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A NEGATIVE PET SCAN EXCLUDES THE DIAGNOSIS OF CANCER IN THYROID NODULES >15 MM DIAMETER

Vriens D, de Wilt JH, van der Wilt GJ, Netea-Maier RT, Oyen WJ, de Geus-Oei LF. **The role of [(18) F]-2-fluoro-2-deoxy-d-glucose-positron emission tomography in thyroid nodules with indeterminate fine-needle aspiration biopsy: Systematic review and metaanalysis of the literature**. Cancer. March 22, 2011. [Epub ahead of print]. doi: 10.1002/cncr.26085.

BACKGROUND

18F-2-fluoro-2-deoxy-d-glucose-positron emission tomography (FDG-PET) has been used mainly for evaluating patients with metastatic cancer. In addition, there are many papers concerning its use in preoperative evaluation of thyroid nodules. The purpose of this meta-analysis was to determine the diagnostic value of FDG-PET for patients with results on fine-needle aspiration (FNA) biopsy that is indeterminate or inconclusive.

METHODS

Five search engines used in November 2010 uncovered 239 publications; only 6 of these papers met the criteria for inclusion. These studies comprised 225 patients. The study used a complex statistical analysis to determine the diagnostic value of FDG-PET for prediction of malignancy based on the data for these subjects.

RESULTS

The FDG-PET was positive in 142 of 225 patients (63%), but the prevalence of malignancy was 26%. The specificity was 48%, indicating that a majority of those with positive FDG-PET did not have cancer. The sensitivity was 95%. The negative predictive value was 96%, and the positive predictive value was 39%. The overall diagnostic value of FDG-PET for determination of thyroid malignancy was 60%. Evaluation of the 164 nodules that were >15 mm led to a sensitivity for detection of thyroid cancer of 100%, but the specificity remained similar, at 47%.

CONCLUSIONS

A negative FDG-PET scan in patients with thyroid nodules >15 mm with indeterminate FNA biopsy results is a useful test to exclude the diagnosis of thyroid cancer. Conversely, a positive FDG-PET result did not identify cancer because approximately 50% of patients with positive scans had benign nodules.

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A NEGATIVE PET SCAN EXCLUDES THE DIAGNOSIS OF CANCER IN THYROID NODULES >15 MM DIAMETER

COMMENTARY • • • • • • • • • • • • • • • • •

We now see many patients with positive FDG-PET thyroid nodules that are incidentally discovered in the workup of various conditions. These nodules deserve FNA biopsy. It is comforting to know that a high proportion are not carcinomas. In evaluation of the FNA biopsy, most nodules classified as indeterminate would be a basis for recommending surgery when the FDG-PET is positive. This meta-analysis shows that only a minority of those with this FNA cytology are malignant. The authors avoided using the standard uptake value (SUV) in their evaluations because of too much heterogeneity in the studies. When PET was first used, it was thought that a higher SUV was a much stronger indication of malignancy, and various threshold SUVs were set, such as 5.0. However, Kim et al. (1), in one of the papers included in the metaanalysis, found that there was no difference in the

mean SUV of benign and malignant nodules; instead, the SUV tended to correlate with size—larger lesions had more intense uptake. However, Traugott et al., in another paper included in the meta-analysis, reported that the mean (±SD) SUV for malignant nodules was 12.7±5.7 and for benign nodules 1.9±2.6 (2). In addition, there is the caveat that the smaller the carcinoma or benign lesion, the less likely the FDG-PET is to be positive.

Although a negative FDG-PET result in a lesion >15 mm can reliably exclude malignancy, many benign lesions will be positive, especially larger lesions. Nevertheless, as the cost of FDG-PET declines, it may find a place for evaluation of nodules in the indeterminate FNA category as a basis for avoiding surgery when the FDG-PET is negative in a nodule >15 mm.

Jerome M. Hershman, MD

References

- Kim JM, Ryu J-S, Kim TY, Kim WB, Kwon GY, Gong G, Moon DH, Kim SC, Hong SJ, Song YK. 18F-fluorodeoxyglucosepositron emission tomography does not predict malignancy in thyroid nodules cytologically diagnosed as follicular neoplasm. J Clin Endocrinal Metab 2007;92:1630-4 (Epub February 6, 2007).
- Traugott AL, Dehdashti F, Trinkaus K, Cohen M, Fialkowski E, Quayle F, Hussain H, Davila R, Ylagan L, Moley JF. Exclusion of malignancy in thyroid nodules with indeterminate fineneedle aspiration cytology after negative 18F-fluorodeoxyglucose positron emission tomography: interim analysis. World J Surg 2010;34:1247-53.

RISK OF PERSISTENT DIFFERENTIATED THYROID CANCER DESPITE NEGATIVE THYROGLOBLIN AND THYROGLOBULIN ANTIBODIES PERFORMED ON SOME COMMERCIAL TESTS

Spencer C, Petrovic I, Fatemi S. **Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer.** J Clin Endocrinol Metab. February 16, 2011 [Epub ahead of print] doi:10.1210/jc.2010-2762.

BACKGROUND

Serum thyroglobulin (Tg) is used as a postoperative tumor marker for persistence and recurrence of differentiated thyroid cancer (1,2). It is recommended that Tg autoantibodies (TgAb) be measured concurrently, because an elevated level interferes with the Tg immunometric assays (IMAs), resulting in a false negative result. In addition, Tg antibody levels may be used quantitatively as a surrogate marker for thyroid cancer in patients with positive levels (3).

RESULTS

This study examined four commercial TgAb assays ability measure serum TgAb while comparing the serum's activity interference with the Tg IMA that causes abnormally low Tg (IMA) to Tg radioimmunoassay (RIA) ratios. The TgAb assays were all standardized against the World Health Organization (WHO) reference serum 65/93. Serum samples from patients with TgAb-negative and TgAbpositive differentiated thyroid cancer had serum Tg measured by both IMA and RIA and TgAb measured by a reference method and three additional methods. Group A was composed of 143 of 785 consecutive specimens that were unequivocally TgAb-positive specimens using the Kronus thyroglobulin assay. But the false negative misclassification using the manufacturer's recommend reference range was found frequently using the Roche Elecsys

2010 (44.1%), Beckman Coulter Access (35%), and Siemens Immulite (62.2%) assays. The high frequency of apparent false negative TgAb misclassification using the manufacture's reference range prompted further investigation using Group B with unequivocally positive Tg RIA level. When the analytic cutoff (lowest level that can be measured with an assay) is used rather than the lower limits of the recommended reference range, all the false negative results were eliminated for the Kronus and the Roche assays. But the Beckman Coulter and the Siemens assays continued to have a high number of false negative misclassifications, at 21.9% and 34.3%, respectively.

CONCLUSIONS

The authors demonstrate that the Tg IMA and Tg RIA values were concordant when TgAb was absent. TgAb interference was present when the Tg IMA to Tg RIA ratio was below 75%. When manufacturer-recommended cutoffs were used, many specimens displaying functional Tg interference were classified as TgAb-negative. False negative misclassification was eliminated for two of four methods by using the analytical sensitivity (AS) as the detection limit for TgAb. misclassifications. AS limits failed to detect interfering TgAb in 20% to 30% of case in other two of four assays. TgAb relationships between values for different specimens were too variable to establish between-method conversion factors.

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RISK OF PERSISTENT DIFFERENTIATED THYROID CANCER DESPITE NEGATIVE THYROGLOBLIN AND THYROGLOBULIN ANTIBODIES PERFORMED ON SOME COMMERCIAL TESTS

COMMENTARY • • • • • • • • • • • • • • • • •

Serum Tg measurement during levothyroxine suppression or after TSH stimulation with neck ultrasound has been the main method of detecting differentiated thyroid cancer persistence or recurrence. This is an important report that shows that four commercial TgAb assays often do not detect TgAb levels that are capable of interfering with the Tg IMA. Clinically, this is critical, as patients with persistent disease can be misclassified as NED (no evidence of disease). Two of the four TgAb assays could predict interference of the Tg IMA when the analytical sensitivity was used instead of the recommended reference range. But two of the four assays missed interfering TgAb in 20% to 30% of cases even when the AS was used. Personally, I have had 2 patients in the past 6 months who presented with neck nodes that were abnormal on sonography

and had recurrent papillary thyroid carcinoma and negative Tg IMA and TgAb by one of the methods described above. Biopsy of the abnormal node and Tg IMA of the node aspirate were both positive for recurrent tumor in my patients. This reminds us that Tg alone may not be sufficient in all patients to reflect tumor status. It is also important to know which assay your laboratory is using to measure TgAb. The results should be reported using the analytic limit rather than the manufacturer's reference range when a serum Tg is simultaneously requested. The dilemma for many of us is when our lab is using one of the two assays that cannot detect interfering antibodies, even when the analytic cutoff is used. I am requesting that our laboratory change the TgAb assays to one of the two that can predict interference of the Tg IMA when the analytic cutoff is used.

Stephanie L. Lee, MD

REFERENCES

- 1. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
- 2. Spencer CA, Bergoglio LM, Kazarosyan M, Fatemi S, LoPresti JS. Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management of patients with differentiated thyroid carcinomas. J Clin Endocrinol Metab 2005;90:5566-75,
- 3. Kim WG, Yoon JH, Kim WB, Kim TY, Kim EY, Kim JM, Ryu JS, Gong G, Hong SJ, Shong YK. Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 2008;93:4683-9 [Epub September 23, 2008].

FALSE POSITIVE AND FALSE NEGATIVE RESULTS OF THYROID CYTOPATHOLOGY REMAIN A CHALLENGE

Wang CC, Friedman L, Kennedy GC, Wang H, Kebebew E, Steward DL, Zeiger MA, Westra WH, Wang Y, Khanafshar E, Fellegara G, Rosa J, Livolsi V, Layman RB.**A large multicenter correlation study of thyroid nodule cytopathology and histopathology.** Thyroid 2011;21:243-51. Epub December 29, 2010.

BACKGROUND

The authors aimed to : (1) review the diagnostic performance of thyroid fine-needle aspiration (FNA) biopsy in a prospective study, (2) perform a meta-review of large FNA studies from centers in the United States published between 2002 and 2010, and (3) assess the concordance of diagnosis when experts review surgical pathology.

METHODS

For the prospective study, FNA specimens and clinical data were collected from 16 U.S. communitybased clinics, 3 U.S. academic centers, and 2 non-U.S. academic sites from August 2008 through January 2010. The diagnostic categories were benign, malignant, indeterminate, and nondiagnostic. The indeterminate category lumped together the three separate categories of the Bethesda system: atypia of undetermined significance or follicular lesion of undetermined significance; follicular (or Hürthle) neoplasm or suspicious for follicular (or Hürthle) neoplasm; and suspicious for malignancy. Eleven studies were selected for the meta-review; the total number of patients was 17,059, of whom 8937 had surgical specimens.

RESULTS

In the prospective study, 753 FNA biopsies were performed; 80% were categorized as benign, 8%

indeterminate, 7% malignant, and 5% nondiagnostic. There were 112 surgical specimens; the malignancy rate in relation to the FNA category was 11% of the benign, 34% of the indeterminate, 98% of the malignant, and none of the nondiagnostic category. Based on these data, the authors calculated that FNA biopsy had a sensitivity of 95%, a positive predictive value of 68%, and a negative predictive value of 89%. These results were similar to the diagnostic performance of FNA biopsy in the meta-review.

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In the meta-review using the Bethesda system of classifying FNA biopsies, the malignancy rate was 12% in the benign category, 16% in the atypia, 25% in the follicular lesion, 62% in the suspicious, 97% in the malignant, and 12% in the nondiagnostic category.

In a review of surgical material by two expert pathologists, there was 11% disagreement with regard to categorizing benign versus malignant between diagnoses by experts and local pathologists and 8% disagreement between the two experts. When the experts conferred about their disagreements, the difference was reduced to 3%.

CONCLUSIONS

False positive and false negative results of thyroid cytopathology remain a challenge. The surgical pathology was benign in two thirds of the indeterminate FNA cytology category.

COMMENTARY • • • • • • • • • • • • • • • •

This report raises several issues. First, it should be noted that this paper emanated from the Veracyte company, which markets a thyroid FNA molecular diagnosis method that is an analysis of 142 genes. It is surprising that, in the prospective study, only 8% of lesions were classified as indeterminate, whereas in the meta-review, the indeterminate category was found in 10% to 26% of reports. In addition, by ignoring the breakdown of the indeterminate category into its three subtypes that had progressively more possibility

FALSE POSITIVE AND FALSE NEGATIVE RESULTS OF THYROID CYTOPATHOLOGY REMAIN A CHALLENGE

of malignancy going from atypia to suspicious for carcinoma, the authors lost the benefit of the Bethesda classification. This is shown in the results of the metareview: a relatively low incidence of malignancy in the atypia category (16%) and a high incidence in the category suspicious for malignancy (62%). These figures must be tempered by the realization that the managing clinician probably used other factors, such as size, appearance on the ultrasound, family history, patient's concern, etc. in the decision as to whether to send a patient for surgical removal of the nodule. This is emphasized by the fact that 11% to 12% of the benign cytology category resulted in diagnoses of malignant lesions at surgical pathological review, although a few were microcarcinomas.

When the clinical factors as noted above do not suggest malignancy, I generally do not recommend surgery for the atypia category because I believe that the likelihood of malignancy does not justify the potential complications of surgery. It should be noted that the authors used the indeterminate FNA classification as a positive diagnosis of cancer in their calculations of predictive values. Of course this increases the false positive percentage.

There is a need for improvement in the diagnosis of thyroid cancer, and molecular markers may provide the progress that is needed in this area. However, these biomarkers for malignancy or benignity are unlikely to entirely replace clinical judgment. In addition, the use of FNA biomarkers depends on obtaining an appropriate sample. And of course, at present there would be a substantial financial cost for molecular markers that examine a large number of genes.

Jerome M. Hershman, MD

BONE METASTASES OF THYROID TUMORS SHOULD BE TREATED WITH BISPHOSPHONATES

Clinical THYROIDOLOGY

Orita Y, Sugitani I, Toda K, Manabe J, Fujimoto Y. **Zoledronic acid in the treatment of bone metastases from differentiated thyroid carcinoma.** Thyroid 2011;21:31-5. Epub November 8, 2010.

BACKGROUND

Bisphosphonates are increasingly being used to delay the growth of bone metastases in a number of cancers, such as in malignant tumors of the lung, breast, prostate, and kidney and in multiple myeloma. They have also been reported to be of value in metastatic thyroid cancer, but most reports include only a small number of cases. Bisphosphonates inhibit osteoclastic bone resorption, and in the cancers mentioned above bisphosphonates are able to decrease the release of markers of bone resorption such as pyridinoline-cross-linked carboxy terminal telopeptide (ICTP).

METHODS AND RESULTS

Among a large cohort of patients with thyroid cancer—1687 patients; 1554 with papillary thyroid carcinoma and 100 with follicular thyroid carcinoma, observed from 1976 through 2008—the records of 50 patients with bone metastases were analyzed. In 28 patients, multiple bone metastases were present at the time of entry into the study.

In Japan, zoledronic acid (ZA) was not available before 2006. This study included patients treated before and after this. By definition, therefore, all patients without ZA treatment were treated before 2006. Standard treatment (radioiodine [¹³¹I], externalbeam radiation, and surgery) was identical in the two groups of patients. During the 2-year observation period, 22 of the 50 patients were treated with ZA. Skeletal-related symptomatic events developed in three patients in this group, as compared with 14 of the 28 patients not treated with ZA.

CONCLUSIONS

Bisphosphonates have emerged as a promising therapeutic tool to slow the progression of bone metastases of many malignant tumors. The present paper, although purely observational, still provides valuable evidence that the beneficial effect of bisphosphonates (in this case, zoledronic acid) also applies to bone metastases of differentiated thyroid tumors. Whether other bisphosphonates, particularly the less expensive and more conveniently applicable ones, have the same effect as zoledronic acid remains a open question.

This retrospective study has its limitations, since the authors compare the efficiency of ZA treatment over a period of 2.5 years with that of data of a group of patients that had been collected over 33 years. Yet, the results (see Figure 1 of the original article) show such a remarkable difference in the survival rate between the two groups that a detailed report of the findings is certainly justified.

Bisphosphonate treatment is not without side effects. In this study, two patients suffered from bisphosphonaterelated osteonecrosis of the jaw, a serious complication that greatly affects quality of life (1). The complications occurred despite regular dental controls and adaption of the dosage to renal function.

The 10% complication rate of osteonecrosis reported in this article is high. This figure is likely to depend on the intensity of treatment. The choice of ZA rather than other bisphosponates may be justified by its allegedly higher efficacy in rapidly progressing tumor metastases. In these cases, its effect can be documented by a marked decrease in ICTP levels. On the other hand, differentiated thyroid carcinomas progress less rapidly, which may explain why the treatment with ZA did not affect ICTP levels. ZA is

BONE METASTASES OF THYROID TUMORS SHOULD BE TREATED WITH BISPHOSPHONATES

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expensive and necessitates monthly infusions. One may be tempted to believe that in the case of slowly progressing bone metastases, pamidronate and other oral preparations of bisphosponates are of similar efficacy. It is hoped that more objective data will be available in the near future.

Albert G. Burger, MD

REFERENCE

1. Silverman SL, Landesberg R. Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. Am J Med 2009;122(2 Suppl): S33-S45.



DOES PLACENTAL IODINE STORAGE COMPENSATE FOR LOW MATERNAL IODINE INTAKE?

Burns R, Azizi F, Hedayati M, Miamian P, O'Herlihy C, Smyth PPA. **Is placental iodine content related to dietary iodine intake? Clin Endocrinol 2011.** doi 0.1111/j.1365-2265.2011.04039.x.

BACKGROUND

The authors' objective is to compare the iodine content of placentas from women giving birth at term in Ireland and Iran, areas with a median urinary iodine (UI) of 79 μ g/L and 206 μ g/L, respectively.

Controversy exists about the role of the placenta in transferring to the fetus iodine ingested by the mother. Although there is evidence of subclinical hypothyroidism or hypothyroxinemia in children born to women with borderline to low dietary iodine intake as assessed by urinary iodine excretion, the majority of mothers and infants show no ill effects from moderate iodine deficiency. Iodine transporters are present in the placenta; however, the proportion of iodine that crosses the placenta by active, as distinct from passive, diffusion or whether iodide stored in the placenta is available to the fetus or is directly related to the iodine content of the diet are unclear. The difference in UI between the two countries is almost certainly related to the policy of mandatory salt iodization undertaken in Iran; in Ireland, iodized salt represents <5% of total salt sales.

METHODS

Placental samples were obtained from 58 women from

Several investigators in the past decade have studied the role of the placenta in iodine metabolism. The subject was nicely reviewed in a recent article by Smyth's group (1). Both iodine transporters, sodium iodine symporter (NIS) and pendrin, have been identified in the placenta (2), as well as deiodinases D3 and to a lesser extent D2. Iodine transporters accumulate iodine in placental cell lines; NIS is upregulated by human chorionic gonadotropin (3) and Ireland and 45 from Iran, delivered at term by elective pre-labor cesarean section, following uncomplicated singleton pregnancies, with normal neonatal outcomes. Tissue iodine content was determined from segments of cotyledons, approximately six per placenta, from different locations within each placenta, periphery and center. Results were expressed as nanograms of iodine per gram of tissue, wet weight.

Clinical

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RESULTS

The mean placental iodine values were 34 ng/g (range, 20 to 269) in women from Ireland and 187 ng/g (range, 20 to 400) in women from Iran (P<0.01). There was a wide variation in iodine values within individual Iranian women, with 42% of them having values <100 ng/g, while only 1% of Irish women had values >100 ng/g. The relationship of placental iodine (in nanograms per gram) to urinary iodine (in micrograms per liter) for the population of pregnant women in Ireland was 1:2, while in the pregnant women in Iran it was 1:1.

CONCLUSIONS

These findings, by demonstrating an apparent ability of the placenta to store iodine in a concentrationdependent manner, suggest a hitherto undetected role for the placenta. Whether placental iodine has a role in protecting the fetus from inadequacies in maternal dietary iodine intake is as yet unknown.

in rats on a low-iodine diet (4). Burns et al. (1) suggest that the placenta has a role not only in uptake but also in storing iodine as a possible means of protecting the fetus from inadequacies in maternal dietary iodine intake. Future research may be directed to a study of disturbances of iodine metabolism as the result of placentas being affected by obstetrical pathologies, such as gestational hypertension, prematurity, and placental abruption, among many others (5).

Jorge H. Mestman, M.D.

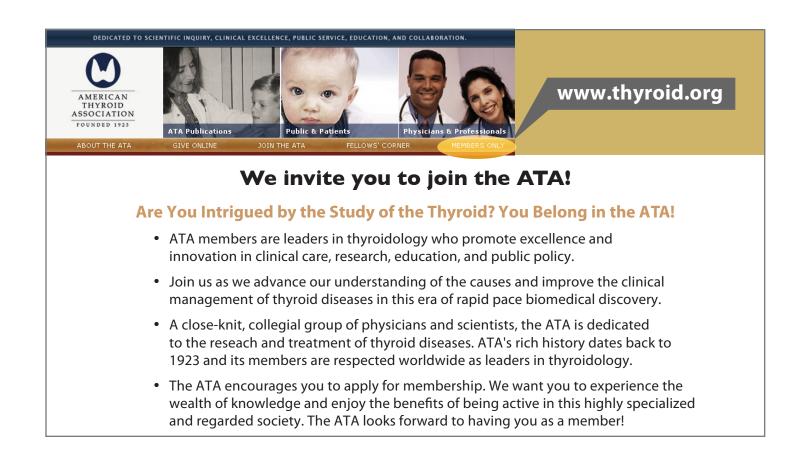
DOES PLACENTAL IODINE STORAGE COMPENSATE FOR LOW MATERNAL IODINE INTAKE?

References

- 1. Burns R, O'Herlihy C, Smyth PPA. The placenta as a compensatory iodine storage organ. Thyroid. March 21, 2011 [Epub ahead of print].
- Bidart JM, Lacroix L, Evain-Brion D, Caillou B, Lazar V, Frydman R, Bellet D, Filetti S, Schlumberger M. Expression of Na+/I– symporter and Pendred syndrome genes in trophoblast cells. J Clin Endocrinol Metab 2000;85:4367-72.
- 3. Arturi F, Lecroix L, Presta I, Scarpelli D, Caillou B, Schlumberger M, Russo D, Bidart JM, Filetti S. Regulation by human chorionic gonadotropin

of sodium/iodide symporter gene expressions in the JAr human choriocarcinoma cell line. Endocrinology 2002;143:2216-20.

- 4. Schröder-van der Elst JP, van der Heide D, Kastelijn J, Rousset B, Obregón MJ. The expression of the sodium/iodide symporter is up-regulated in the thyroid of fetuses of iodinedeficient rats. Endocrinology 2001;142:3736-41.
- 5. Gulaboglu M, Borekci B, Halici Z. Placental tissue iodine level and blood magnesium concentration in pre-eclamptic and normal pregnancy. Int J Gynaecol Obstet 2007;98:100-4. Epub June 19, 2007.



THE PREDICTION FOR MALIGNANCY OF THE CYTOLOGIC DIAGNOSIS "SUSPICIOUS FOR HÜRTHLE-CELL NEOPLASM" IS LOW IN PATIENTS WITH HASHIMOTO'S DISEASE

Roh MH, Jo VY, Stelow EB, Faquin WC, Zou KH, Alexander EK, Larsen PR, Marqusee E, Benson CB, Frates MC, Gawande A, Moore FD Jr, Ciba ED. **The predictive value of the fine-needle aspiration diagnosis "suspicious for a follicular neoplasm, hurthle cell type" in patients with hashimoto thyroiditis.** Am J Clin Pathol 2011;135:139-45.

BACKGROUND

The Hürthle cell's only cytologic pattern can be seen in Hürthle-cell adenomas, Hürthle-cell carcinomas, multinodular goiter, and Hashimoto's thyroiditis. The predictive value for malignancy of this diagnosis varies from 15% to 45%. The purpose of this study was to determine the positive predictive value of a biopsy diagnosis "suspicious for a follicular neoplasm, Hürthle-cell type" (SFNHCT).

METHODS

At 3 institutions, records of patients who had thyroid fine-needle aspiration (FNA) biopsy from 1992 through 2007 were reviewed to find cases with diagnosis of Hürthle-cell neoplasm. Patients with histologic follow-up after a partial or total thyroidectomy were identified, and a diagnosis of Hashimoto's thyroiditis was established based on antibody tests, ultrasound criteria, or pathology. The positive predictive value (PPV) of the cytologic interpretation of SFNHCT for neoplasia and for malignancy were calculated for patients with and without Hashimoto's disease.

RESULTS

Of the 401 patients identified with FNA cytology suspicious for Hürthle-cell neoplasm, 287 (72%) had thyroid surgery. Only 21 (7%) of the 287 patients had Hashimoto's thyroiditis. In 69 (24%) of the 287 patients, the aspirated nodule was found to be malignant. Hürthle-cell carcinomas were found in 41 patients, papillary thyroid cancer in 26, and poorly differentiated cancers in 2. The PPV for malignancy of the cytologic diagnosis of SFNHCT in the non-Hashimoto's group was 25%, but in the Hashimoto's group, it was only 9.5%; the difference did not reach statistical significance.

CONCLUSIONS

Although the lower rate of malignancy in patients with Hashimoto's disease was not statistically different from that in patients with Hashimoto's disease, consideration should be given to classifying the Hürthle-cell cytology in patients with Hashimoto's as atypia of undetermined significance.

This is an excellent study that used the resources and clinical material from three prominent institutions. Nevertheless, the relatively small number of patients with Hashimoto's disease who underwent surgery is probably the basis for the lack of statistical significance in showing that these patients were less likely to have a malignant nodule when the cytologic diagnosis was SFNHCT. The clinicians at these institutions may have been reluctant to send patients with nodules with this cytology to surgery when there was evidence that the patient had Hashimoto's thyroiditis. The malignancy rate of 9.5% in the 21 patients with Hashimoto's disease is similar to that reported in Japanese study of nodules in Hashimoto's patients reviewed in Clinical Thyroidology last month (1); 40 (6.3%) of 638 patients were found to have a cancer. In the current study, the majority of cancers were Hürthle-cell cancers, as predicted by the SFNHCT, but in the Japanese study, the cancers were papillary in 38 and lymphoma in 2. However, this comparison can be faulted because the question asked by the current American study concerns the predictive value of the

THE PREDICTION FOR MALIGNANCY OF THE CYTOLOGIC DIAGNOSIS "SUSPICIOUS FOR HÜRTHLE-CELL NEOPLASM" IS LOW IN PATIENTS WITH HASHIMOTO'S DISEASE

cytologic diagnosis of SFNHCT. I think that the clinician faced with this cytologic diagnosis must use all of the other factors concerning the nodule before making a decision for surgery versus watchful waiting. In the patient with Hashimoto's disease and a small nodule, I would wait rather than send the patient to surgery.

Jerome M. Hershman, MD

REFERENCE

 Mukasa K, Noh JY, Kunii Y, Matsumoto M, Sato S, Yasuda S, Suzuki M, Ito K, Ito K. Prevalence of malignant tumors and adenomatous lesions detected by ultrasonographic screening in patients with autoimmune thyroid diseases. Thyroid 2011;21:37-41. Epub October 9, 2010. Roh MH, et. al.

Clinical THYROIDOLOGY

HIGH DOSES OF SOY PHYTOESTROGEN ARE A RISK FACTOR IN THE PROGRESSION OF SUBCLINICAL TO CLINICAL HYPOTHYROIDISM

Sathyapalan T, Manuchehri AM, Thatcher NJ, Rigby AS, Chapman T, Kilpatrick ES, Atkin SL. **The effect** of soy phytoestrogen supplementation on thyroid status and cardiovascular risk markers in patients with subclinical hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab. February 16, 2011 [Epub ahead of print].

BACKGROUND

The primary aim of this study was to determine the effect of soy phytoestrogen supplementation on thyroid function. Its secondary aim was assessing the effects on cardiovascular risk indexes in patients with subclinical hypothyroidism.

METHODS

The authors conducted a randomized, double-blind, crossover study in a tertiary care setting. Sixty patients with subclinical hypothyroidism participated in the study. Patients with subclinical hypothyroidism comprised those with a serum thyrotropin (TSH) between 5 and 15 mU/L and normal serum free thyroxine (T_4) , verified over a 12-month period. Exclusion criteria included being treated with medications that could interfere with thyroid function, hypertensive drugs, insulin-sensitizing agents, lipidlowering medications, and antibiotics in the previous 6 months. Women contemplating pregnancy were excluded as well. Initially, 75 patients were identified, but 15 were excluded because they were unable to tolerated the soy preparation and 10 because of normalization of the thyroid tests after the screening period. The patients' ages ranged from 44 to 70 years. During the study, subjects were required to avoid food products containing soy, alcohol, vitamin or mineral supplements, and over-the-counter medications. Plasma phytoestrogen levels were measured at each visit. Subjects were randomly assigned to low-dose phytoestrogen (30 g of soy protein with 2 mg of phytoestrogens, representative of a Western diet) or high-dose phytoestrogen (30 g of soy protein with 16 mg of phytoestrogens, representative of a vegetarian diet), supplementation for 8 weeks, and then crossed over after an 8-week washout period. Iodine sufficiency was assessed by a single 24-hour urine iodine estimation.

The primary outcome was progression to overt hypothyroidism (serum TSH >10 mU/L and free T_4 <9 pmol/L), with secondary outcome measures of blood pressure, insulin resistance, lipids, and highly sensitive C-reactive protein (hsCRP).

RESULTS

The mean age of the study group was 57.2 yr; there were 8 male and 52 female subjects with clinical hypothyroidism, of whom 38 (63.3%) were thyroid peroxidase–positive (TPO+).

Six patients (10%) had clinical hypothyroidism after high-dose phytoestrogen and none had it after lowdose phytoestrogen. Of the 6 subjects in whom clinical hypothyroidism developed, 3 had high-dose phytoestrogen supplementation before the low-dose phytoestrogen, and 3 had high-dose phytoestrogen supplementation after low-dose phytoestrogen supplementation. Only 1 patient in whom clinical hypothyroidism developed was TPO+ (no cause was provided for the other 5 patients). TPO antibody titers did not change before or after either supplementation regimen.

For the six patients in whom hypothyroidism developed, TSH values increased by 57% (8.0±0.8 [SD] vs. $13.1\pm0.7 \text{ mU/L}$, P<0.05) and free T₄ decreased by 25% (12.0±0.4 vs. 8.8±0.1 pmol/L, P<0.05). When the six patients in whom overt hypothyroidism developed were compared with the rest of the patients, there were no significant differences in post–high-dose phytoestrogen supplementation daidzein levels (26.3±1 vs. 25±0.9 ng/ml, P = 0.5) or genistein levels (46.1±0.9 vs. 48.6±1.2 ng/ml, P = 0.1). The urine iodine levels were adequate in all patients, including those in whom clinical hypothyroidism developed and the remainder of the patients (272.5±10.2 vs. 234.0±6.2 µg/d; P = 0.2).

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Of the secondary outcomes, there was a significant reduction in both systolic and diastolic blood pressure and significant improvement in insulin resistance and hsCRP levels after the 16-mg phytoestrogen supplementation. but not afer the 2 mg phytoestrogen supplementation. There were no significant changes in lipid profiles.

CONCLUSIONS

Six female patients (10%) in the study progressed into overt hypothyroidism after dietary supplementation with 16 mg of soy phytoestrogen. However, dietary supplementation with 16 mg of soy phytoestrogens significantly reduces the insulin resistance, hsCRP, and both systolic and diastolic blood pressure in these patients, whereas systolic pressure also decreased with 2 mg of phytoestrogens. There is a threefold increased risk (relative risk, 3.6; 95% confidence interval, 1.9 to 6.2) of overthypothyroidism developing in subjects with subclinical hypothyroidism after a few weeks of dietary supplementation with 16 mg of soy phytoestrogens in a vegetarian diet. Conversely, supplementation with 16 mg of soy phytoestrogen significantly reduces insulin resistance, hsCRP, and blood pressure, improving cardiovascular risk profiles in these patients.

This is the first human study showing a statistically significant effect of a few weeks of dietary intake of high concentrations of isoflavones on thyroid function tests in an untreated group of subjects with subclinical hypothyroidism. Unfortunately, the authors did not speculate on the mechanisms by which clinical hypothyroidism developed. Isoflavones bind to both estrogen receptors (ERs) but preferentially bind to ER β ; however the estrogenic effects of isoflavones are not observed in vivo (1). The effect on serum levels of thyroid-binding globulin (not measured in the present study) is very mild, as demonstrated by Duncan et al. in both premenopausal and postmenopausal women (2). In animal studies, isoflavones may inhibit TPO activity, with no effects on serum thyroid hormone levels (3). Goiter in laboratory animals appeared to be due to iodine deficiency, since correction of iodine deficiency prevented goiter formation (4). The effects of soy protein and soybean isoflavones (phytoestrogens) on thyroid function in healthy adults and patients with hypothyroidism were reviewed by Messina and Redmond in 2006 (5), and a systematic review and meta-analysis on the effects of soy products and isoflavones on circulating hormone concentrations in premenopausal and postmenopausal women (6) were just published. Included in the reviews are nine

trials, eight in premenopausal women and one in postmenopausal women. In all the studies but one, subjects were fed isolated soy protein containing varying amounts of isoflavones and for different lengths of time up to 12 months. In most of the trials, thyroid function was not the primary health outcome under investigation. In one Japanese study (7), several groups of patients (both premenopausal and postmenopausal women and men) were fed with 30 g of roasted soy beans for 1 to 3 months. Serum TSH levels increased, although the values remained within the normal range. Messina and Redmond concluded in their review "it is reasonable to ask whether there is a reason for concern that a direct effect of isoflavones on the thyroid might predispose susceptible individuals to developing hypothyroidism. There are no clinical data in support of this contention, but among soy food consumers it is especially prudent to make sure that iodine intake is sufficient." The work of Sathyapalan et al. appears to confirm their prediction; it may be concluded that only very high doses of soy phytoestrogen supplementation may induce clinical hypothyroidism in a minority of patients with subclinical hypothyroidism. The improvement in cardiovascular risk factors despite worsening of thyroid function is of interest.

The other issue to keep in mind is the effect of soy consumption in the absorption of desiccated thyroid

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or levothyroxine, which affects patients on thyroid hormone replacement therapy, requiring an increase in the dosage of hormone or a decrease in cases in which soy protein is discontinued from the diet. Finally, the effect of estrogen replacement on thyroid function in women on thyroid therapy is well known (8) and carefully analyzed in an editorial by the late Robert Utiger (9).

Jorge H. Mestman, MD

References

- 1. Teede HJ, Dalais FS, McGrath BP. Dietary soy containing phytoestrogens does not have detectable estrogenic effects on hepatic protein synthesis in postmenopausal women. Am J Clin Nutr 2004;79:396-401.
- 2. Duncan AM, Merz BE, Xu X, Nagel TC, Phipps WR, Kurzer MS. Soy isoflavones exert modest hormonal effects in premenstrual women. J Clin Endocrinol Metab 1999;84:192-7.
- 3. Chang HC, Doerge DR. Dietary genistein inactivates rat thyroid peroxidase in vivo without and apparent hypothyroid effect Toxicol Appl Pharmacol 2000;168: 244-52.
- 4. Son HY, Nishikawa A, Ikeda T, Imazawa T, Kimura S, Hirose M. Lack of effect of soy isoflavone on thyroid hyperplasia in rats receiving an iodine-deficient diet. Jpn J Cancer Res 2001;92:103-8.
- 5. Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function

in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid 2006;16:249-58.

- 6. Effects of soy protein and isoflavones on circulating hormone concentrations in preand post-menopausal women: a systematic review and meta-analysis. Hum Reprod Update 2009;15:423-
- 7. 440
- Ishizuki Y,Hirooka Y, Murata Y et al: The effects on the thyroid gland of soybeans administered experimentally to healthy subjects. Nipppon Nailbunpu Kashi (Folia Endocrinol) 1991;67:622-629
- 9. Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. N Engl J Med 2001;344:1743-9.
- 10. Utiger RD. Estrogen, thyroxine binding in serum, and thyroxine therapy. N Engl J Med 2001;344:1784-5.

Clinical THYROIDOLOGY

HOW DO YOU DECIDE WHAT DOSE OF THYROXINE IS APPROPRIATE FOR A PATIENT WITH SECONDARY HYPOTHYROIDISM?

Koulouri O, Auldin MA, Agarwal R, Kieffer V, Robertson C, Smith JF, Levy MJ, Howlett TA. **Diagnosis and treatment of hypothyroidism in TSH deficiency compared to primary thyroid disease: pituitary patients are at risk of under-replacement with levothyroxine.** Clin Endocrinol. 2011 [Epub ahead of print]. doi: 10.1111/j.1365-2265.2011.03984.x.

BACKGROUND

Pituitary tumors can destroy thyrotrophs or disrupt their function, causing secondary hypothyroidism as well as affecting other endocrine axes. The treatment of pituitary tumors can further disrupt endocrine axes, producing effects that may be permanent or temporary. What is more, replacing thyroid hormone can exacerbate adrenal insufficiency, and replacing growth hormone can affect the thyroid axis (1).

METHODS

The authors assessed how effective they had been in titrating the levothyroxine $(L-T_4)$ dose empirically to "keep the free T_4 in the middle to upper part of the normal range" in 514 patients with secondary hypothyroidism associated with pituitary tumors. The patients had a wide variety of pituitary tumors and therapies, had been followed for up to 10 years, and had last been seen between 2007 and May 2009. Information on tumor size, history of surgery/ radiotherapy, and data on pituitary hormone and L-T₄ replacement were retrieved, as were the most recent free T₄ and thyrotropin (TSH) values. Patients were divided into those with "low-risk" adenomas, who were at any stage of management as long as they had had no surgery or radiotherapy, and those with "highrisk" macro lesions and/or surgery or radiotherapy. A total of 16 of the 171 low-risk patients were receiving L-T₄, and 131 of 343 high-risk patients were receiving L-T₄. The authors compared the free T_4 levels obtained in these patients with free T₄ levels in some interesting control groups: (1) patients with treated primary hypothyroidism, (2) patients who formerly had been thyrotoxic but now were euthyroid without receiving either L- T_4 or carbimazole, or (3) patients who formerly had been thyrotoxic and now were euthyroid while taking L- T_4 . All controls had to have a free T_4 in the normal range (9 to 25 pmol/L) and a normal TSH (0.3 to 5.0 mIU/L).

RESULTS

No free T₄ below the normal range was observed in patients who had not been prescribed L-T₄. However, 17% of the high-risk group who were not taking $L-T_4$ did have a free T₄ at or below 11 pmol/L, as compared with 8.4% of the control patients who formerly were thyrotoxic and now were euthyroid on no treatment (P<0.0001). In high-risk patients for whom $L-T_4$ had been prescribed, 3.8% had a free T₄ below the lower limit of normal (9 pmol/L). Furthermore, 38% had free T₄ at or below 13 pmol/L, a significantly larger proportion than the 9.5% of the controls who formerly were thyrotoxic and the 13.4% of the patients with primary hypothyroidism for whom L-T₄ had been prescribed (P<0.0001 for both). On the other hand, if the authors had succeeded in obtaining a free T₄ level above 15 to 16 pmol/L in their patients, they would have exceeded the levels found in one third to one half of patients with primary hypothyroidism, suggesting that if they had achieved their aim, some patients with pituitary tumors and hypothyroidism would have been over-replaced.

CONCLUSION

Trying to keep the free T_4 in the middle to upper part of the normal range by empirically titrating the L- T_4 dose left a substantial fraction of patients with pituitary tumor under-replaced, when compared with the free T_4 levels found in controls with primary thyroid disease who were euthyroid.

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Once the possibility of adrenal insufficiency is addressed, a patient with a pituitary tumor who has a low or low-normal free T_4 is generally given L- T_4 , but how much should be given? TSH levels cannot be used as a monitor in secondary hypothyroidism: they may be low, more commonly are inappropriately normal, and may even be slightly above normal. True, when L- T_4 is given, the TSH level will fall further, but when the correct replacement dose is reached, the TSH will be suppressed, often becoming undetectable. On the other hand, aiming for a dose that results in a free T_4 level in the middle to upper range of normal is not patient-specific: the normal reference range is based on a population-average whereas normal individuals control their free T_4 much more closely (2).

One suggested alternative approach is to give all patients under 60 years of age at least a blanket dose of L-T₄ at 1.3 μ g/kg of body weight (3). However the L-T₄ replacement dose in primary hypothyroidism can vary more than threefold between individuals: one size does not fit all.

Clinicians know they must watch for chronic overreplacement in treating primary hypothyroidism to avoid osteoporosis and cardiac arrhythmias, while

References

- 1. Behan LA, Monson JP, Agha A. The interaction between growth hormone and the thyroid axis in hypopituitary patients. Clin Endocrinol (Oxf) 2011;74:281-8. Epub 2011, doi:10.1111/j.1365-2265.2010.03815.x.
- Benhadi N, Fliers E, Visser TJ, Reitsma JB, Wiersinga W. Pilot study on the assessment of the setpoint of the hypothalamus-pituitary-thyroid axis in healthy volunteers. Eur J Endocrinol. 2010;162:323-9. Epub November 19, 2009.

watching for chronic under-replacement to avoid cardiovascular risks. Unfortunately, the risks of over-replacement or under-replacement are more grave in patients who have undergone pituitary surgery—not only during the postoperative period but over the long term—as they have a substantially increased long-term mortality, primarily reflecting vascular death. (The current study did not assess thyroid hormone levels in those pituitary patients who might have died before 2007.) The increase in mortality is true even when patients with a history of Cushing's disease or acromegaly are excluded (4). The standardized mortality ratio is higher in women than in men, and it is even higher in younger patients, although some of this mortality may reflect cerebrovascular problems secondary to radiotherapy for craniopharyngioma (4).

Although a number of thyroxine-responsive gene products have been considered as surrogates for the TSH level, thus far none has proven to be very useful clinically. Perhaps they could be combined along with some physiological parameters to come up with a more satisfactory approach to the hazards of establishing the proper replacement dose of $L-T_4$ for each individual patient with secondary hypothyroidism.

Stephen W. Spaulding, MD

- 3. Ferretti E, Persani L, Jaffrain-Rea ML, Giambona S, Tamburrano G, Beck-Peccoz P. Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism. J Clin Endocrinol Metab1999;84:924-9.
- 4. Sherlock M, Ayuk J, Tomlinson JW, Toogood AA, Aragon-Alonso A, Sheppard MC, Bates AS, Stewart PM. Mortality in patients with pituitary disease. Endocr Rev 2010;31:301-42.

LOW FREE T₄ LEVELS DURING PREGNANCY ARE A RED FLAG THAT NEEDS ATTENTION

Ramos HE, Morandini M, Carre A, Tron E, Floch C, Mandelbrot L, Neri N, De Sarcus B, Simon A, Bonnefont JP, Amiel J, Desguerre I, Valayannopoulos V, Castanet M, Polak M. **Pregnancy in women heterozygous for MCT8 mutations: risk of maternal hypothyroxinemia and fetal care.** Eur J Endocrinol 2011;164:309-14. Epub November 23, 2010.

BACKGROUND

The Allan-Herndon-Dudley syndrome (AHDS) is a rare but very severe congenital X- linked disorder. Clinically, affected patients present with severe muscle hypotonia, with poor muscle development and, frequently, with severe mental retardation. Characteristic laboratory findings in these patients are increased serum total and free triiodothyronine (T₃) levels, low-normal or decreased serum total and free thyroxine (T_4) levels, and normal or borderline increased serum TSH (1). AHDS is caused by mutations of the thyroid hormone transporter, MCT8, that is crucial for a sufficient intracellular supply of thyroid hormones. This is particularly true for the central nervous system. The high expression of the MCT8 transporter in the placenta provides for the transfer of thyroid hormones from the mother to the fetus. Since it is possible that a poorly functioning placental MCT-8 transporter would limit the fetal supply of maternal T₄, the authors studied two mothers who were heterozygous for the AHDS gene.

METHODS AND RESULTS

Two mothers, each having given birth to a boy affected by AHDS, were carefully monitored during their second pregnancy. The first mother had moderate mental retardation and a history of transient hypothyroidism during her first pregnancy; she was now pregnant with twins, one female and one male. The second mother was euthyroid and mentally normal. She had a hitherto unknown mutation of the MCT8 gene. The male fetuses were tested for MCT8 mutations in utero, including direct sequencing of the fetal DNA from chorionic villi. Mutations of the MCT8 gene were excluded. In the first mother, thyroid function was tested every 2 weeks during the first trimester. In the second mother, the first thyrotropin (TSH) measurement was obtained at week 24. Fetal thyroid growth was assessed by ultrasonography, and thyroid function was indirectly monitored by following skeletal maturation, heart rate, mobility and growth.

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During the first mother's first 12 weeks of pregnancy, free T_4 levels were decreased (5.6 to 7.6 pool/L; normal range, 11 to 19) without any variability of serum TSH (0.8 to 0.95 mU/L). The patient was treated with T_4 in increasing doses up to 150 µg per day starting at week 12 until after delivery. Despite this treatment, serum free T_4 levels remained below the normal range while serum TSH was invariably within the normal range. In the second mother, the free T_4 level at week 24 was 11 pool/L and the serum TSH 0.6 mU/L. The patient was treated with 50 µg of T_4 . The three offspring were all normal at birth and during the first weeks postnatally.

CONCLUSIONS

MCT8 is an important transporter of T_4 into the cell. When mutated, such as in AHDS, cells are deficient in thyroid hormones and the affected children have severe hypotonia and mental retardation. Serum free T_4 levels are low and free T_3 levels high normal. MCT8 is strongly expressed in the placenta. In this article, two mothers heterozygous for an MCT8 mutation are described, one presenting with a spuriously low and the other with a frankly reduced serum free T_4 level without concomitantly increased serum TSH. The low free T_4 values were taken as an indication for thyroxine treatment during pregnancy. The nonaffected infants were normal.

It is unlikely that many endocrinologists will be confronted with the dilemma of treating mothers heterozygous for AHDS. The normal outcome of the pregnancies in two mothers heterogeneous for the AHDS gene, as reported in this article, does certainly not warrant the conclusion that T₄ treatment was beneficial. It was undoubtedly not harmful. Yet, this article stresses the importance of an isolated maternal low free T₄ level (in presence of a normal serum TSH level (<2.5 mU/L) for a possible delay in the cognitive functions of the offspring in early childhood. Endocrinologists and obstetricians are now well aware of the importance of closely monitoring thyroid function during pregnancy as well as in pregnant women with a history of present or past thyroid autoimmunity. These patients are likely to receive T₄ treatment, particularly if their serum TSH is above 2.5 mU/L. Less attention is given to serum T₄ levels. However, the remarkable experimental work of Obregon et al. focused on the pathogenic role of low maternal serum T_4 levels (2). Even without considering the special case of AHDS,

- Friesema EC, Visser WE, Visser TJ. Genetics and phenomics of thyroid hormone transport by MCT8. Mol Cell Endocrinol 2010;322:107-13. Epub January 18, 2010.
- 2. Obregon MJ, Calvo RM, Del Rey FE, de Escobar GM. Ontogenesis of thyroid function and interactions with maternal function. Endocr Dev 2007;10:86-98.
- Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy

the authors of this article were right in treating these mothers with thyroxine. In 1999, a clinical article appeared on the subject (3), and last year the first large scale study strongly emphasized the crucial role of low maternal free T_4 levels for the development of cognitive function in early childhood (4). At present, it is not yet clear whether the delayed maturation will be corrected in later life or whether it corresponds to a permanent defect. Nevertheless, endocrinologists and obstetricians must realize that a decreased or borderline low free T_4 , despite normal serum TSH, in a pregnant woman needs attention and that treatment is recommended.

A technical note: The normal range of free T_4 values depend on the kit used in the laboratory. The differences between manufacturers can be substantial. Therefore, it is crucial that all laboratories report the origin of their material and their own normal range, which is still far from standard practice. Also pregnancy stage-dependent reference ranges for free T_4 are needed.

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are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 1999;50:149-55.

 Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. J Clin Endocrinol Metab 2010;95:4227-34. Epub June 9, 2010.

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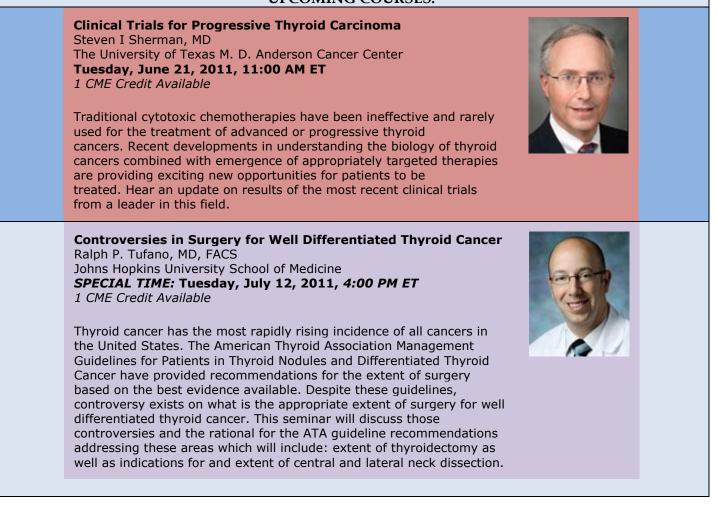
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