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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.

While the Covid-19 pandemic is winding down, it has caused an unprecedented upheaval in our daily lives and presented extremely difficult challenges to our healthcare system. 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/)

December is Thyroid and Development Awareness Month.

In this issue, the studies ask the following questions:

- Are there long-term adverse effects of L-T3 therapy for hypothyroidism?
- Is a history of hypothyroidism associated with dementia?
- What is the risk of missed cancers in the long term follow-up of thyroid nodules?
- Does delaying post-operative RAI therapy for thyroid cancer affect clinical response?
- Can we predict who will develop early hypothyroidism after RAI therapy for Graves' disease?
- What is a useful cutoff of TSH-receptor antibody level in pregnant women with low TSH level in early pregnancy?

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

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HYPOTHYROIDISM

Are there long-term adverse effects of L-T3 therapy for hypothyroidism?

BACKGROUND

Thyroxine (T4) is the main thyroid hormone produced by the thyroid gland. Thyroxine is converted to triiodothyronine (T3) in peripheral tissues and T3 is considered the active form for thyroid hormone action. Because of this relationship, levothyroxine (L-T4) therapy is the most common treatment option for individuals with hypothyroidism. It is identical to thyroxine, gets converted to T3 within peripheral tissues in the same way, is long-acting and is given once daily. Liothyronine (L-T3) alone is not a good replacement option in hypothyroidism even though it is the active hormone because of a shorter half-life requiring twice a day dosing and causing peaks of high levels of T3 that can lead to additional problems including osteoporosis and atrial fibrillation.

L-T4 effectively controls biochemical and clinical features of hypothyroidism in most individuals. However, it is clear that there is a subset of individuals with hypothyroidism who continue to have symptoms on L-T4 alone despite their FT4 and TSH levels in the normal range. Most often, these symptoms include not feeling well, fatigue and brain fog. Sometimes a trial of L-T4 and L-T3 combination therapy can be considered in patients with continued symptoms on L-T4 alone and may result in improvement in symptoms.

Recent studies did not identify significant long-term usage concerns with combination L-T4 and L-T3 therapy. The aim of the present study was to compare the risk of osteoporosis, atrial fibrillation, cancer risk, and mood disorders in patients treated with L-T4 alone versus L-T3 therapy (either alone or in combination with L-T4) in a large patient groups in Korea.

THE FULL ARTICLE TITLE

Yi W et al 2022 Heart failure and stroke risks in users of liothyronine with or without levothyroxine compared with levothyroxine alone: A propensity score-matched analysis. Thyroid 32:764–771. PMID: 35570696.

SUMMARY OF THE STUDY

This study included adult patients receiving thyroid hormone replacement therapy for at least 90 days. Participants were identified using a search of electronic medical records from four hospital systems in Korea. The patient group was divided by L-T3 use, where L-T3 users were defined as those taking L-T3 with or without L-T4 and further subdivided based on history of thyroid cancer. Safety outcomes included osteoporosis (with or without fractures), atrial fibrillation, heart failure, heart disease, stroke, cancer including breast cancer, anxiety disorder, and mood disorder. The study group included 1,887 L-T3 users and 30,303 L-T4–only users. Approximately 90% of the group was between 30 and 70 years of age, ~ 80% were female, and >50% had been on thyroid replacement therapy for >1 year. A total of 1,434 L-T3 users and 3,908 L-T4–only users were included in the final analysis.

Overall, L-T3 users had a 1.7-fold increased risk of heart failure and a 1.8-fold risk of stroke but a significantly decreased risk of anxiety and mood disorders. In the group of thyroid cancer patients, heart failure was the only significant adverse effect that increased in L-T3 users and was not significant in those on this therapy for <1 year.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study found that the use of L-T3 (alone or in combination with L-T4), compared to L-T4 alone, was associated with increased risk of heart failure and stroke, but not osteoporosis, cancer or atrial fibrillation. Additional studies focusing on only the L-T4 and L-T3 combination group are needed, as the dose to L-T3 is much lower than with L-T3 alone. However, until those studies are done, it is important to take into consideration the risk of heart failure and stroke when considering adding L-T3 for the treatment of hypothyroidism.

— Alan P. Farwell, 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.

Levothyroxine (T4): the major hormone produced by the thyroid gland and available in pill form as Synthroid™, Levoxyl™, Tirosint™ and generic preparations.

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.

Triiodothyronine (T3): the active thyroid hormone, usually produced from thyroxine, available in pill form as liothyronine or Cytomel™.

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HYPOTHYROIDISM

A history of hypothyroidism is associated with higher dementia risk in elderly Asians

BACKGROUND

Hypothyroidism is very common and can affect up to 15% of certain populations. Hypothyroidism also may become more common with aging, although this is controversial. Decreased concentration and memory issues are symptoms of hypothyroidism that go away on treatment with thyroid hormone. Dementia is a brain disease that causes memory loss, more commonly seen in the older people, and cases are increasing through the years. Because of these similar symptoms, there has been increasing interest in exploring the role of thyroid function, especially hypothyroidism, in dementia. However, studies observing the associations between hypothyroidism and dementia have yielded mixed results. Moreover, the outcomes of the treatment of hypothyroidism in dementia are not clear, particularly with regard to evidence from Asian populations.

This study examines possible link between hypothyroidism and dementia in the East Asian people.

THE FULL ARTICLE TITLE

Wieland DR et al 2022 Thyroid disorders and dementia risk: A nationwide population-based case-control study. Neurology. Epub 2022 Jul 6. PMID: 35794019.

SUMMARY OF THE STUDY

Researchers collected the health records of 7,843 patients who had new-onset dementia without a previous history of dementia between 2006 and 2013 (case group) and matched them 1:1 according to age, sex, and index date (date enrolled in the study) with subjects who had never been diagnosed with dementia (control group). From these participants, those with a history of hyperthyroidism or hypothyroidism within 1 year before the first diagnosis of dementia (case group) or the index date (control group) were then identified.

The study comprised 15,686 adults in the 2 groups (51.8% female) with an average age of ~75 years. There was pre-existing hypothyroidism in 68 (0.9%) of the subjects with dementia, as compared with 34 (0.4%) of those without dementia. After adjusting for multiple factors that could affect the risk of dementia, having a history of hypothyroidism was found to be positively correlated with the risk of being diagnosed with dementia among those 65 years of age or older. There was pre-existing hypothyroidism in 76 (1.0%) of the subjects in the dementia group and 57 (0.7%) of those in the control group. No significant correlation between the history of hyperthyroidism and the increased risk of developing dementia was found.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study suggested that East Asian patients over the age of 65 years old with history of hypothyroidism had an increased risk of developing dementia than those without hypothyroidism. However, the overall risk was low (<1%). There was no correlation between hyperthyroidism and dementia. While this association is interesting, more studies are needed to determine the role, if any, of hypothyroidism in developing dementia. This is important for physicians to be aware of this association and to consider evaluating for dementia in elderly hypothyroid patients if symptoms develop.

— Joanna Miragaya, MD

HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

Thyroid Hormone Treatment: https://www.thyroid.org/thyroid-hormone-treatment/
Hypothyroidism (Underactive): https://www.thyroid.org/hypothyroidism/
Older Patients and Thyroid Disease: https://www.thyroid.org/thyroid-disease-older-patient/

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.

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.

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.

Dementia: general term for the impaired ability to remember, think, or make decisions that interferes with doing everyday activities. Alzheimer's disease is the most common type of dementia. Though dementia mostly affects older adults, it is not a part of normal aging.

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THYROID NODULES

What is the risk of missed cancer in the long-term follow-up of thyroid nodules?

BACKGROUND

Thyroid nodules are common and up to 65% of the adult population being expected to have this condition. Many thyroid nodules do not result in any symptoms and are not diagnosed. However, the widespread use of radiological tests, such as neck ultrasound, has increased the number of thyroid nodules found on these tests done for other reasons. Biopsy of thyroid nodules can be performed to diagnose cancerous nodules. The decision to undergo this procedure is based on the ultrasound appearance of the thyroid nodules. The use of ultrasound-based risk-stratification systems for thyroid nodules has allowed clinicians to avoid numerous unneeded thyroid biopsies.

The cancer risk of thyroid nodules has been estimated to be 5-15%, based on prior studies. This risk could be overestimated if only thyroid nodules referred for biopsy or surgery are evaluated or if thyroid nodules from a center specialized in thyroid cancer treatment are analyzed, since these centers will attract a higher number of cancerous nodules than those existent in the general population. In addition, the cancer risk can be underestimated when thyroid cancer is missed in case of false negative results of the initial biopsy or short follow-up period, since most thyroid nodules have a slow growth rate over years. This study aimed to assess the cancer rate of thyroid nodules larger than 1 cm in diameter diagnosed by ultrasound during long-term follow-up of up to 23 years.

THE FULL ARTICLE TITLE

Grussendorf M et al. Malignancy rates in thyroid nodules: a long-term cohort study of 17,592 patients. Eur Thyroid J. 2022 Jun 29;11(4):e220027. doi: 10.1530/ETJ-22-0027.

SUMMARY OF THE STUDY

The study included 17,592 consecutive patients diagnosed with a thyroid nodule larger than 1 cm at a single care center in Germany between March 1989 and April 2013. Patients with a nodule larger than 1 cm and one or more ultrasound criteria suspicious for cancer (hypoechoic pattern, irregular margins, microcalcifications) were offered thyroid biopsy. A total of 7776 patients (44.2%) underwent biopsy, while 9816 patients (55.8%) had only a thyroid ultrasound at diagnosis. Based on the results of the initial examination (biopsy with benign results or non-suspicious features on ultrasound), 9568 patients were discharged from the clinic and not included in the study for further analysis. A total of 1293 patients with thyroid nodules larger than 1 cm were referred for surgery after the initial diagnosis, while 6731 individuals underwent long-term follow-up (up to 23 years, average 5 years).

A total of 189 patients in this study confirmed to have thyroid cancer (1.1% of the entire group). Of these, 155 patients (82%) were diagnosed at the time of the first evaluation. All of the remaining cases confirmed to have thyroid cancer (18% of all cancers) were detected within ten years of follow-up: 25 patients (13.2%) in years 2-5 of follow-up and 9 patients (4.8%) in years 6-10 of follow-up. There were no cancers detected in patients who underwent surgery after 10 years of follow-up. The risk of cancer decreased to 0.14% during the first five years of follow-up, and to 0.05% in years 6-10 of follow-up.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this large study with long-term patient follow-up of up to 23 years, the cancer rate of unselected thyroid nodules larger than 1 cm diagnosed on ultrasound was lower than previously reported (1.1% versus 5-15%). During follow-up for more than five years of those patients that did not undergo surgery, the cancer rate dropped to less than 1/1000 cases. These findings may help to reassure patients with newly diagnosed thyroid nodules, and to decrease the number of unneeded diagnostic and therapeutic procedures and shorten the follow-up period.

— Alina Gavrila, MD, MMSC

THYROID NODULES, continued

ATA THYROID BROCHURE LINKS

Thyroid Nodules: https://www.thyroid.org/thyroid-nodules/
Fine Needle Aspiration Biopsy of Thyroid Nodules: https://www.thyroid.org/fna-thyroid-nodules/
Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Thyroid nodule: an abnormal growth of thyroid cells that forms a lump within the thyroid. While most thyroid nodules are non-cancerous (benign), ~5-15% are cancerous (malignant).

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 biopsy: a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or malignant (cancerous). 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.

Hypoechoic thyroid nodule: the nodule appears darker on ultrasound than the surrounding normal thyroid tissue.

Microcalcifications: Small flecks of calcium within a thyroid nodule, usually seen as small bright spots on ultrasonography. These are frequently seen in nodules containing papillary thyroid cancer.

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

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THYROID CANCER

Delayed radioactive iodine therapy does not impact response or survival in patients with thyroid cancer

BACKGROUND

Thyroid cancer is the 9th most common cancer in the world. Overall, thyroid cancer has an excellent prognosis. This is because we have excellent treatment options. Thyroid surgery is the initial treatment in most thyroid cancers. Radioactive iodine therapy, a "magic bullet" that destroys thyroid cancer cells, is considered in patients with intermediate or high risk thyroid cancers to decrease the risk of thyroid cancer returning (recurrence). The vast majority of patients have thyroid cancers that have a low risk of recurrence, so they do not need radioactive iodine therapy after surgery as it may not provide additional benefit. Response to thyroid cancer treatment is monitored with regular neck ultrasounds and blood tests, including for a protein called thyroglobulin. A negative ultrasound and undetectable thyroglobulin level usually means no evidence of thyroid cancer recurrence.

For patients with thyroid cancer undergoing total thyroidectomy followed by radioactive iodine therapy, the initial treatment period can take a lot of time. Following thyroid surgery, patients typically spend the first two weeks recovering before they receive radioactive iodine therapy at 6-10 weeks. In order for radioactive iodine therapy to work and be administered safely, there is a significant amount of work and time that needs to be invested prior to and after the radioactive iodine therapy. This includes 1) obtaining the laboratory studies and an initial uptake scan; 2) having patient go on a low iodine diet for 1-2 weeks before treatment; 3) stimulating the remaining thyroid tissue to be "turned on" to take up the radioactive iodine, either by making the patient hypothyroid or treating with Thyrogen™ (synthetic TSH); 4) isolating from people after the radioactive iodine therapy for up to a week and 5) obtaining the final whole-body scan. Thus, for patients in whom radioactive iodine therapy is recommended, the weeks following thyroid surgery can be very time-consuming. Therefore, requests to delay radioactive iodine therapy are frequent and may include the need to return to work, to undertake family obligations, or in post-partum women to continue breastfeeding.

The goal of this study was to determine whether a delay of more than 3 months in administering radioactive iodine after thyroid surgery would affect how well the thyroid cancer responded to treatment and to determine overall survival in patients with thyroid cancer.

THE FULL ARTICLE TITLE

Cheng F et al 2022 Delay of initial radioactive iodine therapy beyond 3 months has no effect on clinical responses and overall survival in patients with thyroid carcinoma: A cohort study and a meta-analysis. Cancer Med **11:**2386–2396. PMID: 35179295.

SUMMARY OF THE STUDY

This study included adults with thyroid cancer who had received radioactive iodine therapy following thyroid surgery. Patients were divided into two groups based on when the radioactive iodine therapy was administered: the "early RAI" group received radioactive iodine therapy within 3 months of surgery, and the "delayed RAI" group received radioactive iodine therapy more than 3 months after surgery. At 6 to 8 months after treatment with radioactive iodine, patients had bloodwork (thyroid stimulating hormone level and thyroglobulin) and a neck ultrasound to determine how well the thyroid cancer responded to treatment. An "excellent response" to treatment was defined as negative imaging and undetectable Thyroglobulin <0.2 ng/ml or TSH-stimulated Thyroglobulin <1.0 ng/ml.

Between 2015 and 2019, a total of 1224 patients were included in the study in China, with 830 patients in the "early RAI" group and 394 patients in the "delayed RAI" group. Patients were followed for an average of 7.2 months. An "excellent response" to treatment was

THYROID CANCER, continued

observed among 49.4% of patients in the "early RAI" group and among 51.8% of patients in the "delayed RAI" group. The likelihood that patients would have an "excellent response" to the thyroid cancer treatment was similar between those in the "early RAI" group and the "delayed RAI" group.

A review of other studies, which included a total of 38,688 patients from 12 different studies, suggests that delaying radioactive iodine treatment for 3-6 months after thyroid surgery does not affect long-term overall survival for patients with thyroid cancer.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The study findings suggest that for patients with thyroid cancer and for whom radioactive iodine therapy is recommended, a delay of 3-6 months following total thyroidectomy does not appear to affect the likelihood of having an excellent response to treatment or the overall patients' survival. While this data is promising, more studies are needed to determine the best timing of radioactive iodine therapy and its impact on thyroid cancer outcomes.

— Debbie Chen, MD

ATA THYROID BROCHURE LINKS

Thyroid Surgery: https://www.thyroid.org/thyroid-surgery/
Radioactive Iodine Therapy: https://www.thyroid.org/radioactive-iodine/
Low Iodine Diet: https://www.thyroid.org/low-iodine-diet/
Thyroid Cancer (Papillary and Follicular): https://www.thyroid.org/thyroid-cancer/

ABBREVIATIONS & DEFINITIONS

Thyroid cancer: Papillary thyroid cancer is 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). Follicular thyroid cancer is the 2nd most common thyroid cancer.

Thyroidectomy: surgery to remove the entire thyroid gland. When the entire thyroid is removed it is termed a *total thyroidectomy*. When less is removed, such as in removal of a lobe, it is termed a *partial thyroidectomy*.

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.

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

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

THYROID CANCER, continued

Thyroid Hormone Withdrawal (THW): this is used to produce high levels of TSH in patients by stopping thyroid hormone pills and causing short-term hypothyroidism. This is mainly used in thyroid cancer patients before treating with radioactive iodine or performing a whole body scan.

Stimulated thyroglobulin testing: this test is used to measure whether there is any cancer present in a patient that has previously been treated with surgery and radioactive iodine. TSH levels are increased, either by withdrawing the patient from thyroid hormone or treating the patient with recombinant human TSH, then levels of thyroglobulin are measured. Sometimes this test is combined with a whole body iodine scan.

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GRAVES' DISEASE

Radioactive iodine therapy for patients with Graves' disease with positive TPO antibodies is associated with early hypothyroidism

BACKGROUND

Graves' disease is the most common cause of hyperthyroidism in the United States. Radioactive iodine therapy is frequently used to treat Graves' disease. Hypothyroidism or normal thyroid function are both considered successful treatment outcomes after radioactive iodine therapy.
A number of factors have been associated with rates of hypothyroidism after radioactive iodine therapy. These include the patient's age, severity of hyperthyroidism, TSH-receptor antibody (TRAb) levels, thyroid volume and pretreatment with antithyroid drugs. While a majority of patients with Graves' disease will have positive anti-thyroid peroxidase antibodies (anti-TPO) as a marker of their autoimmune disease, not all do. The authors sought to determine whether the presence of positive anti-TPO was associated with the subsequent development of hypothyroidism after radioactive iodine therapy.

THE FULL ARTICLE TITLE

Verdickt S et al 2022 TPO antibody status prior to first radioactive iodine therapy as a predictive parameter for hypothyroidism in Graves' disease. Eur Thyroid J **11**(4):e220047. PMID: 35687484.

SUMMARY OF THE STUDY

This is a study of patients with Graves' disease who received their first radioactive iodine treatment for their hyperthyroidism between 2011 and 2019 and had anti-TPO antibodies measured. They identified 152 patients from 4 thyroid outpatient clinics in Belgium and evaluated them as to their thyroid status (hypothyroidism or cure which was either hypothyroidism or normal thyroid function) at two time points. The first was approximately 6 months after radioactive iodine therapy (using closest evaluation 2-9 months after treatment) and the second 12 months after treatment (using closest evaluation at 9-24 months).

Positive anti-TPO antibodies were identified in 105 (69%) of the patients. These patients were on average younger, had a larger thyroid gland and had more previous episodes of hyperthyroidism compared to patients with negative antibodies. In period 1, 89% of the anti-TPO–positive group and 72% in the anti-TPO–negative group developed hypothyroidism. In period 2, the observation was similar: 88% vs. 72%. This difference was statistically significant even when adjusted for previously known predictive factors such as age, degree of hyperthyroidism, TRAb titer, thyroid volume, pretreatment with anti-thyroid drugs and radioactive iodine dose.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The authors concluded that positive anti-TPO antibodies are another predictor of hypothyroidism after radioactive iodine therapy for Graves' disease. This information can help physicians and patients better understand the risks of developing hypothyroidism subsequent to radioactive iodine therapy and may be a useful took in future studies evaluating the best dose of radioactive iodine to be used.

— Marjorie Safran, MD

ATA THYROID BROCHURE LINKS

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

Radioactive Iodine Therapy: https://www.thyroid.org/radioactive-iodine/

GRAVES' DISEASE, continued

ABBREVIATIONS & DEFINITIONS

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

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

TRAb: 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.

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.

Euthyroid: a condition where the thyroid gland as working normally and producing normal levels of thyroid hormone.

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

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

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THYROID AND PREGNANCY

What is a useful cutoff of TSH-receptor antibody level in pregnant women with low TSH level in early pregnancy?

BACKGROUND

Hyperthyroidism (overactive thyroid gland) with high thyroid hormone levels and a low TSH can cause problems in pregnancy, such as miscarriage, premature delivery, and high blood pressure in mothers, and problem with baby's growth. The most common cause of hyperthyroidism in pregnancy is Graves' disease, where high levels of thyroid stimulating hormone (TSH)-receptor antibody (TRAb) cause thyroid gland to make too much thyroid hormone. Since low TSH levels can occur in normal pregnancy from the effect of high levels of human chorionic gonadotropins (hCG) made by placenta, it is sometimes difficult to tell apart normal transient low TSH levels from Graves' disease in pregnant women. It is important to distinguish between the two conditions because Graves' disease may need treatment to prevent problems during pregnancy, but transient low TSH levels do not.

A key part of the diagnosis depends on the presence of TRAb levels. An undetectable TRAb level effectively rules out Graves' disease. A detectable but low TRAb level can also be normal while an increased level is diagnostic of Graves' disease. However, it is unclear how TRAb levels change during pregnancy, or even if they change. The cutoff of positive TRAb levels is also different in different laboratories using different assays.

It is important to have a good cutoff for TRAb levels in pregnancy to distinguish diagnoses of Graves' disease in pregnancy from low TSH level in normal pregnancy, because only Graves' disease may need treatment. The researchers of this paper studied how often TRAb levels were elevated and how often they were associated with low TSH levels, using a stored blood sample from a large database of pregnant women in Denmark.

THE FULL ARTICLE TITLE

Udall Torp NM et al 2022 TSH-receptor antibodies in early pregnancy. J Clin Endocrinol Metab. Epub 2022 Jun 23. PMID: 35737956.

SUMMARY OF THE STUDY

Patients in this study were selected from 14,323 women in Denmark who had blood samples stored during pregnancy between 2011 and 2015 for a large database. TSH and TRAb levels were measured in the stored blood samples. The hyperthyroid group had 414 women who had TSH level < 0.1mIU/L, suggesting hyperthyroidism. The control group had 524 women who had normal TSH levels between 0.1-2.9mIU/L that were measured before 15 weeks of pregnancy. None of the women in the study had known thyroid disease before pregnancy.

Based on the distribution of TRAb levels in the control group of women, TRAb level of 0.1 IU/L was determined as the cutoff for "positive TRAb" in this study. This was lower than the cutoff recommended by the manufacturer of the assay, which was 1.8 IU/L. Women in the hyperthyroid group were more likely to have positive TRAb levels > 0.1 IU/L compared to women in the control group (6.5% vs 4.6%). When these women were followed for an average of 8 years (ranging from 4-10 years), 52% of women who had TSH < 0.1 mIU/L and TRAb > 1.0 IU/L (positive TRAb) were later diagnosed with hyperthyroidism (24% during pregnancy or within 2 years after delivery), compared to only 8.4% of women who had TSH < 0.1mIU/L and TRAb ≤ 1.0 IU/L (negative TRAb). Among those who had TSH ≥ 0.1mIU/L in control group, less than five women were diagnosed with hyperthyroidism regardless of TRAb levels during the follow up.

A cutoff of > 0.1 IU/L for TRAb levels was generated for pregnant women using a large Danish population data, which was associated with higher likelihood of later diagnosis of hyperthyroidism. In this population, most cases of low TSH in early pregnancy were cases of transiently high levels of thyroid hormone with negative TRAb, with low likelihood of developing hyperthyroidism in the future.

THYROID AND PREGNANCY, continued

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that a low TSH level <0.01 mIU/L in pregnancy was relatively common, occurring in 3.1% of women in this group. This study used a large population of Danish pregnant women with stored blood sample to determine cutoff of TRAb level of 0.1 IU/L as positivity, lower than what was suggested by the manufacturer. Using this cutoff, only 5.1% of women with low TSH had positive TRAb status. Positive TRAb status predicted later development of hyperthyroidism in about half of these women. Since untreated severe hyperthyroidism can have negative impact in pregnancy, it would be important to identify women with hyperthyroidism that need treatment. This study was helpful in assessing a potentially useful cutoff level for TRAb test. However, the clinical application of this result is limited because the study was done only in women in Denmark and using only one assay. The cutoff determined by this study may not be useful in other countries or where other brands of assays for TRAb are used. Given these limitations, it would be important to continue to monitor any pregnant women with low TSH levels in early pregnancy closely to watch for potential development of severe hyperthyroidism that need treatment. Measurement of TRAb levels by any methods would be helpful.

— Sun Y. Lee, MD, MSc

ATA THYROID BROCHURE LINKS

Thyroid Disease in Pregnancy: https://www.thyroid.org/thyroid-disease-pregnancy/
Hyperthyroidism in Pregnancy: https://www.thyroid.org/hyperthyroidism-in-pregnancy/
Graves' Disease: https://www.thyroid.org/graves-disease/

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

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.

TRAb: 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.

hCG: human chorionic gonadotropin — the major hormone produced by the placenta which is closely related to thyroid stimulating hormone (TSH). hCG can bind to the TSH receptors present in thyroid tissue and act like a weak form of TSH to cause the thyroid to produce and release more thyroxine and triiodothyronine. hCG is the hormone measured in the pregnancy tests.

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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.

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www.thyroid.org
ATA Patient Resources:
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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
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