

# Clinical THYROIDOLOGY

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**Clinical Thyroidology**

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# Clinical THYROIDOLOGY

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## METFORMIN SHRINKS THYROID NODULES IN PATIENTS WITH INSULIN RESISTANCE

Rezzonico J, Rezzonico M, Pusiol E, Pistoia F, Niepomnische H. **Metformin treatment for small benign thyroid nodules in patients with insulin resistance.** *Metab Syndr Relate Disord* 2011;9:69-75. Epub December 3, 2010.

### SUMMARY

### BACKGROUND

In a prior study, these authors found that individuals with hyperinsulinemia had an increased thyroid volume as well as an increased number of thyroid nodules.

### METHODS

Eighty women who were thyroid peroxidase antibody-negative and living in an iodine-sufficient area and who had insulin resistance (IR) and solid, benign, hyperplastic thyroid nodules were prospectively evaluated for nodule shrinkage using metformin, levothyroxine, or a combination of the two. Fourteen women did not complete follow-up, leaving 66 women with 75 thyroid nodules. IR was evaluated by homeostasis model assessment (HOMA; fasting serum insulin in microunits per milliliter multiplied by plasma glucose in millimoles per liter divided by 22.5); a HOMA index of >2.5 indicated IR. Nodule volume determined using ultrasound was calculated with the elliptical shape volume formula. Women who qualified were randomly assigned to four treatment groups and followed for 6 months: group 1 (n = 14; 19 nodules) was treated with metformin alone; group 2 (n = 18; 21 nodules) was treated with metformin and levothyroxine; group 3 (n = 19; 20 nodules) was treated with levothyroxine alone; and group 4 (n = 15; 15 nodules) were controls. The metformin dose was 1000 mg twice daily; the dose of levothyroxine was adjusted to keep the serum thyrotropin (TSH) level at 0.11 to 0.99 mU/L. Patients were treated for 6 months and then reevaluated using ultrasound.

### RESULTS

The characteristics of the patients in the groups were similar at baseline (mean age, 43; mean weight, 80 kg; mean body-mass index [the weight in kilograms divided by the square of the height in meters], 31; mean HOMA score, 3.3; mean TSH, 2.55; median nodule volume, 298 mm<sup>3</sup>). Patients treated with levothyroxine had a significant decrease in TSH (mean, 0.59 mU/L). Patients taking metformin had a significant decrease in their HOMA scores into the normal range. All patients on active treatment (groups 1 to 3) had

*continued on next page*

a significant reduction in thyroid volume, with no significant difference in the posttreatment thyroid volume between these three groups. Nodule size was markedly and significantly reduced in both groups treated with metformin (from 364 to 75 mm<sup>3</sup> in group 1 and from 336 to 126 mm<sup>3</sup> in group 2; 74% of nodules were reduced with metformin alone, 95% were reduced with metformin plus levothyroxine treatment), whereas nodule size was unchanged in the other treatment groups. Patients treated with metformin alone had a significantly greater reduction in nodule size than those treated with levothyroxine

alone or those with no treatment. Similar nodule shrinkage with metformin was seen with small (<1 cm) and larger lesions (1 to 2 cm).

### CONCLUSIONS

In patients with small hyperplastic thyroid nodules, metformin produced a significant decrease in nodule size, and the combination of metformin plus levothyroxine showed the best reduction in nodule volume, whereas levothyroxine alone reduced nodule growth but not nodule volume.

### COMMENTARY

This small, relatively brief study reveals a marked reduction in thyroid nodule volume in 74% of these insulin-resistant subjects who were being treated with metformin. The overall reduction in thyroid volume was less impressive, perhaps because only small lesions were included in this study, hence making up a relatively small percentage of total thyroid volume. Combination therapy with metformin plus levothyroxine was associated with a reduction in nodule size in 95% of lesions. In contrast, suppressive therapy with levothyroxine alone did not result in nodule shrinkage, perhaps because the TSH suppression was briefer and TSH was not suppressed to grossly hyperthyroid levels as has been done in prior successful trials (1,2). Past studies evaluating shrinkage of thyroid nodules with levothyroxine suppression have had mixed results, and the

2009 American Thyroid Association management guidelines for thyroid nodules do not recommend levothyroxine suppressive therapy for patients with benign nodules who live in iodine-sufficient areas (3). In this study, metformin treatment appears to offer a tantalizing reduction in thyroid nodule volume, with efficacy seen in a striking percentage of treated patients. As insulin-resistant patients often have multiple associated risk factors for surgery, this would be an important group for further study of non-operative therapies, especially for larger nodules in which cosmesis may be an issue. As the authors point out, we need more studies done with metformin to reproduce these results.

— Jane Weinreb, MD

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## THYROID AUTOIMMUNITY IS ASSOCIATED WITH AN INCREASED RISK OF SPONTANEOUS MISCARRIAGE IN EUTHYROID WOMEN

Chen L, Hu R.

recommended that medical practitioners follow the recommendations suggested by the Endocrine Society Guidelines in Thyroid Disorders in Pregnancy (2); a serum TSH over 2.5 mIU/L in the first trimester of gestation is considered diagnostic of hypothyroidism and is known to potentially affect the outcome of pregnancies, including miscarriages. In the present meta-analysis, serum TSH in the selected articles ranged from 0.3 to 5.0 mIU/L, therefore many of the miscarriages occurred in women suffering from mild hypothyroidism. It has to be kept in mind that many of the studies were published before 2007, when the recommendation for a serum TSH range was given. Serum TSH levels in the antithyroid-antibody-positive women were 0.61 mIU/L higher than in the antithyroid-antibody-negative women (95% CI, 0.51-0.71;  $P < 0.00001$ ).

The other issue discussed by the authors is patient age; women with positive thyroid antibodies in the 9 studies considered were, on average, 1.29 years older than those with negative antibodies; it is known that there is an increase in the incidence of spontaneous miscarriage with age.

In summary, the meta-analysis done by Chen and Hu supports the general medical concept of an increased rate of spontaneous miscarriages in women harboring positive thyroid antibodies, although other factors, such as age, mild thyroid dysfunction, and higher serum TSH values, albeit within normal limits, could contribute to it.

The dilemma for the practitioner in the presence of a euthyroid, antithyroid-antibody-positive woman who wishes to become pregnant or who is in her first trimester is to treat or not to treat with levothyroxine. This is a controversial issue among endocrinologists and obstetricians, with some benefit of treatment reported in the literature (3-5). Considering the higher risk for miscarriages in euthyroid women with thyroid autoimmunity and the potential benefits of levothyroxine therapy, could 50 or 75  $\mu\text{g}$  daily of levothyroxine be harmful to a healthy young woman?

— Jorge H. Mestman, MD

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## THE MEDIAN URINARY IODINE IS LOW IN AMERICAN PREGNANT WOMEN. WHY HAVE WE NOT IMPROVED IODINE INTAKE IN THIS VULNERABLE POPULATION?

Caldwell KL, Makhmudov A, Ely E, Jones RL, Wang RY. **Iodine status of the U.S. Population, National Health and Nutrition Examination Survey, 2005-2006 and 2007-2008.** Thyroid. February 16, 2011 [Epub ahead of print].

### SUMMARY ●●●●●●●●●●●●●●●●●●●●

#### BACKGROUND

Urinary Iodine (UI) for the general population is examined in this report for the periods 2005–2006 and 2007–2008. Two National Health and Nutrition Examination Surveys (NHANES), NHANES III (1988–1994) and NHANES I (1971–1974) that demonstrated a significant reduction in the median UI concentration, raising the fear that the United States was heading toward becoming an iodine-deficient population.

#### METHODS

During 2005–2006 and 2007–2008, participants were selected to participate in the NHANES that reflected the general U.S. population by age, sex, and race/ethnicity. Approximately one third of the 2005–2006 participants, 6 years of age or older, were selected to provide a UI sample, while all the participants in 2007–2008 were tested.

#### RESULTS

The median UI for the general U.S. population in 2005–2006 and 2007–2008 was 164  $\mu\text{g/L}$ , which is

stable and similar to NHANES III in 1988–1994 (1). Similar to prior NHANES, the urinary iodine intake was highest in the children and in persons >70 years of age. In both surveys in this report, children 6 to 11 years of age had median UI concentrations >200  $\mu\text{g/L}$ , but about 5% had severe iodine sufficiency, with a UI of <50  $\mu\text{g/L}$ . All pregnant women (sample size, 184) surveyed during 2005–2008 had a median UI of 125  $\mu\text{g/L}$  (95% confidence interval, 86 to 198) with 56.9% having a UI <150  $\mu\text{g/L}$ . UI concentrations were lower among non-Hispanic black participants and non-Hispanic white and Mexican-American subjects.

#### CONCLUSIONS

These findings confirm the stabilization of UI concentration and adequate iodine nutrition in the general U.S. population since 2000. However, certain groups, such as pregnant women, most likely do not have a sufficient dietary iodine intake according to the World Health Organization (WHO). The clinical impact of this insufficiency is not clear and further study is recommended.

### COMMENTARY ●●●●●●●●●●●●●●●●●●●●

The WHO defines adult iodine nutrition as excessive iodine intake, >300  $\mu\text{g/L}$ ; more than adequate intake, 200–299  $\mu\text{g/L}$ ; adequate intake, 100–199  $\mu\text{g/L}$ ; mild iodine deficiency, 50–99  $\mu\text{g/L}$ ; moderate iodine deficiency, 20–49  $\mu\text{g/L}$  and severe iodine deficiency, <20  $\mu\text{g/L}$  (2). Recommended iodine intake for pregnant women is higher, with a suggested median UI concentration of 150–249  $\mu\text{g/L}$ . The Recommended Daily Allowance (RDA) for iodine of the Institute of Medicine (IOM) Food and Nutrition Board is 90 mg/day for children, 150 mg/day for adults, and 220 mg/day for pregnant women (3). At the level of the general

U.S. population, it is a relief that the decrease in iodine intake that occurred between NHANES I and NHANES III did not continue to decline and has stayed stable, currently at 164 mg/L. The epidemiologists would say that that is adequate, since it means that as a population, the U.S. getting sufficient iodine. But the high iodine intake is in the very young and the elderly, which means there are segments of the population who have, on average, an insufficient iodine intake. U.S. pregnant women (median UI, 125  $\mu\text{g/L}$ ) as a population do not have an adequate intake according to the WHO (recommended, 150–249 mg/L), and they most likely have an insufficient intake as an

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## THE MEDIAN URINARY IODINE IS LOW IN AMERICAN PREGNANT WOMEN. WHY HAVE WE NOT IMPROVED IODINE INTAKE IN THIS VULNERABLE POPULATION?

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individual as compared to the IOM recommended RDA of 220 µg/day. Of concern is that more than half of the women surveyed had a urinary iodine less than 150 µg/L, which is clearly lower than the RDA. I am concerned that despite the widely publicized need for adequate iodine intake in vulnerable populations such as pregnant women, we have not made much headway in eradicating inadequate iodine intake in this group. For your patients who are planning to become or are pregnant, it is important that their prenatal vitamin contain iodine. The vast majority of prenatal vitamins that contain iodine will have 150 µg

per daily dose, which combined with a dietary sources is likely to be adequate. But note that only 51% of prenatal vitamins contain iodine (4), and it is critical that you or your patient check the nutrition label to confirm that her prenatal vitamin contains iodine. This recommendation concurs with the 2006 statement from the American Thyroid Association that women receive 150-µg iodine supplements daily during pregnancy and lactation and that all prenatal vitamin/mineral preparations contain 150 µg of iodine (5).

— **Stephanie L. Lee, MD, PhD**

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are known to release more IL-6. A recent study on a variety of human cells reported that IL-6 blocks their conversion of  $T_4$  to  $T_3$  while increasing their inactivation of both  $T_3$  and  $T_4$ , apparently by depletion of an intracellular thiol co-factor (5). Could the higher

levels of IL-6 in severely obese individuals affect the way such individuals metabolize L- $T_4$ ?

— Stephen W. Spaulding, MD

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# SELENIUM MAY PREVENT GOITER AND THYROID NODULES

Rasmussen LB, et. al.

there was no association between thyroid volume and serum selenium concentration).

The serum selenium concentration was significantly negatively associated with risk for enlarged thyroid gland; the association was significant before iodine fortification, but not after iodine fortification. Furthermore, the risk for an enlarged thyroid gland increased with lower serum selenium concentrations in women but not in men. Low serum selenium concentrations tended to increase the risk for multiple thyroid nodules of more than 10 mm in diameter. In contrast, serum selenium did not influence the risk for solitary nodules.

## CONCLUSIONS

The serum selenium concentration has an effect on thyroid volume and probably multiple nodule formation in areas with mild iodine deficiency; however, the association is weak and appears to be confined to women. The results of the present study as well as some previous studies suggest that sufficient selenium intake is one of the environmental factors that may add to the prevention of goiter and thyroid nodules. Prospective intervention studies are needed to evaluate the potential role of selenium in patients suffering from goiter and thyroid nodularity.

## COMMENTARY ●●●●●●●●●●●●●●●●

The majority of the literature on the effect of selenium on thyroid hormone metabolism and of selenium supplementation therapy originates in Europe. As discussed by the authors, the role of selenium supplementation in preventing goiter or reducing thyroid volume is controversial, perhaps sex- and age-dependent, and related to iodine in the diet. Two recent studies demonstrated the beneficial effect of selenium supplementation in reducing thyroid peroxidase (TPO) antibody titer in women with Hashimoto's thyroiditis. In one study from Greece, l-selenomethionine 200 µg a day given for 12 months caused a significant decrease in serum anti-TPO levels in the first 6 months of treatment, with an additional 8% decrease when the treatment was extended for another 6 months, while withdrawal of the drug caused a 4.8% increase in anti-TPO concentrations (1). In a study from Italy, selenium, 200 µg daily, was given to women during pregnancy

and the postpartum period, who were then compared to control pregnant TPO-positive women who were being given placebo therapy. Postpartum thyroiditis and permanent hypothyroidism were significantly lower in the group receiving therapy as compared with the control group (28.6 vs. 48.6%, P<0.01; and 11.7 vs. 20.3%, P<0.01, respectively) (2). Let me add a note of caution on the potential adverse effects of selenium supplementation. During a mean (±SD) follow-up of 7.7±2.7 years in a group of persons without diabetes who were receiving selenium supplementation or placebo, type 2 diabetes developed in 58 selenium recipients and in 39 placebo recipients (hazard ratio, 1.55; 95% confidence interval, 1.03 to 2.33). The conclusion by the authors was that selenium supplementation does not seem to prevent type 2 diabetes, and it may increase the risk for the disease (3).

— Jorge H. Mestman, MD

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## REOPERATION CURES ONLY HALF OF THE PATIENTS WITH LOCALLY RECURRENT PAPILLARY THYROID CANCER

Yim JH, et. al.

Tg <1 ng/ml (1). In 9% of the patients in the recent U.S. study, no PTC was found in the resected nodes, and none of this group had a biochemical remission despite the identification of recurrent disease based on ultrasound and fine-needle aspiration biopsy of suspected lesions (1). Also worrisome is that about one fourth of those with clinical recurrence in the Korean study had a postoperative stimulated Tg <1 ng/ml. It is not surprising that only 20% of those with a larger burden of disease, indicated by a stimulated

Tg >100 ng/ml, had a biochemical remission. Based on the experience of this Korean group, perhaps it is worthwhile to follow patients with observation only if the stimulated Tg is <5 ng/ml because only one fourth to one half of these patients have a biochemical cure and clinical recurrence was not detected in a 5-year follow up in the patients with a stimulated Tg <5 ng/ml after the reoperation.

— Jerome M. Hershman, MD

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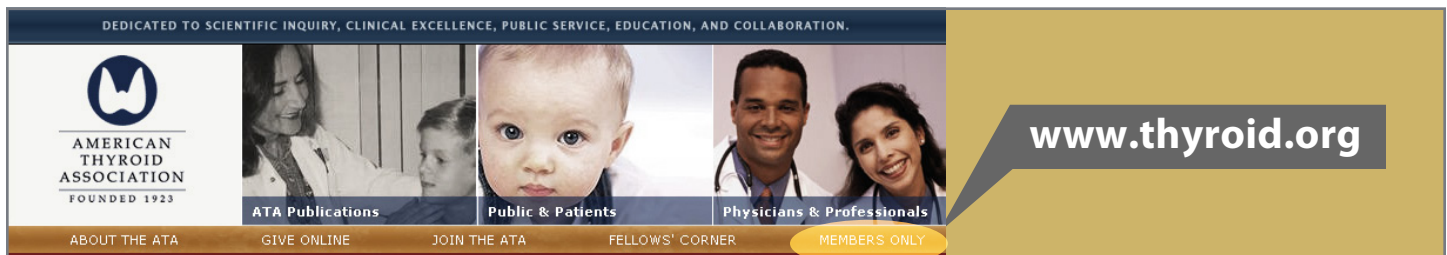
## LOW BASAL SERUM THYROGLOBULIN IN A SENSITIVE ASSAY IS AN EXCELLENT PREDICTOR OF LOW RECURRENCE OF DIFFERENTIATED THYROID CANCER

Malandrino P, et. al.

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The image shows a navigation bar for the American Thyroid Association website. On the left is the ATA logo with the text 'AMERICAN THYROID ASSOCIATION' and 'FOUNDED 1923'. Below the logo are four navigation buttons: 'ABOUT THE ATA', 'GIVE ONLINE', 'JOIN THE ATA', and 'FELLOWS' CORNER'. To the right of these buttons are three images: a woman and child, a baby, and two doctors. Below these images are three buttons: 'ATA Publications', 'Public & Patients', and 'Physicians & Professionals'. On the far right is a large yellow button with the text 'MEMBERS ONLY'. To the right of the navigation bar is a large yellow speech bubble containing the website address 'www.thyroid.org'.

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## WITH THE RISING INCIDENCE OF SECOND CANCERS, SHOULD YOU GIVE RAI TO A LOW-RISK (TINO) THYROID CANCER PATIENT?

Iyher NG, Morris LG, Tuttle RM, Shaha AR, Ganly I. **Rising incidence of second cancers in patients with low-risk (TINO) thyroid cancer who receive radioactive iodine therapy.** Cancer. March 22, 2011 [Epub ahead of print]. doi: 10.1002/cncr.26070.

### SUMMARY ●

#### BACKGROUND

An increase in secondary primary malignancies (SPM) after radioactive iodine (RAI) therapy for differentiated thyroid is a risk that has been seriously recognized for the past 8 years, since the initial report by Rubino et al. (1). During this time, several papers (2) explored this question using the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute, but the purpose of this reanalysis is to determine specifically the pattern in the increase in use of RAI and the pattern of increase of SPM in low-risk patients with differentiated thyroid cancer.

#### METHODS

The SEER 13 cohort database (1973–2006) was queried for patients diagnosed with well-differentiated thyroid cancer (WDTC) including papillary, follicular variant of papillary, and follicular thyroid carcinoma. Patients were excluded if any of the following data were missing: tumor size, extrathyroidal extension, lymph-node status, metastasis status, or RAI administration. Low-risk tumors were defined as those <2 cm intrathyroidal tumors without extrathyroidal extension, lymph-node metastases, or distant metastases in patients <45 years of age. An SPM was defined as a solid or hematologic malignancy that occurs >6 months after diagnosis. The risk of SPM is the standardized incidence ratio (SIR)—the ratio of observed to expected (O/E) second cancers. The excess absolute risk represents the absolute number of additional second cancers attributable to RAI treatment and is calculated as the excess (O/E) number of second cancers in patients per 10,000 person-years at risk.

#### RESULTS

WDTC has increased in incidence from 3.5 per 100,000 population in 1973 to 11.4 per 100,000 in 2007. Thyroid tumor size has been recorded since 1983. Since 1983,

the incidence of low-risk WDTC has increased from 1.2 to 5.2 per 100,000, which accounts for the majority (55.6%) of the increased incidence of WDTC. Among patients <45 years of age who have low-risk tumors, RAI treatment increased from 3.3% in 1973 to 38.1% in 2006. As expected, the rate of overall survival among patients with low-risk WDTC has remained constant during this period, at nearly 100%. For all patients with WDTC, the SIR of SPM at any site was 1.18 (95% confidence interval [CI], 1.10 to 1.25). The SPMs with significantly elevated risk because of RAI were cancers of the salivary gland (SIR, 3.84; 95% CI, 1.66 to 7.56) and kidneys (SIR, 2.62; 95% CI, 1.94 to 3.47) and leukemia (SIR, 2.09; 95% CI, 1.49 to 2.86). The risk of leukemia was especially high in patient <45 year of age (SIR, 5.32; 95% CI, 2.75 to 9.30) as compared with older patients (SIR, 2.26; 95% CI, 1.43 to 3.39).

#### CONCLUSIONS

In the past three decades, the incidence of thyroid cancer has increased more than threefold. Many groups have argued that this increase is due to incidental detection from the increased use of head and neck imaging studies, but nearly 50% of the increased incidence is from tumors >2 cm, suggesting that a significant number of patients have clinically important tumors. The proportion of tumors that were considered low risk in 2007 was 45.6%. Despite the increase in proportion of low-risk tumors, the use of RAI for WDTC has remarkably increased, according to this report to nearly 40% in the low-risk category. Although the rates of RAI increased, overall survival remains excellent, at nearly 100%. This report demonstrates that there were no excess SPMs during the time that RAI was less commonly used in 1973–1981, and the rise in SPM was stepwise over the time that the use of RAI was increasing. The fact that the shapes of the curves of the rise in SPM and the use of RAI are not similar suggests that there may be other factors involved in the development of SPM.

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## OFFICIAL ITALIAN TRANSLATION of the 2009 American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

**American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer.**

Thyroid 2009;19:1167-214.

### **American Thyroid Association (ATA) Acknowledgement to the Translators**

The American Thyroid Association (ATA) wishes to acknowledge the contributions of ATA members Sebastiano Filetti, MD (University of Roma La Sapienza, Rome, Italy), Giuseppe Costante, MD (University of Catanzaro "Magna Græcia", Catanzaro, Italy), Cosimo Durante, MD (University of Roma La Sapienza, Rome, Italy), and Furio Pacini, M.D. (The University of Siena, Siena, Italy) who have contributed their time and expertise to the translation of the Linee Guida dell'American Thyroid Association sulla Gestione dei Pazienti con Noduli Tiroidei e Carcinoma Differenziato della Tiroide from the original English Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer published by the American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer in *THYROID* 2009; 19:1167-1214 with corrections published in *THYROID* 2010; 20:674-675.

The Translators efforts are aimed to facilitate understanding of the guidelines and their rationale to Italian physicians not well acquainted with English language. The document is being presented as it was received by the ATA without additional review or proofreading. The ATA extends deep appreciation to the translators.

### **American Thyroid Association (ATA)**

The American Thyroid Association (ATA) is the leading worldwide organization dedicated to the advancement, understanding, prevention, diagnosis and treatment of thyroid disorders and thyroid cancer. ATA is an international individual membership organization with over 1,400 members from 43 countries around the world. Celebrating its 88th

anniversary, ATA delivers its mission through several key endeavors: the publication of highly regarded monthly journals, *THYROID*, *Clinical Thyroidology* and *Clinical Thyroidology for Patients*; annual scientific meetings; biennial clinical and research symposia; research grant programs for young investigators; support of online professional, public and patient educational programs; and the development of guidelines for clinical management of thyroid disease.

### **ATA Guidelines Disclaimer**

The American Thyroid Association develops Clinical Practice Guidelines to provide guidance and recommendations for particular practice areas concerning thyroid disease and thyroid cancer. The Guidelines are not inclusive of all proper approaches or methods, or exclusive of others. The Guidelines do not establish a standard of care and specific outcomes are not guaranteed.

Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances. A guideline is not intended to take the place of physician judgment in diagnosing and treatment of particular patients.

The ATA develops guidelines based on the evidence available in the literature and the expert opinion of the task force in the recent timeframe of the publication of the guidelines. Management issues have not been and cannot be comprehensively addressed in randomized trials; therefore, the evidence cannot be comprehensive. Guidelines cannot always account for individual variation among patients. Guidelines cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.

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## OFFICIAL ITALIAN TRANSLATION of the 2009 American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Therefore, the American Thyroid Association considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the treating physician and health care professionals with the full consideration of the individual patient's clinical history and physical status. In addition, the guideline concerns the therapeutic interventions used in clinical practice and do not pertain to clinical trials. Clinical trials are a

separate matter, designed to research new and novel therapies, and the guidelines are not necessarily relevant to their purpose.

Guideline development includes an identification of areas for future study and research, indicating the focus for future investigational therapy based on the findings reviewed and synthesized from the latest literature.

It is our pleasure to present the official Italian translation of the 2009 American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The original English version of this document (published in 2009) provides the most up-to-date, evidence-based guide to clinical practice in this field. Each of the recommendations is rooted in an extensive, critical review of the literature in this field by a 11-member task force of experts from the United States, as well as two renowned endocrinologists from Europe, Drs. Martin Schlumberger (France) and Furio Pacini (Italy). As a result of their contributions, the new ATA Guidelines also reflect the important and sometimes differing viewpoints of European endocrinology. The goal of our translation is to both extend and enhance access to this valuable resource by Italian health-care professionals working in this field. Not only those who feel that they have a limited command of the English language, but also even the more experienced readers of English will find this translation a useful tool for exploring the highly important, finer shades of meaning contained in the guidelines. Our ultimate aim is to foster the diffusion in our country of common protocols for the diagnosis, treatment, and follow-up of thyroid disease, approaches based on scrupulously reviewed, carefully weighed scientific evidence. It is our sincere hope that our efforts will spark similar initiatives

in other countries as well (and not only within the European Union). In today's world, where patients, physicians, and researchers are increasingly on the move, widespread familiarity with these guidelines and active attempts to apply the recommendations they contain will help to improve our ability to offer high-quality, cost-effective care to our patients.

— **Sebastiano Filetti, MD**  
Rome, Italy

**TO READ THE GUIDELINES AND ACKNOWLEDGMENT IN ITALIAN, PLEASE OPEN THE PDFs BELOW.**

**Ringraziamento della American Thyroid Association (ATA) ai traduttori (Acknowledgment)**  
(PDF File, 80.3 KB)

**Linee Guida dell'American Thyroid Association sulla Gestione dei Pazienti con Noduli Tiroidei e Carcinoma Differenziato della Tiroide** (PDF File, 1.01 MB)

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## To the Editor:

In his brief review on propylthiouracil (“[Propylthiouracil Is an Old but Still Useful Drug](#)”) in the April 2011 issue of *Clinical Thyroidology*, Dr. Weissel makes one erroneous statement and one personal recommendation with which I disagree. The incorrect statement is that propylthiouracil (PTU)-related agranulocytosis is “independent of the age of the patient.” The study he cited (1) and others (e.g., 2) show that it is actually older persons who are more susceptible to agranulocytosis.

The personal recommendation made by Dr. Weissel that is troubling is the statement that “PTU should be used in preference to MMI [methimazole] also in lactating mothers, since its secretion in the milk is less than that of MMI.” While it is true that PTU crosses breast epithelium less well than MMI does because it is highly protein-bound and ionized at physiologic pH (3), the quantities of both drugs that an infant might ingest are, in fact, quite low. For PTU, it has been estimated that a child might ingest approximately 150 µg per day from a woman taking 200 mg of PTU three times a day (4). It has been calculated that a baby could receive 70 µg of MMI over an 8-hour period after the mother received a single 40-mg dose (5). Because this small amount conceivably could have an effect on a nursing baby’s thyroid function, it was suggested that PTU might be preferred in nursing mothers (6). However, subsequent data from Azizi and colleagues (7-12) show that infants exposed to MMI in breast milk have normal thyroid function (7-9), as well as normal IQ and growth (10-12). These investigators also measured serum MMI levels by high-performance liquid chromatography in 8 infants 2 hours after they breast-fed from mothers who were taking 10 mg of MMI two or three times a day. The serum MMI levels were undetectable in 6 of the 8 babies and were at the limit of detection (0.03 µg/ml) in the other two (12). Serum MMI levels at least 10-fold higher than this are seen in serum in adults after a 10-mg oral dose (13). Therefore, there is no reason not to use methimazole in breast-feeding

women, and in acknowledgment of this fact, the drug is approved for use in lactation, just like PTU, by the American Academy of Pediatrics (14).

Recent concerns raised by the American Thyroid Association and the Food and Drug Administration about potential PTU-induced hepatotoxicity have resulted in recommendations that limit the use of PTU (15,16) to individuals who cannot take MMI, persons with life-threatening thyrotoxicosis, and hyperthyroid women in the first trimester of pregnancy. Breast-feeding is not included in the indications. Because breast-feeding can last for many months or even years (17), the duration of PTU exposure of the mother could place her at increased risk for severe liver toxicity, while a safer drug (i.e., MMI) is available that would not put the baby at increased risk for adverse health consequences. While there are no case reports of infants breast-feeding from mothers taking PTU in whom hepatotoxicity subsequently developed, there are instances of babies with presumed in utero hepatotoxicity from PTU (18).

In light of the foregoing, MMI should be the drug of choice in breast-feeding women. Doses up to 40 mg per day are safe, although the minimum dose that is required to maintain normal thyroid function should be used. This was also the conclusion of a recent extensive review of the available literature (19). Interestingly, the need for an antithyroid drug in the postpartum period is associated with a decreased likelihood that a woman will breast-feed or be advised to breast-feed by a physician (20), indicating a need for greater physician education about the safety of antithyroid drugs in lactation.

— **David S. Cooper, MD**  
Professor of Medicine  
The Johns Hopkins University School of Medicine  
Baltimore, MD 21287

*continued on next page*

## To the Editor, continued

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**Dr. Weissel responds:**

My statement on page 3, 1st paragraph was ... “The prevalence (of agranulocytosis) seems to be independent of the age of the patient and of the dose used.” Dr. Cooper claims that is incorrect. Let me briefly quote from Cooper’s review article (1) that I cited (contrary to Cooper’s suggestion, I did not quote the 1983 paper by Cooper et al.) “Some, but not all, studies have suggested that the risk of agranulocytosis is greater in older patients and that they have a higher rate of death.” In his contribution to the textbook, *The Thyroid: A Fundamental and Clinical Text*, Cooper states: “Elderly patients may be more susceptible to agranulocytosis” (p. 671). I conclude from this repeated cautious phrasing that the author admits uncertainty about the influence of age on this side effect of propylthiouracil (PTU). Dai et al. did not find any correlation of PTU-induced agranulocytosis with age (3).

My personal preference for PTU in lactating women troubles Dr. Cooper. My argument was—and is—that PTU is secreted less in the milk than is MMI. Cooper agrees that this is the case, but he presents a calculation that might give the impression that the infants are at risk of ingesting considerable amounts

of PTU when the lactating mother’s hyperthyroidism is treated with PTU. However, the mother’s dose per day on which his calculation is based is extremely high. His calculation (based on a paper by Momotami et al. [4]) that a baby could receive as much as 150 µg of PTU per day is, at least in Europe, unrealistic. Doses of 600 mg per day for a lactating mother would be necessary for such concentrations, doses that are not given in Europe, where tablets contain only 20 mg in some countries (e.g., Austria). The usual starting dose of PTU in Austria is 300 mg per day for newly diagnosed hyperthyroidism. This dose is subsequently rapidly tapered to a dose of about 60 mg per day. Moreover, Momotami et al. conclude in their article: “Mothers can breast-feed while taking PTU at doses as high as 750 mg daily without adverse effects on thyroid status in their infants.” I am not aware of any paper reflecting the experience of equivalent high doses of methimazole.

— **Michael Weissel, MD**,  
Medical Clinic III  
Medical University of Vienna,  
Austria

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Steven I Sherman, MD  
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Ralph P. Tufano, MD, FACS  
Johns Hopkins University School of Medicine  
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