms. In fact, research has demonstrated that these small thyroid cancers are usually very low risk, and it is unclear of the benefit of proceeding with surgery to remove these cancers. Indeed, it appears that observing these patients without intervention is safe and can avoid surgery. This observation is called active surveillance, and involves frequent neck ultrasounds to make sure the cancer is stable and that no lymph nodes in the neck have signs of cancer. Active surveillance was first described in Japan in the 1990s and it was adopted into Japanese national guidelines in 2011 after it was shown to be safe in appropriately selected patients.

Over time, patients under active surveillance eventually undergo surgery because of cancer growth, development of spread to lymph nodes or if patients or their family members or their doctors become anxious or unsettled at the thought of "doing nothing" and decide to have it removed with surgery, even if there is no change in the cancer. In this study, the authors examined the trends and reasons for surgery after the initiation of active surveillance.

THE FULL ARTICLE TITLE

Sasaki T et al. 2020 Marked decrease over time in conversion surgery after active surveillance of low-risk papillary thyroid microcarcinoma. Thyroid. Epub 2020 Jul 14. PMID: 32664805.

SUMMARY OF THE STUDY

This study looked at the trend in thyroid surgery in patients with low-risk papillary microcarcinoma at Kuma Hospital in Japan from 2005 to 2017. They compared the rate of thyroid surgery before versus after November 2011. They had five (5) groups of low risk patients that underwent thyroid surgery: (1) patients with significant cancer growth or spread to a lymph node, (2) patient preference (3) physician preference (4) surgery due to other thyroid or parathyroid disease and (5) other reasons.

Of 3769 patients with low-risk papillary microcarcinoma, 1481 chose to undergo immediate surgery and 2288 (61%) chose active surveillance. In the active surveillance group, 162 patients (7%) underwent surgery >12 months after starting active surveillance. Surgery occurred mainly for cancer progression (57 patients; average 2.2 years after diagnosis), patient preference (43 patients; average 2.9 years after diagnosis), and physician preference (31 patients; average 2.8 years after diagnosis).

The first-half group (November 2011 or before) included 561 patients and 81 instances of surgery. The second-half group (after November 2011) included 1727 patients and 81 instances of surgery. Overall, patients in the second-half group were significantly less likely to undergo surgery than those in the first-half group (4.2% for second-half group vs. 12.3% for first-half group over 5 years). They noted that the second group had a lower rate of cancer progression, but also, doctors and patients had a lower rate of preference towards surgery, both of which led to the decrease in the rate of surgery.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this study, we are seeing the effect that evidence based medicine is having on the decision making of both patients and doctors. There is more trust in active surveillance for low risk papillary microcarcinoma as an appropriate management strategy because we now have large groups of patients that have been monitored for prolonged periods of time with no adverse outcomes. This shows that, over time, patients who are diagnosed with low risk papillary microcarcinoma can safely avoid surgery as long as they continue with having their cancer monitored.

— Maria Brito, MD

THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/
Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/
Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

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).

Papillary microcarcinoma: a papillary thyroid cancer smaller than 1 cm in diameter.

Active surveillance: the process of observing patients with papillary microcarcinoma and deferring surgery. This requires frequent monitoring of these patients with ultrasounds

CT scan: computed tomography scan is a medical imaging procedure that uses computer-processed combinations of many X-ray measurements taken from different angles to produce cross-sectional (tomographic) images (virtual "slices") of specific areas of a scanned object, allowing the user to see inside the object without cutting

Magnetic resonance imaging (MRI) is a medical imaging technique used in radiology to form pictures of the anatomy and the physiological processes of the body. MRI scanners use strong magnetic fields, magnetic field gradients, and radio waves to generate images of the organs in the body. MRI does not involve X-rays or the use of ionizing radiation, which distinguishes it from CT and PET scans.

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Clinical Thyroidology® for the Public

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.

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

Bite Me Cancer
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

MCT8 – AHDS Foundation
mct8.info
Contact@mct8.info

Thyca: Thyroid Cancer Survivors' Association, Inc.
www.thyca.org
(Toll-free): 877-588-7904
thyca@thyca.org

Thyroid Cancer Alliance
www.thyroidcanceralliance.org
www.thyroidcancerpatientinfo.org
Rotterdam, The Netherlands

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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JOIN US

"The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop for patients and caregivers to find specialists, current clinical trials, general thyroid cancer information, and links to other patient support groups and information."

Mary Catherine Petermann
- Father who was diagnosed with Anaplastic Thyroid Cancer in 2006
- He was treated at Mayo Clinic
- He has clean scans as of October 2016

PLEASE JOIN OUR JOURNEY TO ADVANCED DISCOVERIES AND TREATMENT FOR THYROID DISEASE AND THYROID CANCER

As patients with thyroid disease navigate the challenges to their quality of life and researchers and physicians look for more effective directions, we at the ATA have our own destination– **funding for critical thyroid research, prevention, and treatment.** For 94 years, the ATA has led the way in thyroidology. It's a daily obstacle course to find new drugs, better treatments, advanced surgical methods, and more rapid diagnoses for the 20 million Americans who have some form of thyroid disease.

The ATA has paved the way with management guidelines for clinicians who diagnose and treat thyroid disease. For physicians treating pregnant women diagnosed with thyroid disease, our recent publication presents 97 evidence-based recommendations making sure that best practices are implemented with the latest, most effective treatment.

Through your generous support and donations, research takes the lead and hope is on the horizon. **Will you join us** in our campaign to raise **$1.5 million** for thyroid research, prevention, and treatment? Your compassionate, tax-deductible gift will provide funds for:

- Research grants that pave the way for 1,700 ATA physicians and scientists who have devoted their careers to understanding the biology of and caring for patients affected by thyroid disease.
- Patient education for individuals and families looking for life-changing clinical trials, the best thyroid specialists, and cutting edge treatment and drugs.
- Professional education that offers a wealth of knowledge and leading-edge research for trainees and practitioners.
- A website that is the go-to resource for thyroid information for patients and practitioners alike. In 2016 alone, there were more than 3,700,000 website views of ATA's library of online thyroid information patient brochures.

Donations **of all sizes** will change the future for thyroid patients. You will make a direct impact on patients like Mary Catherine's father as he deals with Anaplastic Thyroid Cancer. You will help scientists like ATA Associate Member Julia Rodiger, Ph.D., a scientist at the National Institutes of Health, as she analyzes thyroid hormones for intestinal stem cell development.

Thyroid Nodules

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is normally located in the lower front of the neck. The thyroid's job is to make thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormone helps the body use energy, stay warm and keep the brain, heart, muscles, and other organs working as they should.

WHAT IS A THYROID NODULE?

The term thyroid nodule refers to an abnormal growth of thyroid cells that forms a lump within the thyroid gland. Although the vast majority of thyroid nodules are benign (noncancerous), a small proportion of thyroid nodules do contain thyroid cancer. In order to diagnose and treat thyroid cancer at the earliest stage, most thyroid nodules need some type of evaluation.

WHAT ARE THE SYMPTOMS OF A THYROID NODULE?

Most thyroid nodules do not cause symptoms. Often, thyroid nodules are discovered incidentally during a routine physical examination or on imaging tests like CT scans or neck ultrasound done for completely unrelated reasons. Occasionally, patients themselves find thyroid nodules by noticing a lump in their neck while looking in a mirror, buttoning their collar, or fastening a necklace. Abnormal thyroid function tests may occasionally be the reason a thyroid nodule is found. Thyroid nodules may produce excess amounts of thyroid hormone causing hyperthyroidism (see *Hyperthyroidism brochure*). However, most thyroid nodules, including those that cancerous, are actually non-functioning, meaning tests like TSH are normal. Rarely, patients with thyroid nodules may complain of pain in the neck, jaw, or ear. If a nodule is large enough to compress the windpipe or esophagus, it may cause difficulty with breathing, swallowing, or cause a "tickle in the throat". Even less commonly, hoarseness can be caused if the nodule invades the nerve that controls the vocal cords but this is usually related to thyroid cancer.

The important points to remember are the following:

- Thyroid nodules generally do not cause symptoms.
- Thyroid tests are most typically normal—even when cancer is present in a nodule.
- The best way to find a thyroid nodule is to make sure your doctor checks your neck!

WHAT CAUSES THYROID NODULES AND HOW COMMON ARE THEY?

We do not know what causes most thyroid nodules but they are extremely common. By age 60, about one-half of all people have a thyroid nodule that can be found either through examination or with imaging. Fortunately, over 90% of such nodules are benign. *Hashimoto's thyroiditis*, which is the most common cause of hypothyroidism (see *Hypothyroidism brochure*), is associated with an increased risk of thyroid nodules. Iodine deficiency, which is very uncommon in the United States, is also known to cause thyroid nodules.

HOW IS A THYROID NODULE EVALUATED AND DIAGNOSED?

Once the nodule is discovered, your doctor will try to determine whether the rest of your thyroid is healthy or whether the entire thyroid gland has been affected by a more general condition such as hyperthyroidism or hypothyroidism. Your physician will feel the thyroid to see whether the entire gland is enlarged and whether a single or multiple nodules are present. The initial laboratory tests may include measurement of thyroid hormone (thyroxine, or T4) and thyroid-stimulating hormone (TSH) in your blood to determine whether your thyroid is functioning normally.

Since it's usually not possible to determine whether a thyroid nodule is cancerous by physical examination and blood tests alone, the evaluation of the thyroid nodules often includes specialized tests such as thyroid ultrasonography and fine needle biopsy.

Thyroid Nodules

THYROID ULTRASOUND:

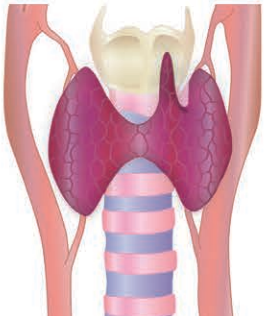
Thyroid ultrasound is a key tool for thyroid nodule evaluation. It uses high-frequency sound waves to obtain a picture of the thyroid. This very accurate test can easily determine if a nodule is solid or fluid filled (cystic), and it can determine the precise size of the nodule. Ultrasound can help identify suspicious nodules since some ultrasound characteristics of thyroid nodules are more frequent in thyroid cancer than in noncancerous nodules. Thyroid ultrasound can identify nodules that are too small to feel during a physical examination. Ultrasound can also be used to accurately guide a needle directly into a nodule when your doctor thinks a fine needle biopsy is needed. Once the initial evaluation is completed, thyroid ultrasound can be used to keep an eye on thyroid nodules that do not require surgery to determine if they are growing or shrinking over time. The ultrasound is a painless test which many doctors may be able to perform in their own office.

THYROID FINE NEEDLE ASPIRATION BIOPSY (FNA OR FNAB):

A fine needle biopsy of a thyroid nodule may sound frightening, but the needle used is very small and a local anesthetic may not even be necessary. This simple procedure is often done in the doctor's office. Sometimes, medications like blood thinners may need to be stopped for a few days before to the procedure. Otherwise, the biopsy does not usually require any other special preparation (no fasting). Patients typically return home or to work after the biopsy without even needing a bandaid! For a fine needle biopsy, your doctor will use a very thin needle to withdraw cells from the thyroid nodule. Ordinarily, several samples will be taken from different parts of the nodule to give your doctor the best chance of finding cancerous cells if they are present. The cells are then examined under a microscope by a pathologist.

The report of a thyroid fine needle biopsy will usually indicate one of the following findings:

1. The nodule is benign (noncancerous).
   - This result is obtained in up to 80% of biopsies. The risk of overlooking a cancer when the biopsy is benign is generally less than 3 in 100 tests or 3%. This is even lower when the biopsy is reviewed by an experienced pathologist at a major medical center. Generally, benign thyroid nodules do not need to be removed unless they are causing symptoms like choking or difficulty swallowing. Follow up ultrasound exams are important. Occasionally, another biopsy may be required in the future, especially if the nodule grows over time.
2. The nodule is malignant (cancerous) or suspicious for malignancy .
   - A malignant result is obtained in about 5% of biopsies and is most often due to papillary cancer, which is the most common type of thyroid cancer. A suspicious biopsy has a 50-75% risk of cancer in the nodule. These diagnoses require surgical removal of the thyroid after consultation with your endocrinologist and surgeon.
3. The nodule is indeterminate. This is actually a group of several diagnoses that may occur in up to 20% of cases. An Indeterminate finding means that even though an adequate number of cells was removed during the fine needle biopsy, examination with a microscope cannot reliably classify the result as benign or cancer.
   - The biopsy may be indeterminate because the nodule is described as a Follicular Lesion. These nodules are cancerous 20-30% of the time. However, the diagnosis can only be made by surgery. Since the odds that the nodule is not a cancer are much better here (70-80%), only the side of the thyroid with the nodule is usually removed. If a cancer is found, the remaining thyroid gland usually must be removed as well. If the surgery confirms that no cancer is present, no additional surgery to "complete" the thyroidectomy is necessary.
   - The biopsy may also be indeterminate because the cells from the nodule have features that cannot be placed in one of the other diagnostic categories. This diagnosis is called atypia, or a follicular lesion of undetermined significance. Diagnoses in this category will contain cancer rarely, so repeat evaluation with FNA or surgical biopsy to remove half of the thyroid containing the nodule is usually recommended.
4. The biopsy may also be nondiagnostic or inadequate. This result is obtained in less than 5% of cases when an ultrasound is used to guide the FNA. This result indicates that not enough cells were obtained to make a diagnosis but is a common result if the nodule is a cyst. These nodules may require reevaluation with second fine needle biopsy, or may need to be removed surgically depending on the clinical judgment of your doctor.



FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*

Thyroid Nodules

NUCLEAR THYROID SCANS:

Nuclear scanning of the thyroid was frequently done in the past to evaluate thyroid nodules. However, use of thyroid ultrasound and biopsy have proven so accurate and sensitive, nuclear scanning is no longer considered a first-line method of evaluation. Nuclear scanning still has an important role in the evaluation of rare nodules that cause hyperthyroidism. In this situation, the nuclear thyroid scan may suggest that no further evaluation or biopsy is needed. In most other situations, neck ultrasound and biopsy remain the best and most accurate way to evaluate all types of thyroid nodules.

MOLECULAR DIAGNOSTICS:

Can any other tests assist in evaluation of thyroid nodules?

Yes, new tests that examine the genes in the DNA of thyroid nodules are currently available and more are being developed. These tests can provide helpful information about whether cancer may be present or absent. These tests are particularly helpful when the specimen evaluated by the pathologist is indeterminate. These specialized tests are done on samples obtained during the normal biopsy process. There are also specialized blood tests that can assist in the evaluation of thyroid nodules. These are currently available only at highly specialized medical centers, however, their availability is increasing rapidly. Ask your doctor if these tests are available and might be helpful for evaluating your thyroid nodule.

HOW ARE THYROID NODULES TREATED?

All thyroid nodules that are found to contain a thyroid cancer, or that are highly suspicious of containing a cancer, should be removed surgically by an experienced thyroid surgeon. Most thyroid cancers are curable and rarely cause life-threatening problems (see *Thyroid Cancer brochure*). Thyroid nodules that are benign by FNA or too small to biopsy should still be watched closely with ultrasound examination every 6 to 12 months and annual physical examination by your doctor. Surgery may still be recommended even for a nodule that is benign by FNA if it continues to grow, or develops worrisome features on ultrasound over the course of follow up.

FURTHER INFORMATION

Further details on this and other thyroid-related topics are available in the patient thyroid information section on the American Thyroid Association® website at *www.thyroid.org*.

For information on thyroid patient support organizations, please visit the *Patient Support Links* section on the ATA website at *www.thyroid.org*