



Clinical Thyroidology® for the Public

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Rosario PW and Calsolari MR. 2018 Serum TSH level stability after 5 years in euthyroid adults at low risk for thyroid dysfunction. Arch Endocrinol Metab. May 17. pii: S2359-39972018005002003. doi: 10.20945/2359-3997000000037.

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Johnson DN et al 2018 Noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTPs) are genetically and biologically similar to adenomatous nodules and distinct from papillary thyroid carcinomas with extensive follicular growth. Arch Pathol Lab Med. Epub 2018 Mar 27. PMID: 29582677.

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The term NIFTP was introduced two years ago to describe select slow growing forms of papillary thyroid cancer that do not seem to grow or spread, and consequently may be able to be treated like benign thyroid nodules. The goal of this study was to characterize the incidence of NIFTP at a large tertiary care endocrine surgery center and determine the cancerous potential of NIFTP.

Parente DN et al 2018 Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: is NIFTP truly benign? World J Surg 42:321–326.

THYROID CANCER13

Is active surveillance reasonable for low-risk papillary thyroid microcarcinomas?

While surgery is usually recommended for patients with thyroid cancer, it is becoming clear that active surveillance could be considered for some patients with low risk small papillary thyroid cancers. Accumulating evidence over years has revealed that there is a low rate of cancer progression during active surveillance, and surgery performed later when progression is noted is safe. The goal of this study was to evaluate the physician acceptance and implementation patterns of active surveillance at Kuma Hospital, as a model that could be used for other institutions around the world.

Ito Y et al 2018 Trends in the implementation of active surveillance for low-risk papillary thyroid microcarcinomas at Kuma Hospital: gradual increase and heterogeneity in the acceptance of this new management option. Thyroid 28:488–495. Epub 2018 Apr 2. PMID: 29608416.





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Editor

Alan P. Farwell, MD, FACE
Boston Medical Center
Boston University School of Medicine
720 Harrison Ave., Boston, MA 02115
American Thyroid Association
Email: thyroid@thyroid.org
www.thyroid.org/patients/ct/index.html

Editorial Board

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American Thyroid Association
6066 Leesburg Pike, Suite 550
Falls Church, VA 22041
Telephone: 703-998-8890
Fax: 703-998-8893
Email: thyroid@thyroid.org

Designed by

Karen Durland, kdurland@gmail.com

Clinical Thyroidology for the Public

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EDITOR'S COMMENTS

Welcome to another issue of *Clinical Thyroidology for the Public*. In this journal, we will bring to you the most up-to-date, cutting edge thyroid research. We 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*, *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.

August is **[Thyroid and Pregnancy Awareness Month](#)**.

In this issue, the studies ask the following questions:

- Can we predict the likelihood of developing neonatal Graves' disease prior to the onset of symptoms?
- Are thyroid levels in the mother associated with child scores on standardized tests?
- How much do thyroid tests change in individuals without thyroid disease?
- Is NIFTP a benign subtype of papillary thyroid cancer?
- Should NIFTP still be considered a cancer?
- Is active surveillance appropriate for small, low risk thyroid cancers?

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



HYPERTHYROIDISM

Hyperthyroidism in infants of mothers with Graves' disease

BACKGROUND

The most common cause of hyperthyroidism in the United States is Graves' disease. This is an autoimmune disorder where antibodies attack the thyroid and turn it on. These antibodies are called TSH receptor antibodies (TRAb). Occasionally, the antibodies go away and the Graves' disease goes into remission. During pregnancy in a mother with Graves' disease, TRAb can cross the placenta and affect the developing baby's thyroid. If the baby is born with these antibodies, they may be hyperthyroid, a condition called neonatal Graves' disease. Symptoms typically develop within the first 2 weeks of life. This disorder lasts only a few weeks until the mother's antibodies go away. Fortunately, TRAb in mothers with Graves' disease often decrease and the disease can go into remission during pregnancy. As such, hyperthyroidism in early infancy and neonatal Graves' disease is rare. Guidelines published by the American Thyroid Association recommend testing pregnant women with Graves' disease for TRAb in the 3rd trimester.

All newborns in the United States are screened for thyroid disease by obtaining a TSH level on a heel stick blood sample right after delivery. This is done mainly to screen for neonatal hypothyroidism, which is vastly more common than neonatal Graves' disease. Although we know of some of the risk factors for developing Graves' disease in the mother, additional studies are necessary to help predict which newborns are at risk. This study was done to look at the risk factors in the newborn that may help predict the likelihood of developing hyperthyroidism and neonatal Graves' disease prior to the onset of symptoms.

THE FULL ARTICLE TITLE

Banigé M et al 2018 Research Group for Perinatal Dys-thyroidism (RPGD) Study Group 2018 Prediction of neonatal hyperthyroidism. J Pediatr Epub 2018 Mar 28. PMID: 29605392.

SUMMARY OF THE STUDY

This study examined the medical records of 415 pregnant women who had Graves' disease and positive TRAb testing during their pregnancy at multiple obstetric centers in Paris, France. Also, in addition to symptoms and signs of hyperthyroidism, blood test reports of infants born to the mothers with this condition and any neck ultrasound data in them were studied. Well defined laboratory ranges were used to diagnose hyperthyroidism in the newborns.

A total of 149 babies (35.9%) had positive TRAb tests, which took an average of 20 days to decline to normal. A total of 23 babies (5.5%) had neonatal hyperthyroidism of varying severity based on clinical symptoms; 17 of these had hyperthyroidism determined by blood testing. The mothers of 20 of the infants with neonatal hyperthyroidism were treated with antithyroid drugs in the 3rd trimester. The infants with neonatal hyperthyroidism were born earlier than the infants without neonatal hyperthyroidism (37 vs. 38.5 weeks) and at lower birth weights (average 2809 vs. 3013 g). Antithyroid drugs were used to treat 17 hyperthyroid infants and 14 of these became hypothyroid and subsequently required levothyroxine treatment.

Among infants of mothers with Graves' disease, a serum TSH <0.9 mIU/L at days 3 to 7 after birth had a higher chance of having higher levels of the thyroid antibody and /or developing hyperthyroidism (although the overall risk was low) that babies with higher TSH levels.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that in addition to the mother's history and laboratory testing, additional tests in the newborn can help predict which newborns are at a higher risk of developing hyperthyroidism. Although further studies are needed to further understand the risk of developing this condition in the newborns, it is helpful to know some of the risk factors that can help predict neonatal Graves' disease before the onset of symptoms.

—Vibhavasu Sharma, MD





HYPERTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

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

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

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

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

ABBREVIATIONS AND 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.

Neonatal Graves' disease: hyperthyroidism that occurs in babies born from mothers with Graves's disease and caused by the transfer of TRAb from the mother to the

baby during pregnancy. The disorder is self-limited in the baby and resolved within a few weeks after birth.

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.

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.

AUGUST Thyroid & Pregnancy *Awareness Month*



AMERICAN THYROID ASSOCIATION®
www.thyroid.org





HYPOTHYROIDISM

First-trimester maternal thyroid function is not associated with child scores on standardized educational tests

BACKGROUND

Thyroid hormone is necessary for development and growth of brain in developing babies during pregnancy. It is well known that untreated overt hypothyroidism in the mother can have significant effects on the brain development of their children. Due to this important role of thyroid hormone, numerous research studies have been conducted in the past to address the relationship between thyroid hormone levels in pregnant women and the status of intelligence and brain development in their children. The brain development affected is the brain's ability and performance in the areas of learning, social skills, focus, attention as well as motor function (for example learning to ride a bike).

So far, the results of these studies have been somewhat different from each other but a evaluation of 37 studies showed that even subclinical hypothyroidism and low thyroid hormone levels without hypothyroidism may be associated with some developmental problems in children. However none of the past research studies evaluated the performance of the children born from mothers with thyroid problems in educational exams.

This present study was aimed to assess any potential relationship between the results of standardized educational assessment tests of children and the thyroid function status of their mother at the time of pregnancy.

THE FULL ARTICLE TITLE

Nelson SM et al 2018 Maternal thyroid function and child educational attainment: prospective cohort study. British Medical Journal; 360:k452. PMID: 29463525

SUMMARY OF THE STUDY

From 1990 to 1992, a total of 14,541 pregnant women were enrolled in a study called Avon Longitudinal Study of Parents and Children (ALSPAC) in Birmingham, England. The study followed the children and their parents for the following two decades. The scores of National Standardized tests taken by the children were used in this study. The tests were done at certain ages. At school entry (ages 4 to 5), every child was assessed for language, math, social skills,

problem-solving and motor skills. National tests were done at ages 7, 11 and 14 covering English, math and science subjects. At age 16, at the end of secondary education, students took an examination called GCSE.

The results of thyroid function tests in the first trimester of pregnancy were available for 4615 of women in this study. Among these women, 0.7% had overt hypothyroidism, 3.6% had subclinical hypothyroidism, 2% had isolated low thyroid hormone levels, 1.2% had subclinical hyperthyroidism and 0.87% had overt hyperthyroidism. Overall, 10% of all women had positive TPO antibodies.

The authors then studied the association between the test results and the thyroid function status of mothers during pregnancy. Any other factor that could influence this association was also considered in the interpretation of the result. Those were education of both parents, age, ethnicity, number of children, smoking status and alcohol use of mother as well as birth weight and sex of babies, gestational age at the time of birth, the method of delivery and head circumference at the time of birth.

No significant relationship was found between the result of thyroid function tests in mothers and the test scores in their children.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

The strength of this study was the large number of subjects and the long duration of follow up. But it is important to mention that the absolute number of mothers who had thyroid disease was relatively small.

Although this study showed no relationship between thyroid dysfunction in mothers and the test performance of their children in school, more studies needs to be done in the future to confirm the these results and helps us to better understand whether treatment is necessary for pregnant women who have mild thyroid disease during pregnancy.

— Shirin Haddady, MD





HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

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

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

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

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

ABBREVIATIONS & DEFINITIONS

Subclinical Hypothyroidism: a mild form of hypothyroidism where the only abnormal hormone level is an increased TSH. There is controversy as to whether this should be treated or not. Hypothyroidism is a condition where the thyroid gland is underactive and doesn't produce enough thyroid hormone.

Hypothyroxinemia: decrease in the blood level of thyroxine (T₄) without change in the level of thyroid stimulating hormone

Overt Hypothyroidism: clear hypothyroidism (underactive thyroid) with an increased TSH and a decreased T₄ level. All patients with overt hypothyroidism are usually treated with thyroid hormone pills.

Subclinical Hyperthyroidism: a mild form of hyperthyroidism where the only abnormal hormone level is a decreased TSH. Hyperthyroidism is a condition where the thyroid gland is overactive and produces too much thyroid hormone.

Overt Hyperthyroidism: clear hyperthyroidism (overactive thyroid) with a decreased TSH and an increased T₄ level. Hyperthyroidism may be treated with anti-thyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

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.





THYROID BLOOD TESTS

Thyroid function tends to remain stable in those without risk factors for hypothyroidism or hyperthyroidism

BACKGROUND

Thyroid function screening is usually done by measuring a TSH blood test. This test is able to confirm that the thyroid is making a normal amount of thyroid hormone, and is thus neither underactive (a condition known as hypothyroidism) or overactive (a condition known as hyperthyroidism). Several medical societies recommend measuring a TSH as part of routine health examinations, while others have found that it may not be worth the cost of doing it in everyone.

If a person has certain risk factors, the chance of developing hypothyroidism or hyperthyroidism is higher than in the general population. One such risk factor is having high blood levels of TPO antibodies. This study was performed to see how stable TSH blood tests are in adults with few risk factors for hypothyroidism or hyperthyroidism. The results can help guide often TSH blood tests should be measured in adults as part of routine health examinations.

THE FULL ARTICLE TITLE

Rosario PW and Calsolari MR. 2018 Serum TSH level stability after 5 years in euthyroid adults at low

risk for thyroid dysfunction. Arch Endocrinol Metab. May 17. pii: S2359-39972018005002003. doi: 10.20945/2359-3997000000037.

SUMMARY OF THE STUDY

This was a study of 1,426 adults living in Brazil who had no risk factors for having hypothyroidism or hyperthyroidism. All adults had a blood TSH level measured at baseline and again five years later. At the first sampling, over 96% had a normal TSH level. Of these, over 99% remained in the normal range five years later. All of the results were unchanged regardless of the individuals' gender or age.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In adults with no significant risk factors for developing hypothyroidism or hyperthyroidism and an initial TSH blood test in the normal range, it is unlikely to be abnormal if checked again five years later. The researchers suggest that in these individuals, repeating TSH screening within this time interval may not be necessary.

— Angela M. Leung, MD, MSc

ATA THYROID BROCHURE LINKS

Thyroid Function Tests: <https://www.thyroid.org/thyroid-function-tests/>
Hypothyroidism (Underactive): <https://www.thyroid.org/hypothyroidism/>
Hyperthyroidism (Overactive): <https://www.thyroid.org/hyperthyroidism/>

ABBREVIATIONS & DEFINITIONS

TSH: Thyroid stimulating hormone (TSH) is produced by the pituitary gland and is important for regulating thyroid function. It is also the best screening blood test to determine if the thyroid is functioning normally.

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.





THYROID BLOOD TESTS, continued

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.

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.





THYROID CANCER

Noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) are similar to benign tumors

BACKGROUND

Thyroid cancer is one of the most rapidly increasing cancers in the United States and over 90% of cases are papillary thyroid cancer. More recently it has become increasingly recognized that there are many different subtypes of papillary thyroid cancer, and that each subtype displays unique cellular features, genetic mutations and clinical behavior. Follicular variant papillary thyroid cancer, a term that was originally used to describe papillary thyroid cancers composed primarily of spherical “follicles” as opposed to the finger-like “papilla” of classical papillary thyroid cancer, is a very common subtype of papillary thyroid cancer. Despite the high incidence of the follicular variant papillary thyroid cancer, it has become a controversial and confusing entity because some cases behave similar to benign thyroid nodules called follicular adenomas whereas other cases are more aggressive cancers and can spread throughout the body.

Adding to the confusion, the term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced two years ago to describe select slow growing and well- circumscribed cases of follicular variant papillary thyroid cancers. Unlike other forms of papillary thyroid cancer, NIFTP tumors do not seem to grow or spread, and consequently may be able to be treated like benign thyroid nodules. The purpose of the following study was to characterize the genetic make-up and clinical behavior of NIFTP tumors and to compare them to both benign tumors and more invasive forms of papillary thyroid cancer.

THE FULL ARTICLE TITLE

Johnson DN et al 2018 Noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTPs) are genetically and biologically similar to adenomatous nodules and distinct from papillary thyroid carcinomas with extensive follicular growth. Arch Pathol Lab Med. Epub 2018 Mar 27. PMID: 29582677.

SUMMARY OF THE STUDY

Investigators reviewed pathology specimens from 61 follicular variant papillary thyroid cancers obtained between 2009 and 2016 from the University of Chicago. Based on their review they reclassified the tumors into: 32 cases (63%) of NIFTPs, 4 cases (7%) of an invasive encapsulated form of follicular variant papillary thyroid cancer, 14 cases (23%) of classic papillary thyroid cancer with extensive follicular growth and 11 cases (18%) of benign follicular adenomas. The investigators then extracted DNA from each specimen and analyzed for mutations in 50 cancer genes and finally the clinical outcome of each case was recorded.

The results showed that NIFTP tumors were similar to benign follicular adenomas. None of the 11 patients with follicular adenomas and none of the 32 cases of NIFTP tumors showed recurrence after initial treatment. All of the patients with papillary thyroid cancer with extensive follicular growth were disease free as well, whereas 3 of the 4 patients with invasive encapsulated form developed metastasis of their cancer. Mutations in the RAS cancer gene were found in 4 (36%) of follicular adenomas, 20 (62%) of NIFTP tumors and 3 (75%) of patients with the invasive encapsulated form. More importantly, no follicular adenoma and no NIFTP tumor had the BRAF V600E cancer gene mutation, a mutation that usually found in cancers that are more similar to classical papillary thyroid cancer.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

While this study is limited by the relatively small number of cases, the results suggest that there is great similarity between NIFTP tumors and benign follicular adenomas. Consequently, much like benign adenomas, patients with NIFTP tumors probably do not need completion thyroidectomy surgery or radioactive iodine therapy. The need for less invasive treatment will hopefully improve patient quality of life and reduce the psychologic stress that comes with a diagnosis of cancer.

— Philip Segal, MD





THYROID CANCER, continued

ATA THYROID BROCHURE LINKS

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

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).

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a new term has been used to describe a type of papillary thyroid cancer which is non-invasive. These cancers behave less aggressively than typical papillary thyroid cancer and have been shown to have low risk for recurrence and low risk for spread outside of the thyroid.

Follicular variant of papillary thyroid cancer: one of the subtypes of papillary thyroid carcinoma, which has been classified to three different forms: non-invasive follicular thyroid neoplasm with papillary-like nuclear features, invasive encapsulated and infiltrative FVPTC.

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

Mutation: A permanent change in one of the genes.

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.

Lymph node: bean-shaped organ that plays a role in removing what the body considers harmful, such as infections and cancer cells.

Total thyroidectomy: surgery to remove the entire thyroid gland.

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

More diagnostic criteria are needed to define noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

BACKGROUND

Thyroid cancer is one of the most rapidly increasing cancers in the United States and over 90% of cases are papillary thyroid cancer. More recently it has become increasingly recognized that there are many different subtypes of papillary thyroid cancer, and that each subtype displays unique cellular features, genetic mutations and clinical behavior. Follicular variant papillary thyroid cancer is a very common subtype of papillary thyroid cancer. Despite the high incidence of the follicular variant papillary thyroid cancer, it has become a controversial and confusing entity because some cases behave similar to benign thyroid nodules whereas other cases are more aggressive cancers and can spread throughout the body.

Adding to the confusion, the term noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was introduced two years ago to describe select slow growing and well-circumscribed cases of follicular variant papillary thyroid cancers. Unlike other forms of papillary thyroid cancer, NIFTP tumors do not seem to grow or spread, and consequently may be able to be treated like benign thyroid nodules. The goal of this study was to characterize the incidence of NIFTP at a large tertiary care endocrine surgery center and determine the cancerous potential of NIFTP.

THE FULL ARTICLE TITLE

Parente DN et al 2018 Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: is NIFTP truly benign? *World J Surg* 42:321–326.

SUMMARY OF THE STUDY

This study is from a single high-volume endocrine surgery center in Canada. Pathology reports from December 2004

to February 2013 were evaluated and all follicular variant papillary thyroid cancer specimens were reviewed by the endocrine pathology team to determine whether they met criteria for NIFTP. Excluded from analysis were other variants of papillary thyroid cancer. The primary outcome was spread to the lymph nodes of the neck at the time of diagnosis or during the follow up period or spread to other parts of the body.

A total of 4790 cases of papillary thyroid cancer were reviewed and 102 (2.1%) of cases met the criteria to be reclassified as NIFTP. The majority (77%) of patients were female and the average age was 46.8 years. Most patients (80%) underwent total thyroidectomy and 44% had radioactive iodine therapy. A total of 5 patients had evidence of spread to the lymph nodes at the time of the initial surgery. With an average follow-up of 5.7 years, 1 patient developed distant spread of the cancer to the lungs.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

While this study found that the incidence of NIFTP was lower than previously reported in other studies, the 6% incidence of spread outside of the thyroid is opposite to the reported benign nature of NIFTP. The presence of spread of the lymph nodes in the neck in 5% of this group at diagnosis suggests that more than just the pathology of the tumor should be taken into account before making a diagnosis of NIFTP. This is important as we learn more about the behavior of NIFTP tumors and determine whether we can really consider NIFTP as a benign tumor. More studies are needed to determine the best management strategies for patients with NIFTP.

— Alan P. Farwell, MD, FACE

ATA THYROID BROCHURE LINKS

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





THYROID CANCER, continued

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).

Follicular variant of papillary thyroid cancer: one of the subtypes of papillary thyroid carcinoma, which has been classified to three different forms: non-invasive follicular thyroid neoplasm with papillary-like nuclear features, invasive encapsulated and infiltrative FVPTC.

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): a new term has been used to describe a type of papillary thyroid cancer which is non-invasive. These cancers behave less aggressively than typical papillary thyroid cancer and have been shown to have low risk for recurrence and low risk for spread outside of the thyroid.

Lymph node: bean-shaped organ that plays a role in removing what the body considers harmful, such as infections and cancer cells.

Total thyroidectomy: surgery to remove the entire thyroid gland.

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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The American Thyroid Association (ATA) – Searching for Answers to Thyroid Cancer
April 17, 2016



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April 17, 2016



Anaplastic Thyroid Cancer – Support Research for Treatments
April 17, 2016



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THYROID CANCER

Is active surveillance reasonable for low-risk papillary thyroid microcarcinomas?

BACKGROUND

Surgery is usually recommended for patients with thyroid cancer. However, it is becoming clear from recent studies that observation without surgery, known as active surveillance, could be considered for some patients with low risk small papillary thyroid cancers. The Kuma Hospital in Japan introduced active surveillance as an alternative to the standard thyroid surgery for low risk papillary thyroid microcarcinomas (cancers < 1 cm on ultrasound) in 1993. Accumulating evidence over years has revealed that there is a low rate of cancer progression during active surveillance, and surgery performed later when progression is noted is safe. The goal of this study was to evaluate the physician acceptance and implementation patterns of active surveillance at Kuma Hospital, as a model that could be used for other institutions around the world.

THE FULL ARTICLE TITLE

Ito Y et al 2018 Trends in the implementation of active surveillance for low-risk papillary thyroid microcarcinomas at Kuma Hospital: gradual increase and heterogeneity in the acceptance of this new management option. *Thyroid* 28:488–495. Epub 2018 Apr 2. PMID: 29608416.

SUMMARY OF THE STUDY

This is a study of 4023 patients who were diagnosed with a low-risk papillary thyroid microcarcinomas and followed at Kuma Hospital between 1993 and 2016. Low-risk papillary thyroid microcarcinomas were defined as measuring 1 cm or less by ultrasound without aggressive features noted on biopsy, without ultrasound evidence for spread to the cancer to lymph nodes in the neck and not located in an area close to the trachea or recurrent laryngeal nerve with the potential of invading these structures. All patients were informed and could choose between active surveillance and immediate surgery. Patients who chose active surveillance had annual neck ultrasounds to evaluate for cancer progression, defined

as cancer growth of at least 3 mm or development of new lymph node metastases. Patients who showed cancer progression were recommended to undergo surgery.

The frequency of applying active surveillance initially increased significantly from 8% in 1993 to 63% in 1996, then it remained stable until 2007, when it started to increase again. There was a marked increase of up to 90% in the final period after 2014, when the first reports regarding the safety of active surveillance were published. There was a significant difference in the frequency of active surveillance use among surgeons, some surgeons recommending active surveillance in most patients during the entire period, while other surgeons performed surgery in most patients and adopted active surveillance only in the final period. Among surgeons, the active surveillance rate increased from 30% in the first period to 83% in the final period.

All endocrinologists showed a high rate of applying active surveillance compared to surgeons during the entire study period (86% vs. 58% for the entire period). In the final period, the use of active surveillance among endocrinologists was 97%.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This analysis showed that close observation without surgery (active surveillance) could be successfully implemented for low risk small papillary thyroid cancers at Kuma Hospital in Japan. However, it required a significant amount of time to be accepted by most surgeons and endocrinologists. Critical for active surveillance is the presence of significant thyroid ultrasound expertise. Large medical centers with high-quality ultrasound surveillance capacity for appropriate patient selection and early detection of cancer progression may be more appropriate to adopt this method.

—Alina Gavrilă, MD, MMSC





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/>

ABBREVIATIONS & DEFINITIONS

Papillary thyroid cancer (PTC): 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 (PMC): a papillary thyroid cancer smaller than 1 cm in diameter.

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

Trachea: a large tube made of cartilage rings located in the neck that conveys air to and from the lungs; the windpipe.

Recurrent laryngeal nerve: branch of the vagus nerve that supplies the muscles that can open the vocal cords.

Active surveillance: close observation without surgery for patient with small, low risk thyroid cancers

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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

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thyroid@thyroid.org

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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

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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 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

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.

Pregnancy and Thyroid Disease

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 ARE THE NORMAL CHANGES IN THYROID FUNCTION ASSOCIATED WITH PREGNANCY?

HORMONE CHANGES. A normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. These changes mean that laboratory tests of thyroid function must be interpreted with caution during pregnancy. Thyroid function tests change during pregnancy due to the influence of two main hormones: human chorionic gonadotropin (hCG), the hormone that is measured in the pregnancy test and estrogen, the main female hormone. HCG can weakly turn on the thyroid and the high circulating hCG levels in the first trimester may result in a slightly low TSH (called subclinical hyperthyroidism). When this occurs, the TSH will be slightly decreased in the first trimester and then return to normal throughout the duration of pregnancy (see Table 1). Estrogen increases the amount of thyroid hormone binding proteins in the serum which increases the total thyroid hormone levels in the blood since >99% of the thyroid hormones in the blood are bound to these proteins. However, measurements of "Free" hormone (that not bound to protein, representing the active form of the hormone) usually remain normal. The thyroid is functioning normally if the TSH, Free T4 and Free T3 are all normal throughout pregnancy.

SIZE CHANGES. The thyroid gland can increase in size during pregnancy (enlarged thyroid = goiter). However, pregnancy-associated goiters occur much more frequently in iodine-deficient areas of the world. It is relatively uncommon in the United States, which is thought to be relatively iodine-sufficient. If very sensitive imaging techniques (ultrasound) are used, it is possible to detect an increase in thyroid volume in some women. This is usually only a 10-15% increase in size and is not typically apparent on physical examination by the physician. However, sometimes a significant goiter may develop and prompt the doctor to measure tests of thyroid function.

WHAT IS THE INTERACTION BETWEEN THE THYROID FUNCTION OF THE MOTHER AND THE BABY?

For the first 10-12 weeks of pregnancy, the baby is completely dependent on the mother for the production of thyroid hormone. By the end of the first trimester, the baby's thyroid begins to produce thyroid hormone on its own. The baby, however, remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make the thyroid hormones. The World Health Organization recommends iodine intake of 200 micrograms/day during pregnancy to maintain adequate thyroid hormone production. The normal diet in the United States contains sufficient iodine so additional iodine supplementation is rarely necessary.

HYPERTHYROIDISM & PREGNANCY

WHAT ARE THE MOST COMMON CAUSES OF HYPERTHYROIDISM DURING PREGNANCY?

Overall, the most common cause (80-85%) of maternal hyperthyroidism during pregnancy is Graves' disease (see [Graves' Disease brochure](#)) and occurs in 1 in 1500 pregnant patients. In addition to other usual causes of hyperthyroidism (see [Hyperthyroidism brochure](#)), very high levels of hCG, seen in severe forms of morning sickness (hyperemesis gravidarum), may cause transient hyperthyroidism. The diagnosis of hyperthyroidism can be somewhat difficult during pregnancy, as 123I thyroid scanning is contraindicated during pregnancy due to the small amount of radioactivity, which can be concentrated by the baby's thyroid. Consequently, diagnosis is based on a careful history, physical exam and laboratory testing.

WHAT ARE THE RISKS OF GRAVES' DISEASE/ HYPERTHYROIDISM TO THE MOTHER?

Graves' disease may present initially during the first trimester or may be exacerbated during this time in a woman known to have the disorder. In addition to the classic symptoms associated with hyperthyroidism, inadequately treated maternal hyperthyroidism can result in early labor and a serious complication known as pre-eclampsia. Additionally, women with active Graves' disease during pregnancy are at higher risk of developing very severe hyperthyroidism known as thyroid storm. Graves' disease often improves during the third trimester of pregnancy and may worsen during the post partum period.



Pregnancy and Thyroid Disease

WHAT ARE THE RISKS OF GRAVES' DISEASE/HYPERTHYROIDISM TO THE BABY?

The risks to the baby from Graves' disease are due to one of three possible mechanisms:

1) UNCONTROLLED MATERNAL HYPERTHYROIDISM:

Uncontrolled maternal hyperthyroidism has been associated with fetal tachycardia (fast heart rate), small for gestational age babies, prematurity, stillbirths and possibly congenital malformations. This is another reason why it is important to treat hyperthyroidism in the mother.

2) EXTREMELY HIGH LEVELS OF THYROID STIMULATING IMMUNOGLOBULINS (TSI):

Graves' disease is an autoimmune disorder caused by the production of antibodies that stimulate thyroid gland referred to as thyroid stimulating immunoglobulins (TSI). These antibodies do cross the placenta and can interact with the baby's thyroid. Although uncommon (2-5% of cases of Graves' disease in pregnancy), high levels of maternal TSI's, have been known to cause fetal or neonatal hyperthyroidism. Fortunately, this typically only occurs when the mother's TSI levels are very high (many times above normal). Measuring TSI in the mother with Graves' disease is often done in the third trimester.

In the mother with Graves' disease requiring antithyroid drug therapy, fetal hyperthyroidism due to the mother's TSI is rare, since the antithyroid drugs also cross the placenta. Of potentially more concern to the baby is the mother with prior treatment for Graves' disease (for example radioactive iodine or surgery) who no longer requires antithyroid drugs. It is very important to tell your doctor if you have been treated for Graves' Disease in the past so proper monitoring can be done to ensure the baby remains healthy during the pregnancy.

3) ANTI-THYROID DRUG THERAPY (ATD). Methimazole (Tapazole) or propylthiouracil (PTU) are the ATDs available in the United States for the treatment of hyperthyroidism (see [Hyperthyroidism brochure](#)). Both of these drugs cross the placenta and can potentially impair the baby's thyroid function and cause fetal goiter. Historically, PTU has been the drug of choice for treatment of maternal hyperthyroidism, possibly because transplacental passage may be less than with Tapazole. However, recent studies suggest that both drugs are safe to use during pregnancy. It is recommended that the lowest possible dose of ATD be used to control maternal hyperthyroidism to minimize the development of hypothyroidism in the baby or neonate. Neither drug appears to increase the general risk of birth defects.

Overall, the benefits to the baby of treating a mother with hyperthyroidism during pregnancy outweigh the risks if therapy is carefully monitored.

WHAT ARE THE TREATMENT OPTIONS FOR A PREGNANT WOMAN WITH GRAVES' DISEASE/HYPERTHYROIDISM?

Mild hyperthyroidism (slightly elevated thyroid hormone levels, minimal symptoms) often is monitored closely without therapy as long as both the mother and the baby are doing well. When hyperthyroidism is severe enough to require therapy, anti-thyroid medications are the treatment of choice, with PTU being the historical drug of choice. The goal of therapy is to keep the mother's free T4 and free T3 levels in the high-normal range on the lowest dose of antithyroid medication. Targeting this range of free hormone levels will minimize the risk to the baby of developing hypothyroidism or goiter. Maternal hypothyroidism should be avoided. Therapy should be closely monitored during pregnancy. This is typically done by following thyroid function tests (TSH and thyroid hormone levels) monthly.

In patients who cannot be adequately treated with anti-thyroid medications (i.e. those who develop an allergic reaction to the drugs), surgery is an acceptable alternative. Surgical removal of the thyroid gland is only very rarely recommended in the pregnant woman due to the risks of both surgery and anesthesia to the mother and the baby.

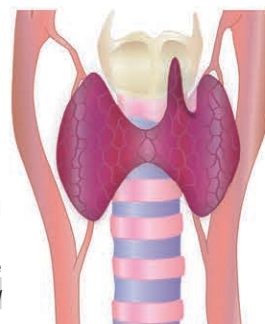
Radioiodine is contraindicated to treat hyperthyroidism during pregnancy since it readily crosses the placenta and is taken up by the baby's thyroid gland. This can cause destruction of the gland and result in permanent hypothyroidism.

Beta-blockers can be used during pregnancy to help treat significant palpitations and tremor due to hyperthyroidism. They should be used sparingly due to reports of impaired fetal growth associated with long-term use of these medications. Typically, these drugs are only required until the hyperthyroidism is controlled with anti-thyroid medications.

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





Pregnancy and Thyroid Disease

WHAT IS THE NATURAL HISTORY OF GRAVES' DISEASE AFTER DELIVERY?

Graves' disease typically worsens in the postpartum period, usually in the first 3 months after delivery. Higher doses of anti-thyroid medications are frequently required during this time. At usual, close monitoring of thyroid function tests is necessary.

CAN THE MOTHER WITH GRAVES' DISEASE, WHO IS BEING TREATED WITH ANTI-THYROID DRUGS, BREASTFEED HER INFANT?

Yes. PTU is the drug of choice because it is highly protein bound. Consequently, lower amounts of PTU cross into breast milk compared to Tapazole. It is important to note that the baby will require periodic assessment of his/her thyroid function to ensure maintenance of normal thyroid status.

TABLE 1:

	1ST TRIMESTER	2ND TRIMESTER	3RD TRIMESTER
TSH.....	Normal or Decreased	Normal.....	Normal
Free T4	Normal	Normal.....	Normal
Free T3	Normal	Normal.....	Normal
Total T4	High	High.....	High
Total T3	High	High.....	High
T3 Resin Uptake	Low.....	Low	Low
(INVERSE MEASURE OF PROTEIN BINDING)			
Free T4 Index (FT4I, FTI)...	Normal	Normal.....	Normal

HYPOTHYROIDISM & PREGNANCY

WHAT ARE THE MOST COMMON CAUSES OF HYPOTHYROIDISM DURING PREGNANCY?

Overall, the most common cause of hypothyroidism is the autoimmune disorder known as Hashimoto's thyroiditis (see *Hypothyroidism brochure*). Hypothyroidism can occur during pregnancy due to the initial presentation of Hashimoto's thyroiditis, inadequate treatment of a woman already known to have hypothyroidism from a variety of causes, or over-treatment of a hyperthyroid woman with anti-thyroid medications. Approximately, 2.5% of women will have a slightly elevated TSH of greater than 6 and 0.4% will have a TSH greater than 10 during pregnancy.

WHAT ARE THE RISKS OF HYPOTHYROIDISM TO THE MOTHER?

Untreated, or inadequately treated, hypothyroidism has been associated with maternal anemia (low red blood cell count), myopathy (muscle pain, weakness), congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants, and postpartum hemorrhage (bleeding). These complications are more likely to occur in women with severe hypothyroidism. Most women with mild hypothyroidism may have no symptoms or attribute symptoms they may have as due to the pregnancy.

WHAT ARE THE RISKS OF MATERNAL HYPOTHYROIDISM TO THE BABY?

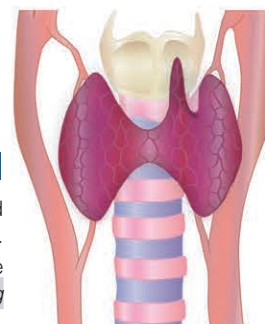
Thyroid hormone is critical for brain development in the baby. Children born with congenital hypothyroidism (no thyroid function at birth) can have severe cognitive, neurological and developmental abnormalities if the condition is not recognized and treated promptly. These developmental abnormalities can largely be prevented if the disease is recognized and treated immediately after birth. Consequently, all newborn babies in the United States are screened for congenital hypothyroidism so they can be treated with thyroid hormone replacement therapy as soon as possible.

The effect of maternal hypothyroidism on the baby's brain development is not as clear. Untreated severe hypothyroidism in the mother can lead to impaired brain development in the baby. This is mainly seen when the maternal hypothyroidism is due to iodine deficiency, which also affects the baby. However, recent studies have suggested that mild brain developmental abnormalities may be present in children born to women who had mild untreated hypothyroidism during pregnancy. At this time there is no general consensus of opinion regarding screening all women for hypothyroidism during pregnancy. However, some physician groups recommend checking a woman's TSH value either before becoming pregnant (pre-pregnancy counseling) or as soon as pregnancy is confirmed. This is especially true in women at high risk for thyroid disease, such as those with prior treatment for hyperthyroidism, a positive family history of thyroid disease and those with a goiter. Clearly, woman with established hypothyroidism should have a TSH test once pregnancy is confirmed, as thyroid hormone requirements increase during pregnancy, often leading to the need to increase the levothyroxine dose. If the TSH is normal, no further monitoring is typically required. This issue should be discussed further with your health care provider, particularly if you are contemplating pregnancy. Once hypothyroidism has been detected, the woman should be treated with levothyroxine to normalize her TSH and Free T4 values (see *Hypothyroidism brochure*).

FURTHER INFORMATION

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Pregnancy and Thyroid Disease

HOW SHOULD A WOMAN WITH HYPOTHYROIDISM BE TREATED DURING PREGNANCY?

The treatment of hypothyroidism in a pregnant woman is the same as for a man or non-pregnant woman, namely, adequate replacement of thyroid hormone in the form of synthetic levothyroxine (see *Hypothyroidism brochure*). It is important to note that levothyroxine requirements frequently increase during pregnancy, often times by 25 to 50 percent. Occasionally, the levothyroxine dose may double. Ideally, hypothyroid women should have their levothyroxine dose optimized prior to becoming pregnant. Women with known hypothyroidism should have their thyroid function tested as soon as pregnancy is detected and their dose adjusted by their physician as needed to maintain a TSH in the normal range. Thyroid function tests should be checked approximately every 6-8 weeks during pregnancy to ensure that the woman has normal thyroid function throughout pregnancy. If a change in levothyroxine dose is required, thyroid tests should be measured 4 weeks later. As soon as delivery of the child occurs, the woman may go back to her usual pre-pregnancy dose of levothyroxine. It is also important to recognize that prenatal vitamins contain iron and calcium that can impair the absorption of thyroid hormone from the gastrointestinal tract. Consequently, levothyroxine and prenatal vitamins should not be taken at the same time and should be separated by at least 2-3 hrs.



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