



Clinical Thyroidology[®] for the Public

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Schneider C et al 2018 Initial evaluation of thyroid dysfunction—are simultaneous TSH and fT₄ tests necessary? PLoS One 13:e0196631.PMID: 29709030.

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Appropriate treatment with thyroid hormone

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Lillevang-Johansen M et al 2018 Over- and under-treatment of hypothyroidism is associated with excess mortality: a register-based cohort study. Thyroid 28:566–574. Epub 2018 Apr 26. PMID: 29631518.

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Macerola E et al 2018 The mutational analysis in the diagnostic work-up of thyroid nodules: the real impact in a center with large experience in thyroid cytopathology. J Endocrinol Invest. Epub 2018 Apr 27. PMID: 29704233.

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Clinical Thyroidology for the Public

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EDITOR'S COMMENTS

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

December is [Thyroid and Development Awareness Month](#).

In this issue, the studies ask the following questions:

- Can the supplement biotin affect thyroid blood tests?
- Does the iodine status in the mother prior to pregnancy affect the brain development in the baby?
- Which is the best screening test for thyroid disorders: TSH alone or with FT₄?
- Is there an increased risk of death in patients with hypothyroidism?
- Can different thyroid cancer descriptions affect a patient's choice of therapy?
- Is testing for a small panel of gene mutations helpful in determining cancer risk in indeterminate thyroid nodules?

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





THYROID FUNCTION TESTS

Biotin supplement use is common and can lead to the false measurement of thyroid hormone in commonly used assays

BACKGROUND

As the pace of clinical care accelerates, there is an increased dependency on laboratory tests to help guide decisions in medicine. However, laboratory tests can be affected by substances that interfere with different assays, leading to false results which in turn can potentially result in the wrong treatments given to patients. One such substance that has become very common is the supplement biotin, a water-soluble B vitamin, which is taken for a variety of proposed health benefits. Most people get sufficient biotin from a well balanced diet, and a daily adequate intake for biotin is approximately 30 mcg/day. Multivitamins typically contain anywhere from 30-300 mcg biotin, while the supplements sold for hair and nail supplements usually range from 5,000 to 10,000 mcgs. High dose biotin is marketed as a means to improve hair and skin health.

There are numerous reports of biotin interference with laboratory testing, specifically with thyroid function tests. Most commonly, biotin use can result in falsely high levels of T₄ and T₃ and falsely low levels of TSH, leading to either a wrong diagnosis of hyperthyroidism or that the thyroid hormone dose is too high. The ATA has recommended that patients stop taking biotin for at least 2 days before thyroid testing to avoid the risk of having a misleading test.

At present, there are no studies that have looked into the extent of biotin use or the blood levels of biotin seen in the general patient population. This study reports the use of multivitamins and biotin supplements by outpatients in Rochester, Minnesota, and also reports plasma biotin levels in patients seen in the Mayo Clinic emergency department.

THE FULL ARTICLE TITLE

Katzman BM et al 2018 Prevalence of biotin supplement usage in outpatients and plasma biotin concentrations in patients presenting to the emergency department. Clin Biochem. Epub 2018 Jul 20. PMID: 30036510.

SUMMARY OF THE STUDY

The goal of this study was to determine how common

biotin consumption was in a population using a questionnaire and also measuring biotin levels in samples collected from patients presenting to the emergency department at Mayo Clinic. A total of 4000 questionnaires were distributed to patients scheduled for blood work during a period of one week (July 10-14, 2017), and 1944 patients returned completed questionnaires. There was a very similar number of male and female responders.

A total of 812 (41.8%) of patients reported taking multivitamins and 149 patients (7.7%) reported taking biotin supplements. Of these, 29.5% did not know what dose they were taking, 8.1% reported taking 10,000 mcgs, 14.8% reported 5,000mcgs, 18.1% reported 1,000 mcg and 47% reported taking less than 1000 mcgs.

Biotin was measured in residual plasma samples from specimens of patients presenting to the emergency department over a two week period representing 1442 unique blood samples. Biotin levels were unmeasurable in 737 samples, > 5ng/mL in 705 samples and >10 ng/mL in 107 (7.4%) of samples. Of these 107 patients, only 2 had biotin reported in their electronic medical records. A total of 14 patients had biotin concentrations >30 mg/mL.

The lowest concentration at which biotin has been reported to interfere in a commonly used assay is 10 ng/ mL, however the concentration at which it may interfere with other assays may be different (higher or lower).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that >7% of patients seen in the emergency department at Mayo Clinic had biotin levels sufficient to cause false lab results with commonly used laboratory assays that measure thyroid hormone. Further, only ~30% of those reported taking biotin or multivitamins. This study is important for patients because it shows the magnitude at which a commonly used supplement can cause false laboratory test results that can lead to misdiagnosis and wrong treatments.

— Jessie Block-Galarza, MD





THYROID FUNCTION TESTS, continued

ATA THYROID BROCHURE LINK

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

ABBREVIATIONS & DEFINITIONS

Biotin: a water-soluble B vitamin that is involved in a wide range of metabolic processes, both in humans and in other organisms, primarily related to the utilization of fats, carbohydrates, and amino acids. It is taken as a supplement frequently to promote skin, hair and nail health.

Thyroxine (T₄): the major hormone produced by the thyroid gland. T₄ gets converted to the active hormone T₃ in various tissues in the body.

Triiodothyronine (T₃): the active thyroid hormone, usually produced from thyroxine.

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.

DECEMBER Thyroid & Development Awareness Month



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THYROID AND PREGNANCY

Higher iodine intake in the mother during pregnancy is associated with higher child IQ

BACKGROUND

Thyroid hormones are important for growth and development. Iodine is a nutrient required to make thyroid hormones. Not enough iodine in the diet can result in lower thyroid hormones in the blood and can lead to hypothyroidism. In pregnancy, more iodine intake is needed to make thyroid hormones in both the mother and the baby. This is important for normal brain development in the baby. Very low levels of iodine in the mother during pregnancy have been associated with subsequent decreased child IQ and school performance. What is not known is whether low iodine levels before pregnancy have any effect on the baby. The goal of this study is to understand the importance of iodine nutrition before pregnancy. This study examines the relationship between iodine status in the mother before pregnancy and the subsequent brain function of the child.

THE FULL ARTICLE TITLE

Robinson SM et al. Preconception maternal iodine status is positively associated with IQ but not with measures of executive function in childhood. *J Nutr* 2018; 148:959–966. PMID: 29767745.

SUMMARY OF THE STUDY

This study followed women and their children in the United Kingdom and examined how iodine status in the mother affected their children overtime. For the study, 12,583 nonpregnant women, aged 20–34 years of age were interviewed and diet and lifestyle factors were assessed. Of those women, 3,158 became pregnant. These women

were followed through pregnancy and the children were followed until 6 to 7 years of age. Information collected before pregnancy included: height, weight, education, smoking status, and diet. Diet in the mother was also evaluated in early and late pregnancy, and iodine intake was calculated. A single spot urine sample was also collected from women at an average of 3.3 years before pregnancy to assess for iodine status and creatinine (a measure of how the kidney works). The Wechsler Abbreviated Scale of Intelligence (IQ test) was completed in 942 children ages 6 to 7. The final group included 654 mother-child pairs. Iodine status in the mother before pregnancy was not associated with gestational age at birth or with birth weight. Iodine status in the mother before pregnancy was positively associated with the child's IQ. Approximately 9% of women had a low urinary iodine levels before pregnancy and the IQ of their children was lower than women with higher urinary iodine levels before pregnancy.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Higher iodine intake in the mother before pregnancy is associated with an increased child IQ at 6 to 7 years of age. This study supports the link between low iodine status in the mother in pregnancy and poorer brain function in children as seen in other studies. This study highlights the importance of iodine nutrition prior to becoming pregnant. Further studies are needed to better understand the importance of low iodine status before pregnancy and the outcome on children.

— Priya Mahajan, MD

ATA THYROID BROCHURE LINKS

Iodine Deficiency: <https://www.thyroid.org/iodine-deficiency/>

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





THYROID AND PREGNANCY, continued

ABBREVIATIONS & DEFINITIONS

Iodine: an element found naturally in various foods that is important for making thyroid hormones and for normal thyroid function. Common foods high in iodine include iodized salt, dairy products, seafood and some breads.

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





THYROID FUNCTION TESTS

TSH alone would be a sufficient screening test for thyroid hormone abnormalities

BACKGROUND

Thyroid problems are common in adults. There are different recommendations on how to screen for abnormal thyroid hormone levels that may indicate a thyroid problem, and therefore, there are many variations in how this is done. Thyroid Stimulating Hormone (TSH) is the most commonly ordered test, with free thyroxine (FT₄) levels ordered at the same time as TSH in 38% of the cases. In a one-step approach, both TSH and FT₄ are measured initially. Alternatively, TSH is measured first, then FT₄ is measured only if TSH is abnormal in a two-step approach. The cost for testing thyroid function in the United States is high, estimated at \$1.6 billion every year. The present study was done to determine whether a one-step approach would be sufficient to screen for thyroid hormone abnormalities, and whether there is a clinical risk score that can be used to predictor risk of developing abnormal thyroid hormone levels.

THE FULL ARTICLE TITLE

Schneider C et al 2018 Initial evaluation of thyroid dysfunction—are simultaneous TSH and fT₄ tests necessary? PLoS One 13:e0196631.PMID: 29709030.

SUMMARY OF THE STUDY

The results of thyroid function tests from 4,471 adults in Bussleton, Australia from 1994 were studied using previously collected records. Those who were taking thyroid medications were excluded from the study. Participants with normal TSH were considered euthyroid (normal thyroid function), those with slightly high TSH and normal FT₄ were considered mildly hypothyroid (subclinical hypothyroidism), those with very high TSH or slightly high TSH with low FT₄ were considered severely hypothyroid (overt hypothyroidism). Participants with low TSH and normal FT₄ were considered mildly hyperthyroid (subclinical hyperthyroidism), and with low TSH and high FT₄ were considered severely hyperthyroid (overt hyperthyroidism).

The proportion of people with normal TSH and low or high FT₄ levels, who would have been missed with a one-step approach were calculated. Various characteristics of participants, including gender, age, smoking status, height, weight, body mass index (BMI), blood pressure, alcohol use, use of thyroid-affecting medications, and menopausal status, were used to determine whether these can be used to calculate a score to predict risk of thyroid hormone abnormalities.

The average age of participants was 51 years (range, 16.5-97) and 55% were women. This population was considered iodine-sufficient and mostly white. Of 4,471 adults, 35 (0.8%) had overt hypothyroidism, 86 (1.9%) subclinical hypothyroidism, 23 (0.5%) overt hyperthyroidism, and 170 (0.5%) subclinical hyperthyroidism. A total of 82 (1.8%) had normal TSH and low FT₄ levels, and 87 (1.9%) had normal TSH and high FT₄ levels. The FT₄ levels were very close to the normal range in a majority (144 participants, 85%) of 169 participants with normal TSH but low or high FT₄ levels.

Significant risk factors for hypothyroidism included being female, age 50 to 75 years, age > 75 years, and BMI ≥ 30kg/m². The only significant risk factor for hyperthyroidism was smoking status. However, both sets of risk factors did not have good level of prediction of thyroid hormone abnormalities.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Only 7% of adults needed both TSH and FT₄ to be checked to determine whether their thyroid hormone levels were abnormal. Even in those with low or high FT₄ but normal TSH, FT₄ levels were very close to normal range, and unlikely to have caused any clinical symptoms that warranted treatment.

Since the majority of patients did not need FT₄ levels to make the diagnosis of thyroid hormone abnormali-





THYROID FUNCTION TESTS, continued

ties, it would be most cost-effective to have a two-step approach in assessing thyroid dysfunction, where TSH is measured and FT₄ is measured only if TSH is abnormal. There are rare cases of hypothyroidism from pituitary

problem, where both TSH and FT₄ levels are low, but these patients typically have other clinical signs that would suggest such diagnosis.

— Sun Y. Lee, MD

ATA THYROID BROCHURE LINKS

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

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

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

ABBREVIATIONS & DEFINITIONS

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.

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

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

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

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

Overt Hyperthyroidism: clear hyperthyroidism with a decreased TSH and an increased T₄ levels.

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

Pituitary gland: this endocrine gland sits at the base of the brain and secretes hormones that control thyroid and adrenal function, growth and reproduction. The pituitary gland secretes TSH to control thyroid function.





HYPOTHYROIDISM

Appropriate treatment with thyroid hormone can decrease the excess death associated with hypothyroidism

BACKGROUND

Hypothyroidism causes a wide range of problems in the body, affecting vital systems like heart and blood vessels. Symptoms of hypothyroidism include feeling slow, sluggish, cold, puffy, constipated and dry skin. In its' extreme form, severe hypothyroidism, known as myxedema coma, can cause death. Hypothyroidism can also increase blood cholesterol levels. Because of this, studies have tried to determine the risk of death in patients with hypothyroidism. Some studies showed an increased risk while others showed either no risk or a decreased risk.

This study aimed to investigate the risk of death in patients with hypothyroidism as well as examining the effects of over- and under-treatment of hypothyroidism with thyroid hormone.

THE FULL ARTICLE TITLE

Lillevang-Johansen M et al 2018 Over- and under-treatment of hypothyroidism is associated with excess mortality: a register-based cohort study. *Thyroid* 28:566–574. Epub 2018 Apr 26. PMID: 29631518.

SUMMARY OF THE STUDY

The study was done in Denmark. Several large national registries were used to collect information about thyroid tests, diagnoses, and filled prescriptions between January 1, 1995 and January 1, 2011. Patients who had at least two elevated TSH levels within a 6-month period or one elevated TSH and two filled thyroid hormone prescriptions in the following year were included in the study. Patients who had thyroid surgery or radioactive iodine treatment, who had earlier hyperthyroidism or pituitary disease, younger than 18 years old, or who were lost to follow-up were excluded from the study. There were 3 groups: 1) hypothyroid patients who were treated with thyroid hormone (2235 individuals, 76.9%),

2) hypothyroid patients who were not treated (673 individuals, 23.1%) and 3) a group of people with normal thyroid function (232,260 individuals). The hypothyroidism group was further divided into 2 groups based on severity: mild and marked hypothyroidism.

There were more women in the hypothyroidism groups (68.1% to 85.6%) compared to those without thyroid problems (55.7%). In the hypothyroidism group, treated patients had higher TSH levels and the untreated group had more additional health problems. Almost all the patients in marked hypothyroidism group were treated with thyroid hormone (96% of females and 95% of males). On the other hand, in the mild hypothyroidism group, 71% of women and only 47% of men were treated. The death rate was significantly higher in the untreated hypothyroidism group compared to those with treated hypothyroidism and those without thyroid problems. Causes of death were similar. Periods of elevated TSH was associated with an increased risk of death in both treated and untreated groups. In the treated group, periods of low TSH (overtreatment) was also associated with an increased risk of death and had a greater impact.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study shows that untreated hypothyroidism was associated with an increased risk of death and appropriate treatment with thyroid hormone decreases this risk. This was true even in the group with mild hypothyroidism. Finally, even with treatment, if the dose of thyroid hormone is not enough, and especially if it is too much, the risk of death was higher. Patients and physicians should discuss treatment goals and make a clear monitoring plan. Regular TSH measurements and follow-ups are important to safely use thyroid hormone, especially to avoid over-treatment.

— Ebru Sulanc, MD, FACE





HYPOTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

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

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

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

ABBREVIATIONS & DEFINITIONS

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

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.

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.

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.





THYROID CANCER

Different thyroid cancer descriptions impact patient anxiety and treatment choices

BACKGROUND

Thyroid cancer is becoming increasingly diagnosed and is the fastest rising cancer in women. Many of these cases are of very small papillary thyroid cancers which may not be clinically meaningful and, thus, may not even need to be treated. Indeed, some physicians are now offering the chance to have the thyroid cancer be monitored (active surveillance), rather than having the cancer removed by surgery. However, a diagnosis of cancer produces a significant emotional response in most patients. Further, it is often difficult for patients to understand the difference between a cancer that can be easily treated and is unlikely to cause death (like most types of thyroid cancer) and a cancer that will require strong chemotherapy, cause hair loss and likely an early death. This study was to see how describing the papillary thyroid cancer in other terms might lead to less patient worry and therefore allow greater use of active surveillance of this low-risk cancer.

THE FULL ARTICLE TITLE

Nickel B et al Effect of a change in papillary thyroid cancer terminology on anxiety levels and treatment preferences: A randomized crossover trial. *JAMA Otolaryngol Head Neck Surg.* 2018 Oct 1;144(10):867-874.

SUMMARY OF THE STUDY

This study was an online survey given to 550 random adults in Australia that had not been diagnosed with thyroid cancer. These volunteers were asked to consider how anxious they were upon hearing different phrases used to describe a new diagnosis of papillary thyroid cancer. The following different phrases characterizing the

papillary thyroid cancer were used: “papillary thyroid cancer”, “papillary lesion”, or “abnormal cells”. They were then presented with three choices of treatment: removing the entire thyroid by surgery, removing only the lobe of the thyroid where the cancer was found, or active surveillance (monitoring the thyroid cancer with no surgery).

There were 550 volunteers who completed the online study (50.7% female, average age 49.9 years). Nearly 9% had a non-thyroid cancer diagnosis and >50% had at least one immediate family member with a cancer diagnosis. The researchers found that the words “papillary thyroid cancer” were associated with the most anxiety. This resulted in more individuals selecting some form of perhaps unnecessary thyroid surgery rather than active surveillance.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Rephrasing how physicians counsel patients regarding a diagnosis of low risk papillary thyroid cancer can influence how thyroid cancer is managed. Use of words other than “cancer” can lower patients’ anxiety about this diagnosis. This can allow patients to have greater comfort in knowing that some cases of low risk thyroid cancers do not necessarily require surgery. Physicians need to balance between providing appropriate information regarding a diagnosis and a patient’s anxiety with a diagnosis. This study provides insight as an approach that may be helpful to patients who are diagnosed with low risk thyroid cancer.

— Angela M. Leung, MD, MSc

ATA THYROID BROCHURE LINKS

Papillary and Follicular Thyroid Cancer: <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).

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



Watch how your donations help find answers to thyroid cancer



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

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Differentiated Thyroid Cancer – Support ATA's ongoing Research
April 17, 2016

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April 17, 2016

♥ 10



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

♥ 11

www.thyroid.org/donate/





THYROID NODULES

Can analysis of a small panel of genetic mutations on samples from thyroid biopsies help us to decide which nodules should be removed?

BACKGROUND

Thyroid nodules are common and are found in over 50% of patients, but thyroid cancer is rare. Thyroid biopsy is an important step in identifying which nodules are benign and which nodules require surgery (suspicious or cancerous on cytology). However, about 30% of the biopsies result in an indeterminate category, meaning that they cannot make a diagnosis based on the cells alone. In the past, many patients with indeterminate biopsies went to surgery, with resulting benign findings. In retrospect, these patients did not require surgery

Further testing has been proposed to categorize these indeterminate nodules into low risk or high risk for cancer. One of the methods used is to analyze the thyroid biopsy specimen for specific genetic mutations, known as molecular markers, which are seen in thyroid cancers. If the biopsy is negative for these mutations, the nodule is considered benign and surgery is not needed. If a mutation is present, the risk of cancer increases anywhere from 40-90%. While several commercially available panels test for a wide range of mutations, the 3 most common mutations associated with aggressive thyroid cancer are BRAF, RAS and TERT. This study evaluated whether analyzing the presence of a limited set of these known mutations could predict which nodules required surgery.

THE FULL ARTICLE TITLE

Macerola E et al 2018 The mutational analysis in the diagnostic work-up of thyroid nodules: the real impact in a center with large experience in thyroid cytopathology. *J Endocrinol Invest*. Epub 2018 Apr 27. PMID: 29704233.

SUMMARY OF THE STUDY

This study looked at a large number of patients (511) in Pisa, Italy who were evaluated by thyroid biopsy of one or more thyroid nodules (total 617 nodules) and performed

genetic testing on all samples looking for mutations in the genes BRAF, RAS and TERT. The genetic testing was not used to determine which patients would go to surgery. They then correlated the frequency and type of mutation to the final pathology in the 167 nodules from 126 patients who ended up having surgery.

The presence of one of the mutations was highly predictive of cancer in the final pathology. In the benign cytology category, 57 of a total of 425 nodules went to surgery and 8 turned out to be follicular variant papillary thyroid cancer. Of these 8, 5 had a RAS mutation. In the indeterminate category, 56 of a total 114 nodules went to surgery, 25 of which turned out to be cancer. In this group, 70% of the nodules with a mutation (1 BRAF, 11 RAS, 1 TERT) turned out to have cancer while only 33% of those without a mutation ended up with cancer. All of the patients in the suspicious or cancerous cytology categories had cancer found at the time of surgery. Of these, 63% of the nodules had mutations (25 BRAF, 2 RAS, 3 TERT).

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study showed that examining thyroid biopsy specimens for a small panel of genetic mutations was highly predictive of cancer on the final pathology. This was most helpful in the indeterminate cytology category, with RAS mutations the most common mutation identified and of those, 80% turned out to be cancer at surgery. Mutation analysis was not helpful in nodules with high-risk cytology categories since all these patients were found to have cancer at surgery. This study adds to the information regarding using molecular testing to further identify patients in whom biopsies are indeterminate that do not need surgery and to target those that would benefit the most from surgery.

— Marjorie Safran, MD





THYROID NODULES, continued

ATA THYROID BROCHURE LINKS

Fine Needle Aspiration Biopsy of Thyroid Nodules: <https://www.thyroid.org/fna-thyroid-nodules/>

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

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% are cancerous.

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

Indeterminate thyroid biopsy: this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS)) or when the diagnosis is a follicular or hurthle cell lesion. Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

Suspicious thyroid biopsy: this happens when there are atypical cytological features suggestive of, but not diagnostic for malignancy. Surgical removal of the nodule is required for a definitive diagnosis.

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.

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

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

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

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.





ATA Alliance for Thyroid Patient Education

GOAL

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

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

WHO WE ARE (in alphabetical order)

AMERICAN THYROID ASSOCIATION

www.thyroid.org

ATA Patient Resources:

<http://www.thyroid.org/thyroid-information/>

Find a Thyroid Specialist: www.thyroid.org

(Toll-free): 1-800-THYROID

thyroid@thyroid.org

BITE ME CANCER

<http://www.bitemecancer.org>

info@bitemecancer.org

GRAVES' DISEASE AND THYROID FOUNDATION

www.gdatf.org

(Toll-free): 877-643-3123

info@ngdf.org

LIGHT OF LIFE FOUNDATION

www.checkyourneck.com

info@checkyourneck.com

THYCA: THYROID CANCER SURVIVORS' ASSOCIATION, INC.

www.thyca.org

(Toll-free): 877-588-7904

thyca@thyca.org

THYROID CANCER ALLIANCE

www.thyroidcanceralliance.org

www.thyroidcancerpatientinfo.org

Rotterdam, The Netherlands

THYROID CANCER CANADA

www.thyroidcancercanada.org

416-487-8267

info@thyroidcancercanada.org

THYROID FEDERATION INTERNATIONAL

www.thyroid-fed.org

tfi@thyroid-fed.org





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We will use your email address to send you *Friends of the ATA e-news* and occasional email updates. We won't share your email address with anyone, and you can unsubscribe at any time.

www.thyroid.org



JOIN US

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.

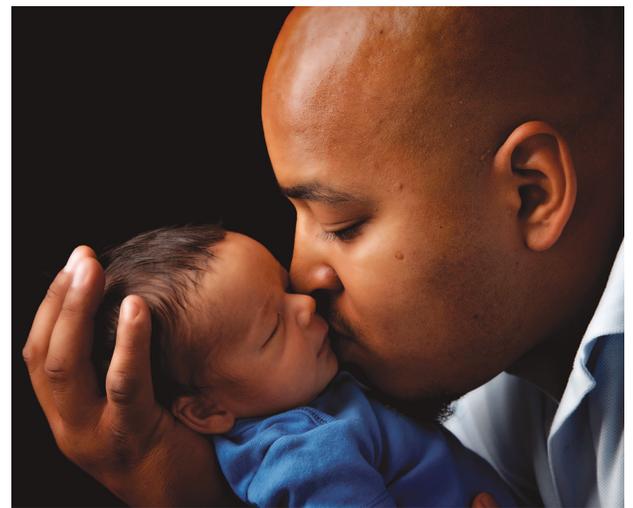


“The ATA was a valuable resource for our family when my dad was diagnosed with Anaplastic Thyroid Cancer. When you're faced with a detrimental diagnosis where even a few days can make the difference in life or death, understanding your options quickly is critical. The ATA website offers a one-stop shop 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.

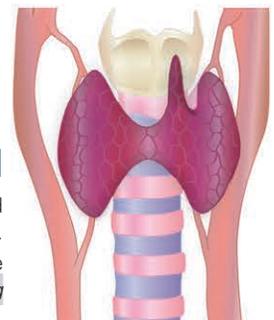
Radioiodine is contraindicated to treat hyperthyroidism during pregnancy since it readily crosses the placenta and is taken up by the baby's thyroid gland. This can cause destruction of the gland and result in permanent hypothyroidism.

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.

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*).

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
<small>(INVERSE MEASURE OF PROTEIN BINDING)</small>			
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.

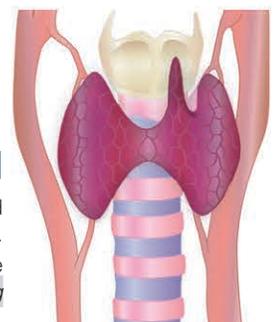
WHAT ARE THE RISKS OF HYPOTHYROIDISM TO THE MOTHER?

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.

FURTHER INFORMATION

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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

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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