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# Clinical Thyroidology for the Public

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### Environmental perchlorate exposure causes slight decreases in the mother's thyroid function during pregnancy

Some environmental chemicals like perchlorate, nitrate and thiocyanate affect the function of sodium iodine transporter and may cause problem with thyroid hormone production. In many studies, long term chronic exposure to perchlorate has not been shown to significantly alter thyroid hormone levels in adults. The goal of this study was to identify the effect of perchlorate on thyroid hormone levels of pregnant women.

Steinmaus C et al Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect. October 20, 2015 [Epub ahead of print].

### Pregnancy does not increase the size of papillary thyroid microcarcinomas

Since thyroid cancer is generally slow growing, some very small (<1cm) cancers are candidates for being watched and not operated on immediately. However, for women with small thyroid cancers that become pregnant, there is concern that the pregnancy might cause such small cancers to grow. This study followed a group of pregnant women with small thyroid cancers that were being watched to see if pregnancy caused a growth in their cancers.

Ito Y et al. Effects of pregnancy on papillary microcarcinomas of the thyroid re-evaluated in the entire patient series at Kuma Hospital. Thyroid 2016;26:156-60. Epub December 15, 2015.

### Low thyroid levels during pregnancy is associated with abnormal metabolism in the mother

It is clear that pregnant women with hypothyroidism have an increased risk of problems with their pregnancy as well as problems with their child's development. Only a few studies have investigated possible abnormalities in the women with hypothyroidism during pregnancy. The goal of this study is to compare the frequency of metabolic abnormalities in pregnant women with mild hypothyroidism and/or hypothyroxinemia with those seen in pregnant women with normal thyroid function.

Knight BA et al. Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters. Eur J Endocrinol 2016;174:51-7.

### Which patients with diabetes should be routinely screened for thyroid diseases?

It is well known that patients with type 1 diabetes mellitus have a greater risk to develop autoimmune thyroid disease, especially Hashimoto's thyroiditis. However, the association between type 2 diabetes mellitus, which is not an autoimmune disease, and autoimmune thyroid disease is less clear. The goal of the study was to investigate the association between type 1 and 2 diabetes mellitus with hypothyroidism and hyperthyroidism.

Fleiner HF et al. Prevalence of thyroid dysfunction in autoimmune and type 2 diabetes: the population-based HUNT Study in Norway. J Clin Endocrinol Metab. November 19, 2015 [Epub ahead of print].

### Metabolic parameters in euthyroid and hypothyroid women on levothyroxine are different

It is known that long-term suppression of TSH with levothyroxine leads to bone loss and has negative cardiac effects, but metabolic function changes of thyroid hormone replacement are not widely understood. This study was done to find if levothyroxine doses high enough to suppress TSH lead to metabolic changes in body composition or energy expenditure.

Samuels MH et al. Effects of levothyroxine replacement or suppressive therapy on energy expenditure and body composition. Thyroid. December 23, 2015 (Epub ahead of print).

### "No Detectable TSH" doesn't always mean a patient has hyperthyroidism or central hypothyroidism

When a TSH is be found to be very low or not detectable, it usually indicates hyperthyroidism or, if the $FT_4$ is low, central hypothyroidism. However, a rare cause could be a mutation in the TSH molecule. The current article describes a new family carrying such a mutation.

Pappa T et al TSHβ variant with impaired immunoreactivity but intact biological activity and its clinical implications. Thyroid 2015;25:869-75. Epub June 15, 2015.

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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 will be providing summaries of research studies that were discussed in a recent issue of *Clinical Thyroidology*, a publication of the American Thyroid Association for physicians. These summaries are present in lay language to allow the rapid dissemination of thyroid research to the widest possible audience. This means that you are getting the latest information on thyroid research and treatment almost as soon as your physicians. As always, we are happy to entertain any suggestions to improve *Clinical Thyroidology for the Public* so let us know what you want to see.

We also provide even faster updates of late-breaking thyroid news through Twitter at @thyroidfriends and on Facebook. Our goal is to provide patients with the tools to be the most informed thyroid patient in the waiting room.

Also check out our friends in the Alliance for Thyroid Patient Education. The Alliance member groups consist of: the *American Thyroid Association*, *Bite Me Cancer*, the *Graves' Disease and Thyroid Foundation*, the *Light of Life Foundation*, *ThyCa: Thyroid Cancer Survivors Association*, *Thyroid Cancer Canada and Thyroid Federation International*.

**March is** Medullary Thyroid Cancer Awareness Month.

**In this issue, the studies ask the following questions:**

1. Does environmental perchlorate affect the mother's thyroid function during pregnancy?
2. Does pregnancy affect the growth of small papillary thyroid cancers?
3. Do low thyroid levels affect metabolic parameters in the mother during pregnancy?
4. Which patients with diabetes should be routinely screened for thyroid disease?
5. Does levothyroxine treatment affect energy expenditure in hypothyroid women?
6. What are the causes of a suppressed TSH?

We welcome your feedback and suggestions. Let us know what you want to see in this publication. I hope you find these summaries interesting and informative.

**— Alan P. Farwell, MD, FACE**

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## THYROID AND PREGNANCY

# Environmental perchlorate exposure causes slight decreases in the mother's thyroid function during pregnancy

### BACKGROUND

Iodine is an important part of thyroid hormone and it is actively transported into thyroid cells by special gates located on the cell wall, called "sodium iodine transporters". Some environmental chemicals like perchlorate, nitrate and thiocyanate affect the function of sodium iodine transporter and may cause problem with thyroid hormone production. The amount of perchlorate in the environment is very controversial, as it is a major component of rocket fuel and high concentrations of perchlorate are found in regions around air force and other military bases. In many studies, long term chronic exposure to perchlorate has not been shown to significantly alter thyroid hormone levels in adults.

However, the story may be different in developing babies during pregnancy. Thyroid hormone is important for brain development before and after birth. The production of thyroid hormone is increased in pregnant women to meet with the higher demand of pregnancy. Some studies have shown that even modest decline of thyroid hormone level in pregnancy might be enough to cause changes like lowering IQ in offspring. The goal of this study was to identify the effect of perchlorate on thyroid hormone levels of pregnant women.

### THE FULL ARTICLE TITLE

Steinmaus C et al Thyroid hormones and moderate exposure to perchlorate during pregnancy in women in Southern California. Environ Health Perspect. October 20, 2015 [Epub ahead of print].

### SUMMARY OF THE STUDY

This study was conducted in San Diego County, California. The urinary level of Iodine and perchlorate and the blood level of thyroid hormone, TSH, TPO antibody and Thyroglobulin antibody were measured in 1476 women in early stages of pregnancy.

The statistical analysis showed women with higher level of perchlorate had relatively lower levels of thyroid hormone and higher level of TSH. This effect was modest and not enough to cause major thyroid dysfunction in most women. However, this correlation was more significant in women with a higher level of urinary iodine and in women with positive levels of TPO antibody and Thyroglobulin antibody. The same effect was seen for nitrate and thiocyanate.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY

This study showed that environmental exposure to perchlorate, thiocyanate and nitrate might cause slight changes in thyroid hormone production. The effect would be more concerning in individuals with positive TPO antibody and Thyroglobulin antibody (basically women who are prone to develop thyroid dysfunction). Considering the large number of pregnant women exposed to these substances and the critical role of thyroid hormone in pregnant mother and her unborn baby, attention to this matter is important. Public effort to minimize the contamination of water supply and other forms of environmental exposures to these chemicals is essential.

— Shirin Haddady, MD

### ATA THYROID BROCHURE LINKS

Thyroid Disease And Pregnancy: http://www.thyroid.org/thyroid-disease-pregnancy/

### ABBREVIATIONS AND DEFINITIONS

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

TPO antibodies: 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.

Thyroglobulin 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.

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## THYROID CANCER

# Pregnancy does not increase the size of papillary thyroid microcarcinomas

### BACKGROUND

Thyroid cancer is the fastest rising cancer in women. Since thyroid cancer is generally slow growing, some very small (<1cm) cancers are candidates for being watched and not operated on immediately (papillary microcarcinomas). However, for women with small thyroid cancers that become pregnant, there is concern that the pregnancy might cause such small cancers to grow. This is because of the high levels of pregnancy hormone known as hCG, which is known to stimulate growth of the thyroid gland. This study followed a group of pregnant women with small thyroid cancers that were being watched to see if pregnancy caused a growth in their cancers.

### THE FULL ARTICLE TITLE

Ito Y et al. Effects of pregnancy on papillary microcarcinomas of the thyroid re-evaluated in the entire patient series at Kuma Hospital. Thyroid 2016;26:156-60. Epub December 15, 2015.

### SUMMARY OF THE STUDY

Over a 20-year period, 50 pregnant women at Kuma hospital in Japan with small thyroid cancers were followed during and after their pregnancy for growth of their thyroid cancers. All patients had an ultrasound to evaluate their small cancer within 1 year before their pregnancy and within 1 year after giving birth. Some patients also had an additional ultrasound during their pregnancy. The researchers were looking to see if the cancer grew by 3mm or more during the pregnancy. The same radiologist reviewed all of the images without knowing the dates of the studies or the names of the patients.

For 90% of the women, their small cancers did not change in size during their pregnancy. In 4 patients, the cancers grew by 3mm or more and 2 of those 4 patients then had surgery for their cancer (they were 1.7cm and 1.8cm) In 1 patient, the cancer actually shrunk by 3mm. Over the 20 years of the study, 6 more women had their thyroid removed for different reasons: 2 by choice, 1 for an overactive thyroid, 1 for an enlarging thyroid gland, and 2 after they were found to have abnormal lymph nodes during annual follow-up exams.

### WHAT ARE THE IMPLICATIONS OF THE STUDY?

This study shows that it is safe to watch small cancers during pregnancy. This means that if you have a known, small thyroid cancer it is ok to get pregnant. Moreover, if a small thyroid cancer is discovered during your pregnancy it is ok to wait until after surgery to have it treated.

— Melanie Goldfarb MD, MS, FACS, FACE

### ATA THYROID BROCHURE LINKS

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

Thyroid Cancer: http://www.thyroid.org/thyroid-cancer/

### ABBREVIATIONS AND DEFINITIONS

Thyroid Ultrasound: a common imaging test used to evaluate the structure of the thyroid gland. Ultrasound uses soundwaves to create a picture of the structure of the thyroid gland and accurately identify and characterize nodules within the thyroid. Ultrasound is also frequently used to guide the needle into a nodule during a thyroid nodule biopsy.

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

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## HYPOTHYROIDISM AND PREGNANCY

# Low thyroid levels during pregnancy is associated with abnormal metabolism in the mother

### BACKGROUND

It is clear that pregnant women with clear hypothyroidism (low thyroxine level and increased TSH level) have an increased risk of problems with their pregnancy as well as problems with their child's development, especially in brain development. Multiple studies have also reported that mild hypothyroidism (normal thyroxine level and increased TSH level) can cause the same problems at a lower rate. There are few, if any studies looking at the effects of hypothyroxinemia (low thyroxine level and normal TSH level) during pregnancy. Only a few studies have investigated possible abnormalities in the mother women with hypothyroidism or hypothyroxinemia during pregnancy. In particular, metabolic abnormalities, such as abnormal weight gain, increased triglyceride (fat) levels and a tendency toward diabetes, are frequently seen in non-pregnant patients with hypothyroidism. The goal of this study is to compare the frequency of metabolic abnormalities in pregnant women with mild hypothyroidism and/or hypothyroxinemia with those seen in pregnant women with normal thyroid function.

### THE FULL ARTICLE TITLE

Knight BA et al. Maternal hypothyroxinaemia in pregnancy is associated with obesity and adverse maternal metabolic parameters. Eur J Endocrinol 2016;174:51-7.

### SUMMARY OF THE STUDY

This is a study of 956 healthy, non-diabetic, white pregnant women who were enrolled in the Exeter Family Study of Childhood Health, UK from 1999 to 2004. The average age was 30.1 years and the average body mass index (BMI) was 27.9 kg/m2. Height and weight were measured and fasting blood samples for thyroid and metabolic tests were collected at 28 weeks of pregnancy. A total of 133 (13.9%) women had subclinical hypothyroidism and 82 (8.6%) had hypothyroxinemia.

Women with hypothyroxinemia had higher BMI, glucose and triglyceride levels than women with normal thyroid function. There was no difference in these parameters between women with mild hypothyroidism and those with normal thyroid function.

In the entire group of pregnant women, the lower the free $T_4$ levels, the higher the BMI, glucose and triglyceride levels. TSH levels in the mother did not correlate with any metabolic parameter.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study demonstrates that hypothyroxinemia in the mother is associated with worse metabolic abnormalities, including increased obesity and higher glucose and triglyceride levels as compared to pregnant women with normal thyroid function, similar to findings of a prior smaller study. Surprisingly, this study showed no difference in metabolic abnormalities between pregnant women with subclinical hypothyroidism and those with normal thyroid function. It is not known whether obesity in the mother results in the thyroid abnormalities and metabolic changes or whether the thyroid abnormalities causes obesity and the metabolic changes in pregnancy. Further studies are needed to find the free $T_4$ threshold to diagnose maternal hypothyroxinemia and whether thyroid hormone treatment for this condition has benefits for either the mother or the baby.

— Alina Gavrila, MD, MMSC

### ATA THYROID BROCHURE LINKS

Hypothyroidism: http://www.thyroid.org/hypothyroidism/

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

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

## HYPOTHYROIDISM AND PREGNANCY, continued

### ABBREVIATIONS & DEFINITIONS

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

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

Hypothyroxinemia: a condition characterized by a low thyroxine ($T_4$) level in the blood with a normal TSH level.

Thyroxine ($T_4$): the major hormone produced by the thyroid gland. $T_4$ gets converted to the active hormone $T_3$ in various tissues in the body. Free $T_4$ is the $T_4$ that is not bound to proteins and affects the function of different body tissues.

Triiodothyronine ($T_3$): 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.

Metabolism: all the chemical processes in the body, especially those that cause food to be processed to produce energy and result in body growth.

Body-mass index (BMI): a standardized measure of obesity calculated by dividing the weight by the square of the height. A normal BMI is 18.5-24.9, overweight is 25-30 and obese is >30 kg/m2.

Triglycerides: a major form of fat circulating in the blood and stored by the body.

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## AUTOIMMUNE THYROID DISEASE

# Which patients with diabetes should be routinely screened for thyroid diseases?

### BACKGROUND

Autoimmune diseases occur when the immune system, which usually attacks germs and bacteria, gets confused and attacks our own bodies. Type 1 diabetes mellitus is an autoimmune disease where the insulin-producing cells in the pancreas are destroyed. Hashimoto's thyroiditis is an autoimmune disease where the thyroid cells are destroyed while Graves' disease is an autoimmune disease where the immune system turns on the thyroid cells. Patients with type 1 diabetes mellitus have a greater risk to develop autoimmune thyroid disease, especially Hashimoto's thyroiditis. However, the association between type 2 diabetes mellitus, which is not an autoimmune disease, and autoimmune thyroid disease is less clear. The goal of the study was to investigate the association between type 1 and 2 diabetes mellitus with hypothyroidism and hyperthyroidism.

### THE FULL ARTICLE TITLE

Fleiner HF et al. Prevalence of thyroid dysfunction in autoimmune and type 2 diabetes: the population-based HUNT Study in Norway. J Clin Endocrinol Metab. November 19, 2015 [Epub ahead of print].

### SUMMARY OF THE STUDY

The adult population of Nord-Trøndelag in Norway gets surveyed frequently trough the HUNT study. Surveys adults between 1995 and 1997 (HUNT2) and adults between 2006 and 2008 (HUNT3) were included. Participants reported whether they had diabetes mellitus, hypothyroidism or hyperthyroidism and provided a non-fasting blood sample. They also included data from the Norwegian Prescription Database, linking prescription refills with participants after 2004. Antibodies for autoimmune diabetes mellitus or autoimmune thyroid disease were obtained, as well as TSH measurement to evaluate thyroid function. For the analysis, patients older than 40 years were included. Both, the HUNT2 and HUNT3 databases showed that women and men with type 1 diabetes had a significant increased risk to have hypothyroidism (about twice the risk). The HUNT3 database showed that men with type 1 diabetes had 4 times higher chance of having hypothyroidism, and women with type 1 diabetes had twice the chance of having this same condition. Also, women and men with type 1 diabetes had a higher risk to develop hyperthyroidism in the HUNT2 database, while in the HUNT3 database the association was only present in men. In addition, only men with type 2 diabetes had an increased risk of having hyperthyroidism in the HUNT2 database. There was no association between type 2 diabetes and hypothyroidism in both HUNT2 and 3.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

This study confirms the importance of obtaining screening TSH level in men and women with type 1 diabetes mellitus, to screen for hypothyroidism and hyperthyroidism. In contrast, it is not necessary to obtain TSH levels in every patient with type 2 diabetes. However, it is interesting to note that men with type 2 diabetes seem to be at higher risk to develop hyperthyroidism, although this needs to be confirmed in other populations. In any event, this study shows that it is important for patients with diabetes to be aware of symptoms and signs associated with thyroid diseases.

— Liuska Pesce, MD

### ATA THYROID BROCHURE LINKS

Hypothyroidism: http://www.thyroid.org/hypothyroidism/

Hyperthyroidism: http://www.thyroid.org/hyperthyroidism/

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

### ABBREVIATIONS & DEFINITIONS

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

## AUTOIMMUNE THYROID DISEASE, continued

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

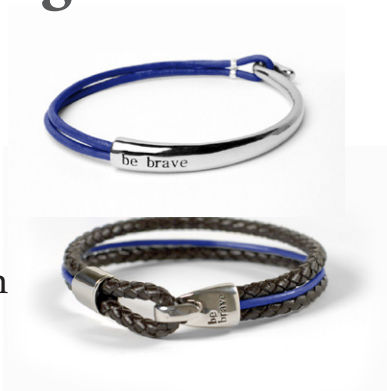
Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Diabetes mellitus: A condition where there is high blood sugar because of lack of insulin (type 1 diabetes) or inability of insulin to work properly (type 2 diabetes)

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.

# 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 February is **Medullary Thyroid Cancer Awareness Month** and a bracelet is available through the ATA Marketplace to support thyroid cancer awareness and education related to thyroid disease.



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## HYPOTHYROIDISM

# Metabolic parameters in euthyroid and hypothyroid women on levothyroxine are different

### BACKGROUND

It is known that long-term suppression of TSH with levothyroxine leads to bone loss and has negative cardiac effects, but metabolic function changes of thyroid hormone replacement are not widely understood. Metabolism is measured by determining the resting energy expenditure (REE). It is thought that doses of thyroid hormone more than required for maintaining a normal TSH may increase metabolism, REE and food intake and decrease lean body mass. Indeed, previous studies have shown that REE was higher in patients on TSH suppressive doses of thyroid hormone but these studies were done for short time frames, and some used $T_3$ replacement or combination $T_4/T_3$ rather than $T_4$ alone.

This study was done to be more thorough in its measurements and estimates of energy expenditure. It also compared 3 groups: healthy controls, hypothyroid women on typical levothyroxine doses, and hypothyroid women on suppressive doses of levothyroxine.

This study was done to find if levothyroxine doses high enough to suppress TSH lead to metabolic changes in body composition or energy expenditure.

### THE FULL ARTICLE TITLE

Samuels MH et al. Effects of levothyroxine replacement or suppressive therapy on energy expenditure and body composition. Thyroid. December 23, 2015 (Epub ahead of print).

### SUMMARY OF THE STUDY

A total of 26 women on suppressive levothyroxine doses, 80 women on long-term levothyroxine replacement therapy with normal TSH levels and 16 euthyroid women not on levothyroxine were evaluated. The TSH-suppressive group was comprised of women treated for low risk thyroid cancer who were without evidence of disease (16) and women were over-treated for hypothyroidism after radioactive iodine therapy (5) or for primary hypothyroidism (5). The replacement group consisted of women hypothyroid due to primary hypothyroidism (62), primary hypothyroidism plus lobectomy for benign reasons (4), post-radioactiveiodine hypothyroidism for Grave's disease (9), post-partum thyroiditis followed by permanent hypothyroidism (3), or thyroidectomy for nodular goiter or very low risk thyroid cancer (2). The healthy group was comprised of 16 healthy women without thyroid nodules or thyroid dysfunction.

The three groups were similar in age (39-41 years old) and BMI (average 25-27 years old). The TSH was similar in the healthy control group and the hypothyroid group on usual replacement (2.13 vs 2.08). The TSH was lower in the suppressive group (0.14 +/- 0.02). Free $T_4$ was highest in the suppressive TSH group, with the next highest levels in the euthyroid replacement group, then lowest in the normal controls. The free $T_3$ values were similar in the suppressive TSH group and the normal controls, and lower in the euthyroid replacement group. Body composition (including lean body mass, fat mass, % fat mass) was not different in the three groups. Dietary intake and physical activity were also the same in all groups. However, REE was lower by 6% in the levothyroxine group with normal TSH values than the suppressive TSH group and 4% lower than normal controls. The REE correlated with free $T_3$ levels, but not TSH or free $T_4$ values.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

Women on suppressive doses of levothyroxine have similar metabolic profiles to healthy controls. There was no lean muscle mass loss, fat loss, or higher REE with higher than physiologic doses of thyroid hormone. No positive or negative effects on body composition were noted in women on suppressive doses of levothyroxine alone.

The study raises more questions about REE in patients with normal TSH values on levothyroxine replacement. REE was slightly lower in this group, but this group did not have different levels of BMI or body composition, reassuringly. However, the free $T_3$ levels were lower, which may raise further questions about using $T_3$ in combination with free $T_4$. It should be noted that previous studies of combination therapy ($T_4$ plus $T_3$) have not shown any

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## HYPOTHYROIDISM, continued

differences in weight from $LT_4$ monotherapy. More studies will be helpful to determine risks and benefits before combination therapy can be widely accepted.

— Julie Hallanger Johnson, MD

### ATA THYROID BROCHURE LINKS

Thyroid and Weight: http://www.thyroid.org/thyroid-and-weight/

### ABBREVIATIONS & DEFINITIONS

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.

TSH: thyroid stimulating hormone — produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

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

Triiodothyronine ($T_3$): the active thyroid hormone, usually produced from thyroxine, available in pill form as Cytomel™.

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

Resting energy expenditure (REE): general procedure done to measure metabolism and metabolic rate

Body Composition: The human body is composed of fat mass, muscle mass (lean body mass) and bone mass. Total body water is included in the measurements of muscle mass.

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## THYROID FUNCTION TESTS

# "No Detectable TSH" doesn't always mean a patient has hyperthyroidism or central hypothyroidism

### BACKGROUND

The most frequently ordered test to screen patients for thyroid disease is the TSH. This hormone is released by the pituitary gland in response to the blood levels of active thyroid hormones (free $T_4$ and free $T_3$). TSH levels are opposite the thyroid hormone levels. Therefore, if the blood thyroid hormone levels are low, the TSH will be elevated and vice versa.

Occasionally, when screening a person who does not appear to have obvious thyroid disease, a TSH will be found to be very low or not detectable. In those cases, if the free $T_4$ is low, one might consider the diagnosis of central hypothyroidism (a problem with the pituitary gland) or the effect of another illness on TSH levels. If the free $T_4$ is normal or high, then a diagnosis of hyperthyroidism might be considered. However, this study illustrates a different diagnostic possibility, showing that the physician must keep an open mind when evaluating thyroid tests, especially when the patient does not have any symptoms.

In a prior study, a group of 20 patients who had a TSH that was not detectable by the commonly used assays, was found to have a mutation involving one of the chains that make up the TSH molecule. The TSH with this mutation was found to have normal function, but almost half of the patients were inappropriately treated because their TSH levels were not detectable.

The current article describes all studies done on a new family carrying the same mutation, and reports results that indicate that the mutation described changes only a very small portion of the molecule that is needed for the attachment of the TSH to the antibodies used in the assays, therefore TSH is not detected although is present in normal quantities and has normal function.

### THE FULL ARTICLE TITLE

Pappa T et al TSHβ variant with impaired immunoreactivity but intact biological activity and its clinical implications. Thyroid 2015;25:869-75. Epub June 15, 2015.

### SUMMARY OF THE STUDY

The first member of the family that was studied was a 4 year old boy. He had a TSH that was not detectable, a free $T_4$, free $T_3$ and total $T_4$ that were normal. His 10 year old brother had identical thyroid tests. Their mother, older brother and sister had a normal TSH. The father declined testing. None of them had evidence of thyroid disease.

Their blood samples were analyzed by 5 different available commercial assays (that use different technologies and reagents).In addition, studies were done to make sure that there was no evidence of another substance that was interfering with the tests. Computer modeling was done that showed that the variant TSH behaved normally once it attached to the active site at its receptor.

### WHAT ARE THE IMPLICATIONS OF THIS STUDY?

As mentioned before, the samples from this family were analyzed using 5 different commercially available assays. The two boys, who were homozygous for the mutation described, did not have a detectable TSH in two of the assays, but normal in other three. Therefore, after all results were evaluated, it was concluded that the mutation does not affect function, but it does not allow the TSH to interact with the antibodies used for detection in some commercial assays.

This study is important for patients because it shows that patients who have these types of mutations may be told that they have thyroid disease because their TSH is low and that they need treatment, when actually their thyroid function is normal. This particular mutation may be present in 0.2% to 0.3% of the general population, and may be up to 5 times more common in individuals from Bangladesh, India, Sri Lanka and Pakistan.

In cases like this, when an individual does not appear to have a thyroid problem yet the TSH is very low or not detectable, and the rest of the thyroid function panel is normal, it may be worth repeating the TSH at a facility that uses a different assay.

— Jessie Block-Galarza, MD

### ATA THYROID BROCHURE LINKS

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

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## THYROID FUNCTION TESTS, continued

### ABBREVIATIONS & DEFINITIONS

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

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.

Homozygous: Having identical pairs of genes for a particular hereditary characteristic.

Mutation: A permanent change in one of the genes.

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

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

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.

TSH receptor: A molecule (protein) located on the thyroid cell surface that binds TSH and stimulates the production of the thyroid hormones within the thyroid cell.

# 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 towards the improvement of thyroid education and resources for patients.

## WHO WE ARE (in alphabetical order)

- **American Thyroid Association**
- **Bite Me Cancer**
- **Graves' Disease and Thyroid Foundation**
- **Light of Life Foundation**
- **ThyCa: Thyroid Cancer Survivors' Association, Inc.**
- **Thyroid Cancer Canada**
- **Thyroid Federation International**

## AMERICAN THYROID ASSOCIATION

**www.thyroid.org**
ATA Patient Resources: http://www.thyroid.org/patients/
Find a Thyroid Specialist: www.thyroid.org
Phone (toll-free): 1-800-THYROID
e-mail: thyroid@thyroid.org

**ATA Mission:** The ATA leads in promoting thyroid health and understanding thyroid biology.
**ATA Vision:** The ATA is the leading organization focused on thyroid biology and the prevention and treatment of thyroid disorders through excellence and innovation in research, clinical care, education, and public health.
**ATA Values:** The ATA values scientific inquiry, clinical excellence, public service, education, collaboration, and collegiality.

To further our mission, vision and values the ATA sponsors "Friends of the ATA" online to advance the information provided to patients and the public such as this publication, *Clinical Thyroidology for the Public*. We welcome your support.

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AMERICAN THYROID ASSOCIATION FOUNDED 1923

Light of Life Foundation checkyourneck.com

GRAVES' DISEASE & THYROID FOUNDATION

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

Thyroid Federation International

Thyroid Cancer Canada
Cancer de la thyroïde Canada

BITE ME cancer® attitude is everything.

# ATA Alliance for Thyroid Patient Education

**Continued...**

## BITE ME CANCER

**http://www.bitemecancer.org**

Bite Me Cancer was formed as a nonprofit foundation in September, 2010, by Nikki Ferraro, who was 17-years old at the time. Nikki was diagnosed with a rare form of thyroid cancer in April 2010 when she was a junior at Chantilly HS in Virginia. Nikki was determined to lead a Relay for Life team just two weeks after her diagnosis. She named the team Bite Me Cancer and experienced immediate success. When Nikki decided to create a foundation a few months later, she wanted to continue the legacy of her team name and thus her foundation became the Bite Me Cancer Foundation.

e-mail: info@bitemecancer.org

## GRAVES' DISEASE AND THYROID FOUNDATION

**www.gdatf.org**

Phone (toll-free): 1-877-NGDF-123 or 643-3123

e-mail: Gravesdiseasefd@gmail.com

Founded in 1990, the Graves' Disease Foundation offers support and resources to Graves' disease patients, their families, and health care professionals. Their mission is to find the cause of and the cure for Graves' thyroid disease through research, to improve the quality of life for persons with Graves' disease and their caregivers and to educate persons with Graves' disease, their caregivers, healthcare professionals, and the general public about Graves' disease and its treatment. The web site features a monitored bulletin board.

## LIGHT OF LIFE FOUNDATION

**www.checkyourneck.com**

email: info@checkyourneck.com

The Light of Life Foundation, founded in 1997, is a nonprofit organization that strives to improve the quality of life for thyroid cancer patients, educate the public and professionals about thyroid cancer, and promote research and development to improve thyroid cancer care.

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AMERICAN THYROID ASSOCIATION
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# ATA Alliance for Thyroid Patient Education

**Continued...**

## THYCA: THYROID CANCER SURVIVORS' ASSOCIATION, INC.

**www.thyca.org**
Phone (toll-free): 877 588-7904
e-mail: thyca@thyca.org

ThyCa: Thyroid Cancer Survivors' Association, Inc., founded in 1995, is an international nonprofit organization, guided by a medical advisory council of renowned thyroid cancer specialists, offering support and information to thyroid cancer survivors, families, and health care professionals worldwide.

## THYROID CANCER CANADA

**www.thyroidcancercanada.org**
Phone: 416-487-8267
Fax: 416-487-0601
e-mail: info@thyroidcancercanada.org

Thyroid Cancer Canada is a non-profit organization founded in 2000. The organization works towards creating an environment in which people who are dealing with thyroid cancer, especially the newly diagnosed, are met with support and information. Their goals & objectives include facilitating communication among thyroid cancer patients, providing credible information about the disease, providing emotional support, and assisting thyroid cancer patients with voicing their needs to health care professionals and those who are responsible for health care policy.

## THYROID FEDERATION INTERNATIONAL

**http://www.thyroid-fed.org/**
e-mail: tfi@thyroid-fed.org

Thyroid Federation International (TFI) was established in Toronto in 1995. Thyroid Federation International aims to work for the benefit of those affected by thyroid disorders throughout the world by providing a network of patient support organizations.

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# Thyroid Hormone Treatment

## 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.

## THYROID HORMONE TREATMENT

Thyroid hormone is used in two situations:

1. to replace the function of the thyroid gland, which is no longer functioning normally (*"replacement therapy"*) and
2. to prevent further growth of thyroid tissue (*"suppression therapy"*). Suppression therapy is used primarily in patients with thyroid cancer to prevent recurrence or progression of their cancer.

## DEFINITION, THERAPY & TREATMENT

### THYROID HORMONE REPLACEMENT THERAPY

Many people have a thyroid gland that cannot make enough thyroid hormone for the body's needs. This is called Hypothyroidism and may be caused by a non-functioning thyroid gland (*for example Hashimoto's disease*), by destruction of thyroid gland by surgery or radiation treatment or by a non-functioning pituitary gland (see *Hypothyroidism Brochure*). Hypothyroidism, is the most common reason for needing thyroid hormone replacement.

The goal of thyroid hormone treatment is to closely replicate normal thyroid functioning. Pure, synthetic thyroxine (T4) works in the same way as a patient's own thyroid hormone would. Thyroid hormone is necessary for the health of all the cells in the body. Therefore, taking thyroid hormone is different from taking other medications, because its job is to replace a hormone that is missing. The only safety concerns about taking thyroid hormone are taking too much or too little. Your thyroid function will be monitored by your physician to make sure this does not happen.

### HOW IS THE DOSE OF THYROID HORMONE CHOSEN?

When someone is first started on thyroid hormone the initial dose is carefully selected based on information such as a person's weight, age, and other medical conditions. The dose will then need to be adjusted by a physician to keep the thyroid function normal. The physician will make sure the thyroid hormone dose is correct by performing a physical examination and checking TSH levels.

There are several brand names of thyroid hormone available. Although these all contain the same synthetic T4, there are different inactive ingredients in each of the brand names. In general, it is best for you to stay on the same brand name. If a change in brand name is unavoidable, you should be sure your physician is aware of the change, so that your thyroid function can be re-checked. If your pharmacy plan changes your thyroid hormone to a generic preparation, it is important for you to inform your physician.

## A LISTING OF THE FDA-APPROVED MEDICINES

| PRODUCT | FDA RATING | MANUFACTURING |
|---|---|---|
| Unithroid® | AB | (Stevens)*+ |
| L-Thyroxin | AB | (Mylan) *# |
| Levo-T® | BX | (Alara) |
| Levoxyl® | BX | (Jones)* |
| Novothyrox® | BX | (GenPharm) |
| Synthroid® | BX | (Abbott)* |
| Levothroid® | BX | (Forest/ Lloyd)* |
| Levolet® | BX | (Vintage) |

LEGEND:

AB = interchangeable
BX = not interchangeable
* = currently available
\+ = This is BX rated vs the other name brand LT4s
\# = This is AB rated only to Unithroid and is considered the only "generic".

# Thyroid Hormone Treatment

## HOW DO I TAKE THYROID HORMONE?

Thyroid hormone is easy to take. Because it stays in your system for a long time, it can be taken just once a day, and this results in very stable levels of thyroid hormone in the blood stream. When thyroid hormone is used to treat hypothyroidism, the goal of treatment is to keep thyroid function within the same range as people without thyroid problems. Keeping the TSH level in the normal range does this. The best time to take thyroid hormone is probably first thing in the morning on an empty stomach. This is because food in the stomach can affect the absorption of thyroid hormone. However, the most important thing is to be consistent, and take your thyroid hormone at the same time, and in the same way, every day. If you are taking several other medications, you should discuss the timing of your thyroid hormone dose with your physician. Sometimes taking your thyroid hormone at night can make it simpler to prevent your thyroid hormone from interacting with food or other medications.

Do not stop your thyroid hormone without discussing this with your physician. Most thyroid problems are permanent, and therefore most patients require thyroid hormone for life. If you miss a dose of thyroid hormone, it is usually best to take the missed dose as soon as you remember. It is also safe to take two pills the next day; one in the morning and one in the evening. It is very important that your thyroid hormone and TSH levels are checked periodically, even if you are feeling fine, so that your dose of thyroid hormone can be adjusted if needed.

## DOES THYROID HORMONE INTERACT WITH ANY OTHER MEDICATIONS?

Taking other medications can sometimes cause people to need a higher or lower dose of thyroid hormone. Medications that can potentially cause people to need a different dose of thyroid hormone include birth control pills, estrogen, testosterone, some anti-seizure medications (for example Dilantin and Tegretol), and some medications for depression. Yet other products can prevent the absorption of the full dose of thyroid hormone. These include iron, calcium, soy, certain antacids and some cholesterol-lowering medications. For all these reasons, it is important for people taking thyroid hormone to keep their physician up to date with any changes in the medications or supplements they are taking.

## SHOULD I TAKE THYROID HORMONE WHILE I AM PREGNANT?

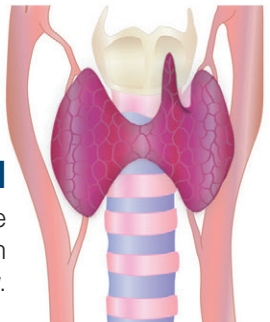
Since thyroid hormone is a hormone normally present in the body, it is absolutely safe to take while pregnant. Indeed, it is very important for pregnant women, or women who are planning to become pregnant, to have normal thyroid function to provide the optimum environment for her baby. Women who are taking thyroid hormone often need an increased dose of thyroid hormone during their pregnancy, so it is important to have thyroid hormone and TSH levels measured once you know that you are pregnant. You should discuss the timing of thyroid blood tests with your physician, but often thyroid function is checked at least every trimester.

## WHAT ABOUT "NATURAL" THYROID HORMONES?

Desiccated (*dried and powdered*) animal thyroid (*Armour®*), now mainly obtained from pigs, was the most common form of thyroid therapy before the individual active thyroid hormones were discovered. People can still buy it over the Internet—legally if it's sold as a food supplement, but illegally if it's sold as a medicine. It is also available still as a prescription. Since pills made from animal thyroid are not purified, they contain hormones and proteins that never exist in the body outside of the thyroid gland. While desiccated thyroid contains both T4 and T3, the balance of T4 and T3 in animals is not the same as in humans, so the hormones in animal thyroid pills aren't necessarily "natural" for the human body. Further, the amounts of both T4 and T3 can vary in every batch of desiccated thyroid, making it harder to keep blood levels right. Finally, even desiccated thyroid pills have chemicals (binders) in them to hold the pill together, so they are not completely "natural". Desiccated animal thyroid is rarely prescribed today, and there is no evidence that desiccated thyroid has any advantage over synthetic T4.

## FURTHER INFORMATION

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



# Thyroid Hormone Treatment

### WHAT ABOUT T3?

While most actions of thyroid hormone are most likely due to T3, most T3 in the body comes from the conversion of T4. The conversion of T4 to T3 is normal in hypothyroid patients. T3 has a very short life span in the body, while the life span of T4 is much longer, ensuring a steady supply of T3. A preparation of synthetic T3 (*Cytomel®*) is available. After taking a tablet of Cytomel® there are very high levels of T3 for a short time, and then the levels fall off very rapidly. This means that T3 has to be taken several times each day, and even doing this does not smooth out the T3 levels properly. In addition, it is impossible to avoid having too much thyroid hormone in the system soon after each dose of T3 is taken. High T3 levels can lead to unpleasant symptoms such as rapid heart beat, insomnia and anxiety. High T3 levels also can harm the heart and the bones. Another concern with using T3 treatment is that the body is deprived of the ability to adjust the conversion of T4 to T3 to regulate the supply of T3 according to the body's own needs. Thus, there is no indication for the use of T3 alone for the treatment of hypothyroidism.

### WHAT ABOUT COMBINED T4 AND T3 TREATMENT?

Some hormone preparations containing both T4 and T3 are available in the United States (*Thyrolar®*). Combination T4/T3 preparations contain much more T3 than is usually produced naturally within the body. Because of this, they can have the same side effects as T3 given by itself. It is also given once a day, ignoring the short life span of T3 in the body. There has been interest in whether a combination of T4 and T3, with a lower amount of T3 given more than once a day, might result in better treatment of hypothyroidism, especially in those patients that do not feel completely normal on T4 alone. In these cases, Cytomel® (T3) is taken in addition to T4. A trial period of 3 – 6 months is reasonable to determine if combination T4 and T3 therapy will help.

## WILL THYROID HORMONE HELP ME IF I HAVE HYPOTHYROID SYMPTOMS BUT NORMAL THYROID HORMONE LEVELS?

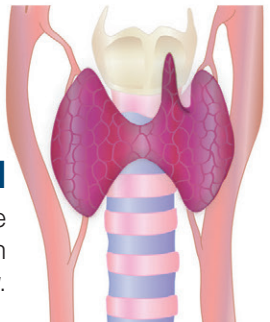
Some people with normal thyroid blood tests have symptoms that are similar to symptoms of hypothyroidism. Several scientific studies have looked at whether T4 therapy would be of benefit to patients with symptoms that overlap with hypothyroid symptoms and normal thyroid function. In all cases, there was no difference between T4 and a placebo (sugar pill) in improving symptoms or well-being.

## THYROID HORMONE SUPPRESSION THERAPY FOR BENIGN NODULES AND GOITER

In the past, thyroid hormone suppression therapy was used to prevent benign thyroid nodules and enlarged thyroid glands from growing. More recent evidence has shown that this practice is not effective in regions of the world that have adequate iodine intake (such as the USA). Moreover, excess thyroid hormone can increase the risk or heart rhythm problems and bone loss making the use of thyroxine for suppressing benign thyroid tissue more risky than beneficial in iodine sufficient populations.

## TREATMENT OF THYROID CANCER

After surgery for thyroid cancer, thyroid hormone is needed both to replace the function of the removed thyroid gland and to keep any small or residual amounts of thyroid cancer cells from growing (see *Thyroid Cancer brochure*). Thyroid hormone suppression therapy is also an important part of the treatment of thyroid cancer and is effective in stopping the growth of microscopic thyroid cancer cells or residual thyroid cancer. In this case, the benefit of preventing the growth of residual thyroid cancer cells outweighs the risks of a mild increase in the risk of fast, irregular heart rhythms, exacerbation of chest pain and decreased bone density. A physician should closely monitor this kind of treatment. The duration of suppression therapy in cancer patients currently being debated.



## FURTHER INFORMATION

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