AMERICAN THYROID ASSOCIATION
ATA | Founded 1923

Clinical Thyroidology for the Public

VOLUME 10 • ISSUE 8 • AUGUST 2017

www.thyroid.org

While it is clear that overt hypothyroidism in the mother during pregnancy can affect the baby's brain development or cause other problems with the pregnancy, it is not clear if subclinical hypothyroidism would have similar adverse effects. Previous studies that have been done on this topic have shown mixed results. In the current study, the authors studied the effect of subclinical hypothyroidism detected before pregnancy on complications of pregnancy.

Chen S et al. Preconception TSH levels and pregnancy outcomes: a population-based cohort study in 184,611 women. Clin Endocrinol (Oxf). March 25, 2017 [Epub ahead of print].

Both hypothyroidism and hyperthyroidism in the mother can affect pregnancy outcomes as well as the baby's development. Although there have been a number of studies linking abnormal thyroid function to increased risk of pregnancy complications, universal screening for thyroid disease during pregnancy is still debated. These authors sought to examine thyroid function during early pregnancy in Danish women and correlate the levels with the diagnosis of thyroid disease before or after pregnancy.

Andersen Sl and Olsen J. Early Pregnancy Thyroid Function Test Abnormalities in Biobank Sera from Women Clinically Diagnosed with Thyroid Dysfunction Before or After Pregnancy. Thyroid. 2017. 27(3): 451-459.

Congenital hypothyroidism is a disorder in which babies are born with low thyroid hormone levels and is estimated to occur in 1:1700 newborns. Identifying the cause of congenital hypothyroidism has important genetic implications. This study was done to determine whether ultrasound of the thyroid could have a role in the early diagnosis of congenital hypothyroidism and to determine whether delaying ultrasound could provide misleading information.

Borges MF et al. Timing of thyroid ultrasonography in the etiological investigation of congenital hypothyroidism. Arch Endocrinol Metab. February 13, 2017 [Epub ahead of print]. doi:10.1590/2359-3997000000239

There have been several studies suggesting potential associations between mild thyroid problems and heart problems. This study was done to assess the associations between mild hypothyroidism or mild hyperthyroidism and common risk factors for heart disease such as cholesterol levels, blood pressures, and diabetes and events such as a heart attack and stroke.

Martin SS et al. Thyroid Function, Cardiovascular Risk Factors, and Incident Atherosclerotic Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study. J Clin Endocrinol Metab. 2017 Jun 12. doi: 10.1210/jc.2017-00986. [Epub ahead of print]

Thyroid nodules are frequently detected by other imaging tests such as CT, MRI and PET-CT. It is not clear whether these imaging tests can accurately predict thyroid cancer by themselves without the need for a neck ultrasound. The aims of the present study are to a) evaluate whether the size of thyroid nodules discovered on CT, MRI or PET-CT correlate with measurements at subsequent ultrasound and b) to determine the impact of applying the radiology recommendations on thyroid nodule outcomes.

Ní Mhuircheartaigh JM et al. Correlation between the size of incidental thyroid nodules detected on CT, MRI or PET-CT and subsequent ultrasound Clin Imaging 2016;40:1162-6.

Ideally, identifying those at higher risk of cancer recurrence would potentially allow the more aggressive therapies to be utilized when appropriate for patients with high risk papillary thyroid cancer. Recently, 2 specific molecular markers, BRAF^{v600E} and TERT promotor mutations have been associated with aggressive tumor behavior and worse outcomes in papillary thyroid cancer. This study aimed to determine the prognosis of papillary thyroid cancer in patients with either of these mutations alone or in combination by a review of the current studies.

Moon S et al. Effects of coexistent BRAF^{V600E} and TERT promoter mutations on poor clinical outcomes in papillary thyroid cancer: a meta-analysis. Thyroid. March 7, 2017 [Epub ahead of print].

AMERICAN THYROID ASSOCIATION
ATA | Founded 1923
www.thyroid.org

CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**
A publication of the American Thyroid Association
VOLUME 10 • ISSUE 8 • AUGUST 2017

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*.

August is Thyroid and Pregnancy Awareness Month.

In this issue, the studies ask the following questions:

- Does an increased TSH prior to pregnancy affect pregnancy outcomes?
- Do abnormal thyroid levels in pregnancy predict thyroid problems after pregnancy?
- What is the role of ultrasound in the diagnosis of the cause of congenital hypothyroidism
- Is there an association between thyroid levels and the risk for heart problems?
- Does the size of nodules found on CT, MRI or PET-CT scans correlate with the size measured on ultrasound?
- Do BRAF and TERT promoter mutations affect prognosis in 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

CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION

www.thyroid.org

THYROID AND PREGNANCY

Higher TSH values before pregnancy are associated with adverse pregnancy outcomes

BACKGROUND

Thyroid hormone has an important role in brain development of the baby during pregnancy. It is clear that overt hypothyroidism (increased TSH levels and low thyroid hormone levels) in the mother, especially early in pregnancy, can affect the baby's brain development or cause other problems with the pregnancy. It is not clear if subclinical hypothyroidism (increased TSH levels and normal thyroid hormone levels) would have similar adverse effects. Previous studies that have been done on this topic have shown mixed results.

In the current study, the authors studied the effect of subclinical hypothyroidism detected before pregnancy on complications of pregnancy.

THE FULL ARTICLE TITLE

Chen S et al. Preconception TSH levels and pregnancy outcomes: a population-based cohort study in 184,611 women. Clin Endocrinol (Oxf). March 25, 2017 [Epub ahead of print].

SUMMARY OF THE STUDY

Between 2010 and 2012, 248,501 patients were enrolled in this study in 30 different provinces in China. A free exam is offered in rural china to couples planning pregnancy within 6 months. Before pregnancy, health related information and a blood test for TSH were obtained. In the study period, 194,154 pregnancies occurred, but subjects with pregnancy loss or twin and triple pregnancies and with TSH (obtained before pregnancy) level less than 0.48 and more than 10 mIU/l were excluded from the study. A total of 184,611 pregnant women who had a TSH level between 0.48 to 10 mIU/l before pregnancy were selected. These patients were divided into 3 groups: TSH level of 0.48 to 2.49 mIU/L (considered normal), TSH 2.5-4.29 mIU/L and TSH 4.3-10 mIU/L. The rate of pregnancy complications like miscarriage, premature delivery and caesarean delivery, as well as birth weight of their newborn compared between these groups.

The results showed, as compared with mothers with a TSH 0.48-2.49 mIU/L, mothers with a TSH level between 2.50 to 4.29 mIU/L prior to pregnancy were more likely to have a miscarriage, premature delivery, vaginal delivery assisted with forceps and vacuum while mothers with TSH level between 4.3 to 10 mIU/L had higher rate of miscarriage, loss of pregnancy in second half of pregnancy, premature delivery, cesarean section and large infants.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that higher TSH levels before pregnancy, even when they are borderline high, may be associated with a higher rate of miscarriage, pregnancy loss, cesarean section and large infants. The connection between a TSH level before pregnancy and complications of pregnancy has not been studies in such a large scale before. What is not clear is whether treating mothers with higher TSH levels would have any effect on these results, so more studies should be done to evaluate this possibility. However, this study suggests that women with borderline high TSH level should have subsequent TSH testing in the beginning of pregnancy and be referred for treatment if necessary.

— Shirin Haddady, MD

ATA THYROID BROCHURE LINKS

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

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

ABBREVIATIONS & DEFINITIONS

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.

THYROID AND PREGNANCY, continued

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.

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

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 **August** is **Thyroid and Pregnancy Awareness Month** and a bracelet is available through the **ATA Marketplace** to support thyroid cancer awareness and education related to thyroid disease.

AMERICAN THYROID ASSOCIATION

www.thyroid.org

THYROID AND PREGNANCY

Thyroid function in pregnancy

BACKGROUND

Thyroid hormone is important during pregnancy for normal development of the baby. Both hypothyroidism and hyperthyroidism in the mother can affect pregnancy outcomes as well as the baby's development. Thyroid hormone requirements increase during pregnancy and many women with hypothyroidism on thyroid hormone replacement require an increased dosage during this time. Although there have been a number of studies linking abnormal thyroid function to increased risk of pregnancy complications, universal screening for thyroid disease during pregnancy is still debated. These authors sought to examine thyroid function during early pregnancy in Danish women and correlate the levels with the diagnosis of thyroid disease before or after pregnancy.

THE FULL ARTICLE TITLE

Andersen Sl and Olsen J. Early Pregnancy Thyroid Function Test Abnormalities in Biobank Sera from Women Clinically Diagnosed with Thyroid Dysfunction Before or After Pregnancy. Thyroid. 2017. 27(3): 451-459.

SUMMARY OF THE STUDY

These investigators conducted study of pregnant women enrolled in the Danish National Birth Cohort who gave birth to a single baby between 1997 and 2003. All women had thyroid function tests (TSH and Free T_4) performed in early pregnancy (testing ranged between 5 and 19 weeks gestation) and saved in a Biobank for analysis. Some women were included as part of a random sample of all participants in the study and some were included on the basis of having known thyroid disease before the early pregnancy blood sample. The authors examined women who never received a diagnosis of thyroid disease, women who had a pre-existing diagnosis and women who were diagnosed after the early pregnancy blood sample up to 5 years after delivery. They categorized the early pregnancy blood sample as either consistent with hyperthyroidism or hypothyroidism, subclinical or overt.

Results indicated that thyroid dysfunction was common in women during early pregnancy. In women without known thyroid disease before or after the pregnancy, approximately 12% had abnormal thyroid function tests during early pregnancy. This percentage was higher in women with known thyroid disease (34.8%), particularly those who were currently receiving thyroid treatment during pregnancy (55.7%). In women who were identified later as developing thyroid disease after the early pregnancy blood sample and up to 5 years post delivery, approximately one third (36.6%) had evidence of unidentified thyroid dysfunction in early pregnancy. In other words, women who were diagnosed with thyroid disease after the pregnancy had high rates of unidentified abnormal thyroid function during the pregnancy.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Thyroid dysfunction is common during early pregnancy, especially in women with known thyroid disease. Over 50% of Danish women being treated for thyroid disease during pregnancy had abnormal thyroid function tests in early pregnancy, highlighting the need for close monitoring of women with thyroid disease during pregnancy to ensure they have normal thyroid hormone levels while on treatment. Women with thyroid disease that was diagnosed after pregnancy showed high rates of abnormal thyroid levels during the prior pregnancy, indicating some thyroid dysfunction. The long term effects of this unidentified thyroid hormone abnormality on pregnancy outcome requires further research.

—Whitney W. Woodmansee, MD

ATA THYROID BROCHURE LINKS

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

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

THYROID AND PREGNANCY, continued

ABBREVIATIONS & DEFINITIONS

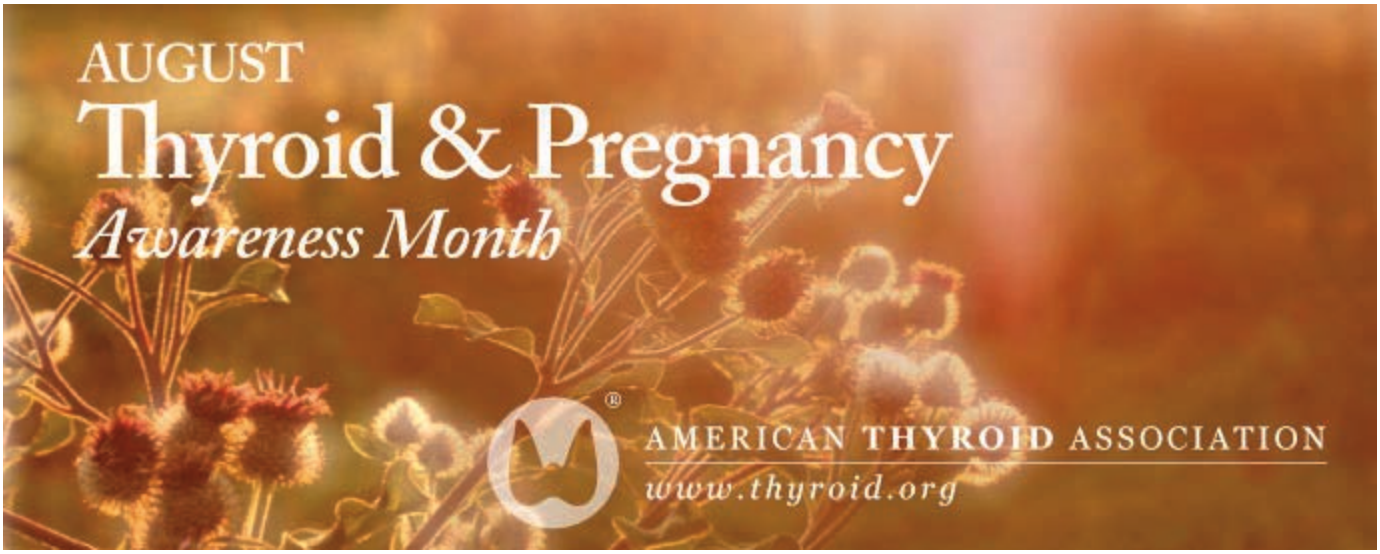
Subclinical Hypothyroidism: a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not.

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.

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.

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.



CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION

www.thyroid.org

HYPOTHYROIDISM

Delaying ultrasonography in congenital hypothyroidism may give misleading results.

BACKGROUND

Congenital hypothyroidism is a disorder in which babies are born with low thyroid hormone levels, either because the thyroid did not develop properly (thyroid dysgenesis) or because the thyroid has problems in one of the needed steps to make thyroid hormones (thyroid dyshormonogenesis). Congenital hypothyroidism is estimated to occur in 1:1700 newborns in the most recent literature and, if left untreated or if treatment is delayed, it irreversibly affects brain development. Thyroid scintigraphy is a procedure in which a radioactive compound which is taken up by the thyroid gland is used to determine the location of the gland or to confirm the absence of thyroid tissue. This procedure needs to be done when the child is not on thyroid hormone, either prior to starting treatment or after holding treatment for some weeks.

Thyroid ultrasound and thyroid scintigraphy have been used to determine the cause of congenital hypothyroidism, whether due to dyshormonogenesis or dysgenesis. In dysgenesis, the gland may be absent, smaller, or in an abnormal position. In dyshormonogenesis, the gland is usually normal or larger in the absence of thyroid hormone replacement. Thyroid dyshormonogenesis may be inherited in 25% of the children in a family, so it is important to make the right diagnosis of this condition for genetic counseling. Since the outcomes of congenital hypothyroidism depend on starting treatment as soon as possible after diagnosis, diagnostic studies to determine the etiology of congenital hypothyroidism are usually delayed after the age of three years, or not done at all, which may cause uncertainty in the patient and lack of adequate genetic counseling. This study was done to determine whether ultrasound of the thyroid could have a role in the early diagnosis of congenital hypothyroidism and to determine whether delaying ultrasound could provide misleading information.

THE FULL ARTICLE TITLE

Borges MF et al. Timing of thyroid ultrasonography in the etiological investigation of congenital hypothyroidism. Arch Endocrinol Metab. February 13, 2017 [Epub ahead of print]. doi:10.1590/2359-3997000000239

SUMMARY OF THE STUDY

A total of 44 patients with a diagnosis of congenital hypothyroidism from the state of Minas Gerais, Brazil, were invited to have thyroid US at the Universidade Federal do Triângulo Mineiro in Uberaba, Brazil. All except three accepted the invitation and participated in the study (23 females and 18 males), ranging in age from 0.2 to 45 years. All were receiving treatment and were considered to have congenital hypothyroidism, except for 1 patient, whose elevation in TSH was transient and had resolved. Patients were divided in two groups: Group 1 (23 patients) included patients diagnosed by the State Neonatal Screening program and Group 2 (21 patients) included patients who had been followed in the city of Uberaba's Municipal Health Unit. In Group 1, 15 patients had already undergone ultrasound and scintigraphy between ages 3 and 4. In Group 2, 15 of the patients had previously undergone ultrasound, but only two had undergone thyroid scintigraphy. Information related to these prior studies was obtained from the medical records. The second ultrasound was compared to the initial one, when available. When a thyroid was found, measurements were obtained to calculate the thyroid volume. The volumes were compared with reference ranges from medical references or from normal children to determine whether glands were bigger, normal or smaller than normal.

The major results of the study were that 24.5% of patients (10 patients) did not have a visible thyroid on ultrasound. All of these patients were diagnosed with thyroid dysgenesis. A total of 4 of these patients had previously undergone thyroid scintigraphy and 8 had undergone another US. In only 5/8 patients, there was complete agreement between the two ultrasounds, however, the second ultrasound identified all cases of dysgenesis. In 31 patients, the thyroid was noted in its normal location. In 18 patients, the thyroid was normal size, but 1 of these patients had only one lobe (half the thyroid) and another had transient elevation of TSH level, which resolved. Therefore, 16 patients were given a diagnosis of dyshormonogenesis. The thyroid was smaller than normal in 13 patients; in 6 of these patients, the initial ultrasound

HYPOTHYROIDISM, continued

showed the thyroid size to be normal and in 4 the thyroid volume in the second ultrasound was less than in the initial US. Therefore, these 6 patients were also assigned a diagnosis of dyshormonogenesis. In the remaining 7 of these 13 patients, 1 was diagnosed as having central hypothyroidism and the other 6 were variously referred to as having small thyroids (hypoplasia or thyroid dysgenesis). Half of the patients with small thyroid glands on the second US may have been diagnosed with dysgenesis instead of dyshormonogesis if they had not one an initial US earlier in life.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Thyroid ultrasound is a test that can be obtained in early infancy without delaying treatment for congenital hypothyroidism. Ultrasound can give valuable information in making an accurate diagnosis for the cause of congenital hypothyroidism, especially when done in early infancy when delaying thyroid ultrasound may lead to the wrong diagnosis of thyroid dysgenesis in the patients in which thyroid hormone replacement can decrease the size of the thyroid. As thyroid dyshormonogenesis may be inherited in 25% of the children in a family, it is important to make the right diagnosis of this condition for genetic counseling.

— Liuska Pesce, MD

ATA THYROID BROCHURE LINKS

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

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

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.

Congenital hypothyroidism: hypothyroidism that exists at birth either because the thyroid did not develop properly (thyroid dysgenesis) or because the thyroid has problems in one of the needed steps to make thyroid hormones (thyroid dyshormonogenesis). Congenital hypothyroidism is estimated to occur in 1:1700 newborns.

Thyroid dysgenesis: a cause of congenital hypothyroidism where the thyroid did not develop properly

Thyroid dyshormonogenesis: a cause of congenital hypothyroidism where the thyroid has problems in one of the needed steps to make thyroid hormones. Thyroid dyshormonogenesis may be inherited in 25% of the children in a family

Central hypothyroidism: a rare cause of hypothyroidism where the thyroid gland is normal and the problem is inadequate TSH secretion from the pituitary gland.

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.

TSH: Thyroid Stimulating Hormone — the hormone that stimulates the thyroid gland to make thyroid hormones. High TSH correlates with primary hypothyroidism

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 nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

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

CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION

www.thyroid.org

HYPOTHYROIDISM

Thyroid function, cholesterol levels, and heart disease

BACKGROUND

The risk for developing heart disease is higher in individuals with certain risk factors, which include high cholesterol, high blood pressure, and diabetes. Thyroid hormone has clear effects on the heart and on cholesterol levels. Patients with hyperthyroidism have an increased risk for irregular heart rhythms (atrial fibrillation) while patients with hypothyroidism have higher cholesterol levels. Because of this, there have been several studies suggesting potential associations between mild thyroid problems and heart problems. However, whether mild hypothyroidism or mild hyperthyroidism may be related to cardiovascular disease remains uncertain. This study was done to assess the associations between mild hypothyroidism or mild hyperthyroidism and common risk factors for heart disease such as cholesterol levels, blood pressures, and diabetes and events such as a heart attack and stroke.

THE FULL ARTICLE TITLE

Martin SS et al. Thyroid Function, Cardiovascular Risk Factors, and Incident Atherosclerotic Cardiovascular Disease: The Atherosclerosis Risk in Communities (ARIC) Study. J Clin Endocrinol Metab. 2017 Jun 12. doi: 10.1210/jc.2017-00986. [Epub ahead of print]

SUMMARY OF THE STUDY

The study examined data from the Atherosclerosis Risk in Communities (ARIC) Study, a group of men and women from the general U.S. population without prior known heart attack, stroke, or heart failure. Collected blood drawn in 1990-1992 was measured for thyroid function tests to determine whether individuals had normal thyroid function, hypothyroidism, or hyperthyroidism. If hypothyroidism or hyperthyroidism was found, it was categorized as either mild or moderate/severe.

From over 11,000 individuals (average age 57 years, 58% women, 76% Caucasian), 12% had either hypothyroidism or hyperthyroidism. Only 5% were taking a cholesterol-lowering medication. The researchers found that hypothyroidism, particularly if it was moderate/severe, was associated with increased cholesterol levels. However, neither hypothyroidism nor hyperthyroidism was associated with increased blood pressure, diabetes, heart attacks, or strokes.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this study drawn from a large adult sample of the U.S. general population, hypothyroidism was associated with higher cholesterol levels, particularly in those with more moderate or severe hypothyroidism. However, even though having higher cholesterol is a cardiovascular disease risk factor, there were no significant differences in the proportions of individuals who had heart attacks or strokes based on thyroid function alone.

— Angela M. Leung, MD, MSc

ATA THYROID BROCHURE LINKS

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

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.

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.

Lipids: the general term used to describe fat molecules in the blood. Examples of blood lipids include cholesterol, HDL ("good) cholesterol, LDL ("bad") cholesterol and triglycerides.

CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION

www.thyroid.org

THYROID NODULES

Incidental thyroid nodules detected on CT, MRI, or PET-CT scans correlate well with subsequent ultrasound evaluation

BACKGROUND

Thyroid nodules are very common and are present in up to 50% of adults. Neck ultrasound is the best imaging test to evaluate thyroid nodules, because it can detect features that have been proven to predict malignancy. The American Thyroid Association has published evidence-based ultrasound criteria for evaluating thyroid nodules for the possibility of cancer. Those nodules which exhibit concerning ultrasound features can then be evaluated with a thyroid biopsy, while those that do not can be safely followed.

Thyroid nodules are often discovered by the patient noting a lump in the neck or by a provider during a physical exam. However, thyroid nodules are also frequently detected by other imaging tests such as computerized tomography (CT scan), magnetic resonance imaging (MRI scan) and positron-emission tomography-CT (PET-CT) that are done to evaluate problems other than the thyroid. When a nodule is discovered by an imaging test done for another reason, it is called an incidental thyroid nodules. It is not clear whether these imaging tests can accurately predict thyroid cancer by themselves without the need for a neck ultrasound. The American College of Radiology (ACR) recently published recommendations that use age, nodule size and specific imaging features to determine which incidental thyroid nodules need further evaluation with neck ultrasound and which do not. However, the accuracy of these guidelines has not been thoroughly studied.

The aims of the present study are to a) evaluate whether the size of thyroid nodules discovered on CT, MRI or PET-CT correlate with measurements at subsequent ultrasound and b) to determine the impact of applying the ACR recommendations on thyroid nodule outcomes.

THE FULL ARTICLE TITLE

Ní Mhuircheartaigh JM et al. Correlation between the size of incidental thyroid nodules detected on CT, MRI or PET-CT and subsequent ultrasound Clin Imaging 2016;40:1162-6.

SUMMARY OF THE STUDY

This study examined 307 patients who had had a thyroid ultrasound over a two year period because an incidental thyroid nodule was previously found (within 6 months) on CT, MRI or PET-CT. Nodule size was compared between the image and subsequent thyroid ultrasound. The authors also determined the number of cases of thyroid cancer that would have missed if the ACR recommendations had been followed from the outset.

Of the 307 patients included, 229 had thyroid nodules discovered on CT scan, 69 on MRI scan and 9 on PET-CT scan. The average nodule size from all imaging studies was 15.6 mm. The average nodule size of the same nodules when measured by ultrasound was 17.5 mm indicating a tendency for other imaging studies to underestimate nodule size. If the ACR recommendations were applied, ultrasound would not have been recommended for 151 patients (49.2%). Applying the ACR recommendations would have decreased the number of ultrasounds by 24% of the total study group and only a single cancer would have been missed.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study addresses a common clinical problem. Incidental thyroid nodules are commonly identified on imaging studies done for other reasons than thyroid problems, but recommending further ultrasound evaluation for each one would be very expensive, may lead to increased patient anxiety and may be unecessary. The investigators found that CT, MRI or PET-CT are more likely to underestimate the size of a thyroid nodule as compared with ultrasound. However, the size difference does not appear to be clinically significant. More importantly, this study shows that using the ACR recommendations effectively identifies most cases of thyroid cancer while reducing the number of unnecessary thyroid ultrasounds. Physicians now have a means of determining which incidental nodules identified on non-ultrasound imaging need to be further evaluated with an ultrasound and which do not.

— Phillip Segal, MD

ATA THYROID BROCHURE LINKS

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/

THYROID NODULES, continued

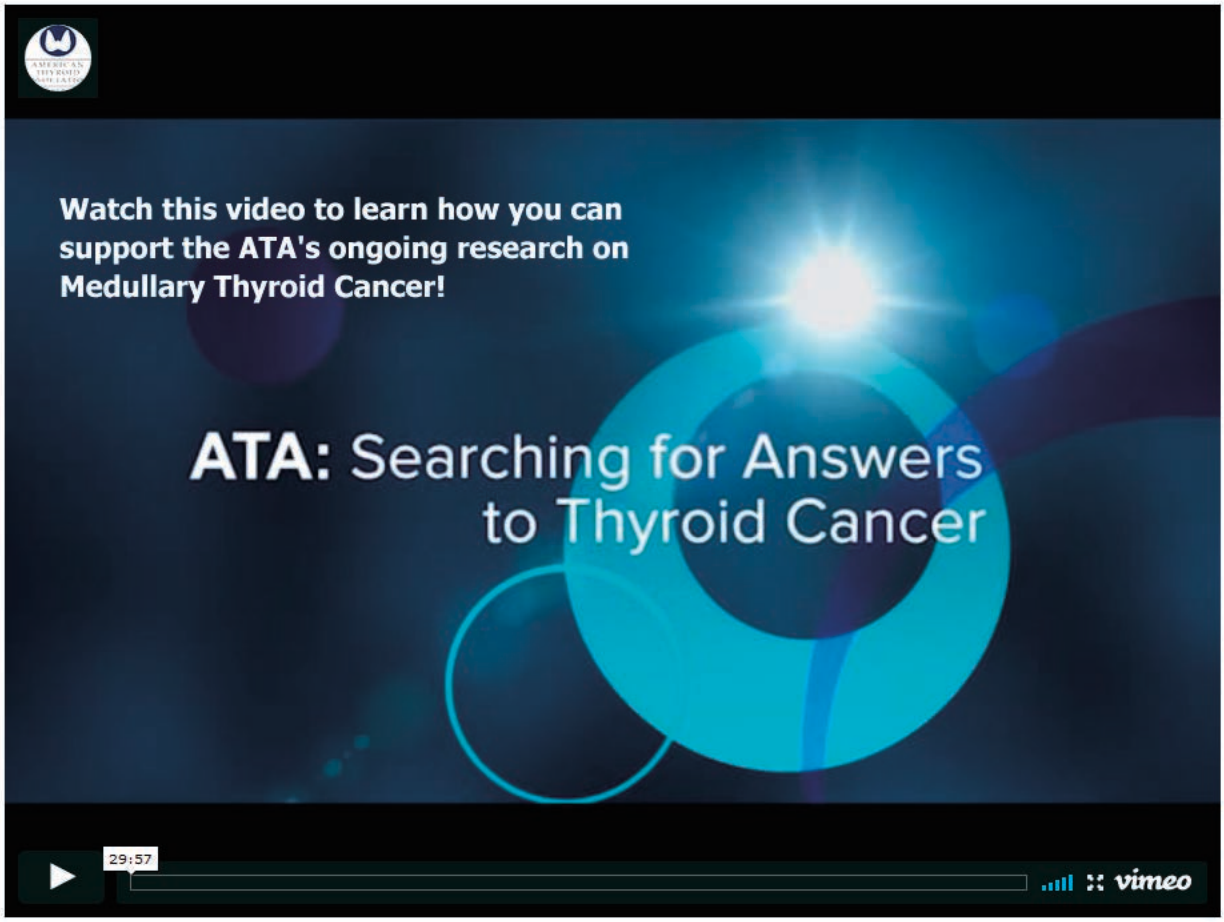
ABBREVIATIONS & DEFINITIONS

Positron-Emission-Tomography (PET) scans: a nuclear medicine imaging test that uses a small amount of radiolabeled glucose to identify cancer. Since cancer cells are more active than normal cells, the cancer cells take up more of the radiolabeled glucose and show up on the PET scan. PET scans are frequently combined with CT scans to accurately identify where the cancer is located.

Thyroid fine needle aspiration biopsy (FNAB): a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (Benign), ~5% are cancerous.

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 nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.



CLINICAL **THYROIDOLOGY** FOR THE **PUBLIC**

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION

www.thyroid.org

THYROID CANCER

The combination of BRAF^{600E} mutation and TERT promotor mutations increases risk of recurrence and death in papillary thyroid cancer

BACKGROUND

Most patients with papillary thyroid cancer have an excellent prognosis, but predicting which patients do not do well has been an ongoing area of interest. Ideally, identifying those at higher risk of cancer recurrence would potentially allow the more aggressive therapies to be utilized when appropriate for patients with high risk papillary thyroid cancer. A lot of recent work has identified molecular markers, which are mutations in cancer-related genes that can help in the diagnosis of thyroid cancer on thyroid biopsy specimens. More recently, 2 specific molecular markers, BRAF^{v600E} and TERT promotor mutations have been associated with aggressive tumor behavior and worse outcomes in papillary thyroid cancer. The BRAF^{v600E} mutation is quite common in papillary thyroid cancer so using this mutation alone to predict outcome has been challenging, though it has been associated with poor prognosis. The TERT promoter mutation alone was not shown to cause adverse outcomes in some previous studies, though other studies suggested it was associated with a more aggressive clinical picture.

This study aimed to determine the prognosis of papillary thyroid cancer in patients with either of these mutations alone or in combination by a review of the current studies.

THE FULL ARTICLE TITLE

Moon S et al. Effects of coexistent BRAF^{V600E} and TERT promoter mutations on poor clinical outcomes in papillary thyroid cancer: a meta-analysis. Thyroid. March 7, 2017 [Epub ahead of print].

SUMMARY OF THE STUDY

A literature review was done to identify studies that included BRAF^{V600E} and TERT promoter mutations in thyroid cancer. A total of 13 studies were identified. Data was extracted and reviewed for clinical information to include the number of males and females, age at diagnosis, cancer stage, spread to lymph nodes, extrathyroidal extention, spread outside of the neck, cancer recurrence and death.

A total of 4347 patients with papillary thyroid cancer were evaluated in the study and 283 patients had both BRAF^{v600E} and TERT promoter mutations. A BRAF^{v600E} mutation alone was related to advanced age at time of diagnosis, advanced cancer stage, extrathyroidal extension of tumor, and spread to lymph nodes, compared with no mutation. A TERT promoter mutation alone was associated with older age at diagnoses, spread to lymph node and spread outside of the neck. The combination of BRAF^{v600E} and TERT promoter mutations together when compared with no mutations was associated with older age at diagnosis, male gender, advanced cancer staging, extrathyroidal extension, spread to lymph node and spread outside of the neck.

Overall, the combination of BRAF^{600E} and TERT mutations was associated with high recurrence rate when compared with no mutations. Further, it was noted that the combination of mutations also had a higher risk of death than no mutations or BRAF^{v600E} alone, although few patients were in this group.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that molecular marker analysis can be used to identify patients that have more aggressive thyroid cancer. The combination of BRAF^{v600E} and TERT promotor mutations worsens the prognosis for papillary thyroid cancer. Additionally, a limited data set suggested higher risk of death with the combination of BRAF^{600E} and TERT promoter mutations.

As we improve our understanding of the molecular changes in thyroid cancer, we will improve our ability to identify patients that have a more aggressive thyroid cancer. Ultimately this knowledge will lead to improved treatment options. Future studies must aim to determine if identifying these mutations at the time of diagnosis can lead to improved outcomes for patients at higher risk.

— Julie Hallanger Johnson, MD

ATA THYROID BROCHURE LINKS

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

THYROID CANCER, continued

ABBREVIATIONS & DEFINITIONS

Molecular markers: genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the Afirma™ Gene Expression Classifier and Thyroseq™

Cancer-associated genes: these are genes that are normally expressed in cells. Cancer cells frequently have mutations in these genes. It is unclear whether mutations in these genes cause the cancer or are just associated with the cancer cells. The cancer-associated genes important in thyroid cancer are BRAF, RET/PTC, TERT and RAS.

BRAF gene: this is gene that codes for a protein that is involved in a signaling pathway and is important for cell growth. Mutations in the BRAF gene in adults appear to cause cancer.

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

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

Light of Life Foundation
checkyourneck.com

GRAVES' DISEASE & THYROID FOUNDATION

Thyroid Federation International

BITE ME CANCER!

ThyCa: Thyroid Cancer Survivors' Association, Inc.
www.thyca.org

Thyroid Cancer Canada
Cancer de la thyroïde Canada

Graves' Disease

WHAT IS THE THYROID GLAND?

The thyroid gland is a butterfly-shaped endocrine gland that is located in the lower front of the neck. The thyroid makes thyroid hormones, which are secreted into the blood and then carried to every tissue in the body. Thyroid hormones help the body use energy, stay warm and keep the brain, heart, muscles, and other organs working appropriately.

WHAT IS GRAVES' DISEASE?

Graves' disease is an autoimmune disease that leads to a generalized overactivity of the entire thyroid gland (*hyperthyroidism*). It is the most common cause of hyperthyroidism in the United States. It is named after Robert Graves, an Irish physician, who described this form of hyperthyroidism about 150 years ago. It is 7-8 times more common in women than men.

WHAT CAUSES GRAVES' DISEASE?

Graves' disease is triggered by a process in the body's immune system, which normally protects us from foreign invaders such as bacteria and viruses. The immune system destroys foreign invaders with substances called antibodies produced by blood cells known as lymphocytes. Sometimes the immune system can be tricked into making antibodies that cross-react with proteins on our own cells. In many cases these antibodies can cause destruction of those cells. In Graves' disease these antibodies (called the thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulins (TSI) do the opposite – they cause the cells to work overtime. The antibodies in Graves' disease bind to receptors on the surface of thyroid cells and stimulate those cells to overproduce and release thyroid hormones. This results in an overactive thyroid (*hyperthyroidism*).

WHAT ARE THE SYMPTOMS OF GRAVES' DISEASE?

- *Hyperthyroidism*

  The majority of symptoms of Graves' disease are caused by the excessive production of thyroid hormones by the thyroid gland (see *Hyperthyroidism brochure*). These may include, but are not limited to, racing heartbeat, hand tremors, trouble sleeping, weight loss, muscle weakness, neuropsychiatric symptoms and heat intolerance.

- *Eye disease*

  Graves' disease is the only kind of hyperthyroidism that can be associated with inflammation of the eyes, swelling of the tissues around the eyes and bulging of the eyes (called *Graves' ophthalmopathy or orbitopathy*). Overall, a third of patients with Graves' disease develop some signs and symptoms of Graves' eye disease but only 5% have moderate-to-severe inflammation of the eye tissues to cause serious or permanent vision trouble. Patients who have any suggestion of eye symptoms should seek an evaluation with an eye doctor (an ophthalmologist) as well as their endocrinologist.

  Eye symptoms most often begin about six months before or after the diagnosis of Graves' disease has been made. Seldom do eye problems occur long after the disease has been treated. In some patients with eye symptoms, hyperthyroidism never develops and, rarely, patients may be hypothyroid. The severity of the eye symptoms is not related to the severity of the hyperthyroidism.

  Early signs of trouble might be red or inflamed eyes, a bulging of the eyes due to inflammation of the tissues behind the eyeball or double vision. Diminished vision or double vision are rare problems that usually occur later, if at all. We do not know why, but problems with the eyes occur much more often and are more severe in people with Graves' disease who smoke cigarettes.

- *Skin disease*

  Rarely, patients with Graves' disease develop a lumpy reddish thickening of the skin in front of the shins known as pretibial myxedema (called Graves' dermopathy). This skin condition is usually painless and relatively mild, but it can be painful for some. Like the eye trouble of Graves' disease, the skin problem does not necessarily begin precisely when the hyperthyroidism starts. Its severity is not related to the level of thyroid hormone.

Graves' Disease

HOW IS THE DIAGNOSIS OF GRAVES' DISEASE MADE?

The diagnosis of hyperthyroidism is made on the basis of your symptoms and findings during a physical exam and it is confirmed by laboratory tests that measure the amount of thyroid hormones (thyroxine, or T4, and triiodothyronine, or T3) and thyroid-stimulating hormone (TSH) in your blood (see the *Hyperthyroidism brochure*). Clues that your hyperthyroidism is caused by Graves' disease are the presence of Graves' eye disease and/or dermopathy (see above), a symmetrically enlarged thyroid gland and a history of other family members with thyroid or other autoimmune problems, including type 1 diabetes, rheumatoid arthritis, pernicious anemia (due to lack of vitamin B12) or painless white patches on the skin known as vitiligo.

The choice of initial diagnostic testing depends on cost, availability and local expertise. Measurement of antibodies, such as TRAb or TSI, is cost effective and if positive, confirms the diagnosis of Graves' disease without further testing needed. If this test is negative (which can also occur in some patients with Graves' disease), or if this test is not available, then your doctor should refer you to have a radioactive iodine uptake test (RAIU) to confirm the diagnosis.

Also, in some patients, measurement of thyroidal blood flow with ultrasonography may be useful to establish the diagnosis if the above tests are not readily available.

HOW IS GRAVES' DISEASE TREATED?

The treatment of hyperthyroidism is described in detail in the *Hyperthyroidism brochure*. All hyperthyroid patients should be initially treated with beta-blockers. Treatment options to control Graves' disease hyperthyroidism include antithyroid drugs (generally methimazole [Tapazole®], although propylthiouracil [PTU] may be used in rare instances such as the first trimester of pregnancy), radioactive iodine and surgery.

Antithyroid medications are typically preferred in patients who have a high likelihood of remission (women, mild disease, small goiters, negative or low titer of antibodies). These medications do not cure Graves' hyperthyroidism, but when given in adequate doses are effective in controlling the hyperthyroidism.

If methimazole is chosen, it can be continued for 12-18 months and then discontinued if TSH and TRAb levels are normal at that time. If TRAb levels remain elevated, the chances of remission are much lower and prolonging treatment with antithyroid drugs is safe and may increase chances of remission. Long term treatment of hyperthyroidism with antithyroid drugs may be considered in selected cases.

If your hyperthyroidism due to Graves' disease persists after 6 months, then your doctor may recommend definitive treatment with either radioactive iodine or surgery.

If surgery (thyroidectomy) is selected as the treatment modality, the surgery should be performed by a skilled surgeon with expertise in thyroid surgery to reduce the risk of complications.

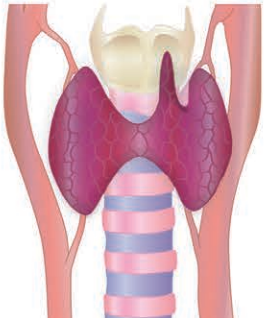
Your doctor should discuss each of the treatment options with you including the logistics, benefits and potential side effects, expected speed of recovery and costs. Although each treatment has its advantages and disadvantages, most patients will find one treatment plan that is right for them. Hyperthyroidism due to Graves' disease is, in general, controllable and safely treated and treatment is almost always successful.

WHAT WILL BE THE OUTCOME OF TREATMENT?

If you receive definitive treatment for your Graves' hyperthyroidism (such as radioactive iodine or surgery), you will eventually develop hypothyroidism (underactive thyroid). Even if you are treated with antithyroid drugs alone, hypothyroidism can still occur. Your doctor will check your *thyroid function tests* frequently to assess thyroid function following treatment. When hypothyroidism occurs, you will need to take a thyroid hormone tablet once a day at the right dose (see *Hypothyroidism brochure*).

OTHER FAMILY MEMBERS AT RISK

Graves' disease is an autoimmune disease and has a genetic predisposition. However, no specific gene has been identified for screening to date.



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*