CLINICAL THYROIDOLOGY

VOLUME 22 • ISSUE 9 SEPTEMBER 2010

CLINICAL THYROIDOLOGY **FOR PATIENTS**

A publication of the American Thyroid Association

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A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION
FOUNDED 1923

CLINICAL THYROIDOLOGY

VOLUME 22 • ISSUE 9 SEPTEMBER 2010

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Clinical Thyroidology

EDITORS' COMMENTS

This is the ninth 2010 issue of *Clinical Thyroidology*.

EDITORS' CHOICE ARTICLES are particularly important studies that we recommend you read in their entirety.

SEARCH FOR PREVIOUS ISSUES OF *Clinical Thyroidology* Many of our readers have asked for a quick way to find articles published in this journal over the past years. Now you can access previous issues using key words, author names, and categories such as Hyperthyroidism, Thyroid cancer, or other terms pertaining to thyroidology. You will find this by simply clicking the following URL: http://thyroid.org/professionals/publications/clinthy/index.html.

FIGURES The articles in *Clinical Thyroidology* contain figures with the ATA logo and a CT citation with the volume and issue numbers. We encourage you to continue using these figures in your lectures, which we hope will be useful to you and your students.

WHATS NEW On the last page of the journal, in addition to the section HOT ARTICLES AND REVIEWS, we have added CURRENT GUIDELINES that have relevance to thyroidologists, endocrinologists, surgeons, oncologists, students, and others who read this journal. We hope you will find this useful.

We welcome your feedback and suggestions.

Ernest L. Mazzaferri, MD, MACP
Jennifer A. Sipos, MD

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Pertechnetate scintigraphy is a low-cost and widely available option for patients who require postsurgery imaging that avoids thyroid stunning

Kueh SS, Roach PJ, Schembri GP. Role of tc-99m pertechnetate for remnant scintigraphy post-thyroidectomy. Clin Nucl Med 2010;35:671-4.

SUMMARY

BACKGROUND

Patients with differentiated thyroid cancer (DTC) are usually treated with total thyroidectomy with radioactive iodine (^{131}I) remnant ablation (RRA) followed within a few days by posttreatment whole-body uptake scans (RxWBS) to evaluate the efficacy of the initial therapy. Follow-up evaluations 8 to 12 months after the initial therapy require imaging studies, usually neck ultrasonography, and diagnostic whole-body scans (DxWBS) using small amounts of ^{131}I, although DxWBS has largely been abandoned because of the low sensitivity of this imaging study and the possibility of stunning producing a suboptimal response to any ^{131}I therapy that is required. Although ^{123}I can be used, it is expensive and often unavailable. This retrospective study investigated the efficacy of technetium-99m pertechnetate as a potential alternative for remnant scintigraphy (DxWBS) for follow-up after surgery and ^{131}I remnant ablation.

Patients and Methods

All patients with histologically proven DTC had a postoperative DxWBS using pertechnetate followed by subsequent treatment with ^{131}I for remnant ablation. Study patients were identified from a database in the Royal North Shore Hospital Department of Nuclear Medicine, Sydney, Australia, from 1995 through 2006. Pertechnetate scintigraphy was performed between 3 and 6 weeks after total thyroidectomy, and a subsequent RRA was performed within a week after the pertechnetate scan (range, 2 to 7 days). Prior to postoperative scintigraphy and RRA, patients were not treated with levothyroxine, and all patients were instructed to adhere to a low-iodine diet.

Pertechnetate scans were performed 10 minutes after an intravenous injection of 5.4 mCi (200 MBq) of pertechnetate, after which the patients drank a glass of water immediately before the pertechnetate imaging to eliminate esophageal uptake before the study.

Thyroid RRA was performed with 108 to 162 mCi (4000 to 6000 MBq) of ^{131}I administered via an oral capsule followed by an RxWBS scan 3 days after the administration of ^{131}I. Images of the thyroid-bed region were reviewed by two nuclear medicine physicians (reporters) who were aware of the clinical history, but were unaware of other imaging results. A hard-copy film of the pertechnetate scan was viewed first on a viewing box by both reporters concurrently, who classified the scan as either positive, negative, or equivocal. The reporters then viewed the DxWBS ^{131}I hard-copy scan and classified it as positive, negative, for thyroid remnant or equivocal for remnant ablation, with individual foci labeled only as positive. A direct comparison was then made of the pertechnetate and ^{131}I DxWBS to determine whether sites of uptake were concordant between the two scans. The RxWBS ^{131}I scan was regarded as the standard against which the pertechnetate scan was compared. The patient results were analyzed on both a per-patient and a per-site basis.

RESULTS

Per-Patient Results (Figures 1 and 2)

The study group comprised 70 consecutive patients with DTC who had both postoperative pertechnetate scintigraphy followed by ^{131}I RRA. The study subjects were 13 men (19%) and 57

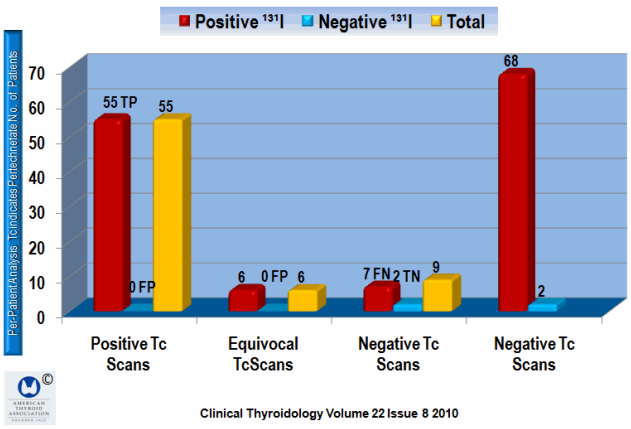

Figure 1. This figure shows the result of per-patient analysis. Tc = pertechnetate; TP = true positive; FN = false negative; FP = false positive; TN = true negative. Data for this figure are derived from Table 1 of Kueh et al.

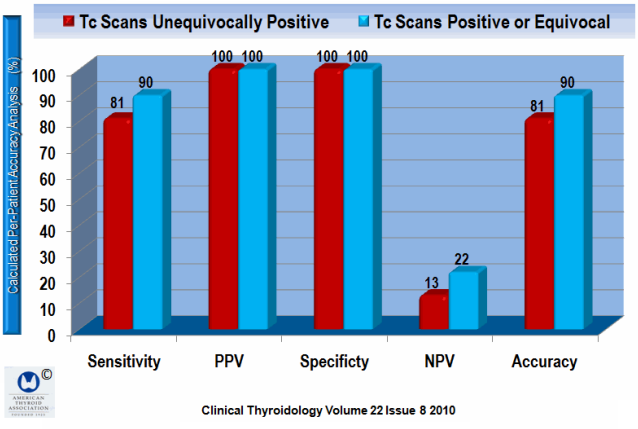

Figure 2. This figure shows the calculated per-patient analysis. NPV = negative predictive value; PPV = positive predictive result. Accuracy is the total accuracy of the per-site analysis.

women (81%) who ranged in age from 11 to 85 years. For the per-patient analysis, pertechnetate scans were considered positive if they had any definite sites of uptake. Of the 70 patients, 2 (3%) had negative ^{131}I scans (DxWBS); both of these patients also had negative pertechnetate scans *(Figure 1)*. Among the remaining 68 patients, 55 (81%) were positive for at least one site on the pertechnetate scan, 6 (9%) had equivocal uptake, and 7 (10%) were negative. However, 54 of the 55 positive pertechnetate scans (98%) showed pertechnetate uptake that correlated with at least one site on the postablation ^{131}I scan. One patient (2%) had uptake at discrepant sites, even though both ^{131}I RxWBS and pertechnetate scans were positive. All six equivocal pertechnetate scans were also positive on the RxWBS scan; however, in 2 (33%) of the equivocal scans, discrepant sites of ^{131}I uptake were again noted. The per-patient analysis revealed a sensitivity for pertechnetate scintigraphy of 81% when the pertechnetate scan was unequivocally positive *(Figure 2)*. If the scan was either positive or equivocal, the sensitivity was 90%. The positive predictive value (PPV) of pertechnetate was 100% for both analyses.

Per-Site Analysis (Figures 3 and 4)

The pertechnetate sites were considered to be accurate on the per-site analysis if they showed concordant uptake at sites that correlated precisely with those seen on the postablation ^{131}I RxWBS scans. ^{131}I RxWBS scans showed a total of 166 positive foci. Of this group, 101 foci (61%) were unequivocally positive on pertechnetate scans, 12 (7%) had equivocal uptake, and 53 (32%) were not detected. Also, the pertechnetate scans showed definite uptake at five sites where the ^{131}I scan was negative and equivocal uptake at another 21 sites, which showed no uptake on ^{131}I. The per-site analysis revealed a sensitivity of 61% if pertechnetate foci were unequivocally positive *(Figure 3)* and a PPV of 95% if pertechnetate foci were either positive or equivocal; the sensitivity was 68% and PPV 81% *(Figure 4)*.

CONCLUSION

Pertechnetate scintigraphy is a low-cost and widely available option for patients who require postsurgery imaging, which avoids thyroid stunning.

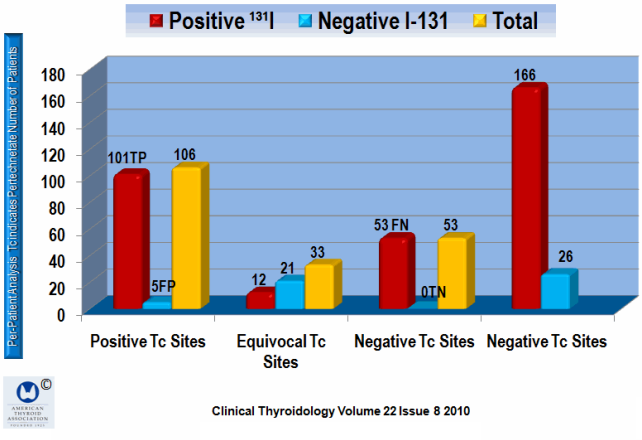

Figure 3. This figure shows the result of per-site analysis (see the definitions for PPV and NPV in Figure 2).

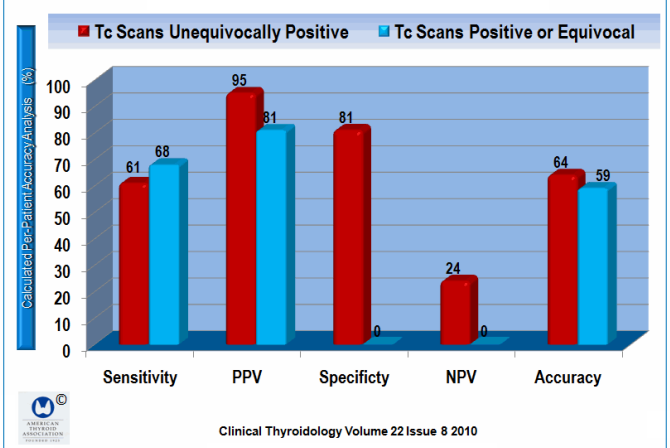

Figure 4. This figure shows the calculated result per-image analysis (%).

COMMENTARY

Patients with DTC often require posttherapy imaging to assess the efficacy of the initial therapy and to assess the therapy during follow-up in patients with evidence of residual or resistant disease. This is particularly true for patients with high-risk disease who require further ^{131}I therapy. Thus there are several reasons why postoperative scanning may be indicated in patients with DTC. Relatively low ^{131}I activities of 1 to 5 mCi [37 to 187 MBq]) often have a low sensitivity for identifying residual disease, which, in addition, also may be associated with stunning (1;2). Moreover, images with small amounts of ^{131}I often have low diagnostic sensitivity (3). There are several limitations in this study; one is that pertechnetate was not compared with low-dose ^{131}I scintigraphy and thus cannot be compared with the relative accuracy of pertechnetate with that of the wide use of smaller amounts of ^{123}I. Some authors (4) have suggested that pertechnetate has a low sensitivity in detecting extrathyroidal and metastatic disease, thus leaving some question about its use. Nonetheless, pertechnetate scans correlated well with postablation scans (the standard), and they are inexpensive, avoids stunning, and according to the data in this study, are highly accurate, with a sensitivity that is 80% with a high PPV (>95%), indicating that pertechnetate scans have a place in the follow-up of patients with DTC, especially those with high-risk tumors.

— Ernest L. Mazzaferri, MD, MACP

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Heterophile interference is not a factor in the day-to-day measurement of serum Tg levels, with fewer than 0.5% of blood samples encountered over an extended period in patients with thyroid cancer or controls

Verburg FA, Wäschle K, Reiners C, Giovanella L, Lentjes EG. Heterophile antibodies rarely influence the measurement of thyroglobulin and thyroglobulin antibodies in differentiated thyroid cancer patients. Horm Metab Res 2010. 10.1055/s-0030-1254132 [doi]

SUMMARY

BACKGROUND

Serum thyroglobulin (Tg) measurements play key roles in the follow-up management and treatment of patients with differentiated thyroid cancer (DTC). However, serum antithyroglobulin antibodies (TgAb) are present in approximately 25% of patients with DTC, which produces substantial alterations in the immunometric measurement of Tg, leaving Tg factitiously low, usually in the undetectable range. The other spurious alteration with Tg immunometric assays occurs with heterophile antibodies (HABs; antibodies that can bind to animal antigens such as antibodies [mouse, goat or rabbit] used in immunoassays) that are not as prevalent, but produce equally important alterations in serum Tg measurements, usually increasing the serum Tg level that is often in the range that suggests persistent disease; although Tg levels may be low in some cases. The aim of this study was to determine the impact of heterophile antibodies on the measurement of serum Tg recovery and TgAb levels in patients with DTC. HABs can interfere with immunometric assays by forming a bridge between capture and detection antibody, which may result in a falsely lower or even a false positive result in the case of an absent analyte. On the other hand, HABs may bind to the capture antibody in such a way that binding of the analyte is hindered, thus casing a false negative result. Most immunometric assays contain additives to reduce HAB interference; this has not been completely successful in blocking HAB interference.

Methods and Study Patients

This is a study of 201 patients that were undergoing follow-up for DTC in the authors' hospitals in Germany, Switzerland, and The Netherlands. Also, 52 control samples were studied. Half of the samples were treated by incubating for 1 hour in HAB-blocking tubes (HABBT). Multiple series of controls were anonimyzed before use: 10 serum samples from patients with Hashimoto's thyroiditis, 10 serum samples from patients with isolated elevation of TgAb levels; 10 serum samples from healthy subjects, and 19 serum samples from patients with a poor Tg recovery independent of TgAb status.

Procedures

Samples were obtained from patients for clinical follow-up and sent for regular Tg measurement. After Tg measurement, any remaining serum samples were frozen to –20°C until the experiment was performed. After thawing, the samples were centrifuged for 5 minutes at 3000 rpm, after which the samples were split: 5 ml was left standing untreated at room temperature for 1 hour and 0.5 ml was incubated for 1 hour at room temperature in HABBT. After incubation, the samples were again centrifuged for 5 minutes at 3000 rpm. Tg, Tg recovery, and TgAb levels were measured in each of the HABBT-treated and untreated samples. The blocked and untreated samples were measured together in the same run using the same kit; all samples in the experiment were measured using kits for the same lot. The Tg-plus method was standardized against the international standard CRM-457, which has a lower detection limit of 0.04 µg/L and a functional sensitivity of 0.2 µg/L.

Criteria for Sample Analyses

For each sample, the differences were calculated between the original Tg value and the Tg measurement obtained after HABBT treatment. The difference was considered significant if the HABBT-treated sample differed from the untreated sample by more than threefold the samples in the same run, as both samples were analyzed within the same run. The ±3 SD cutoff was used because statistically only 0.2% of the measurement would be expected to fall outside this range, which makes this a highly specific cutoff that is not likely to be influenced by random experimental error produced by sample manipulation. This was done because of the high coefficient of variation in the range of TgAb values that are considered negative.

RESULTS

Thyroglobulin Tests

Only 2 of 201 (1%) patient samples had a significant deviation between the native and HABBT-treated samples. In one case the Tg sample dropped from 11.2 µg/L to 8.0 µg/L after HABBT treatment; in another sample a native Tg of 6.3 µg/L was reduced to 4.1 µg/L after HABBT treatment. The Tg levels after HABBT treatment in neither of these patients was great enough to have affected the clinical management.

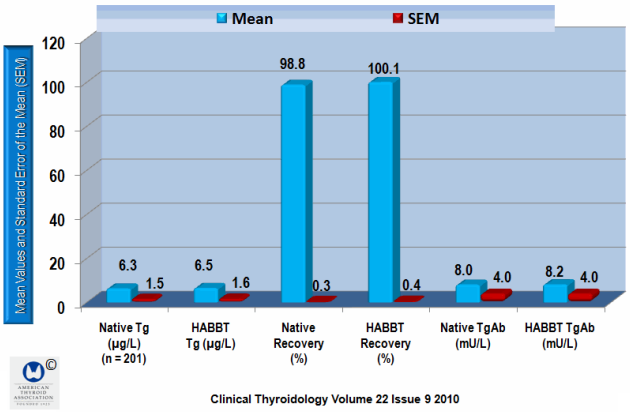

Figure 1. This figure shows the means (±SEM) before (native) and after heterophile antibody blocking tube (HABBT) treatment for thyroglobulin (Tg) levels, Tg recovery rates, and anti-Tg antibody (TgAb). Fewer than 0.5% of blood tests had HAB interference with Tg measurement.

Controls

In none of the 52 control samples was a significant difference in Tg levels found between the native and HABBT-treated samples.

Thyroglobulin Recovery Tests

A significant difference in TgAb levels could not be found between the native and HABBT-treated samples.

Controls

A significant decrease in Tg recovery was found in one patient between the native (129 mIU/L) and the HABBT-treated sample (39 mIU/L). All 51 other samples were free from apparent HAB interference.

CONCLUSION

Two patients had a moderate, but significant lowering of Tg levels after an HABBT treatment of serum Tg that was too little to affect clinical management. None of the 52 controls showed HAB interference in Tg measurement. Neither patients with DTC nor controls experienced HAB interference, and all patients with thyroid cancer and all but one control were found to have interference in TgAb measurement. In all, a possible HAB interference was encountered in 3 of 759 tests (0.4%). The authors concluded that one can assume that heterophile antibody interference is not a factor to be reckoned with in the daily practice of Tg measurement in the treatment and follow-up of patients with DTC.

COMMENTARY

The main observation in this study was that only 3 of 759 tests (0.4%) had possible HAB influence. Moreover, falsely elevated Tg values (n = 2) and TgAb (n = 1) were involved in all 3 cases.

There is no consensus regarding the frequency of HAB interference on different tumor marker immunoassays, with ranges reported from 1% to 80% in the literature (1). One of the earlier studies of HAB influence on serum Tg levels, by Preissner et al. (2) in 2003, suggested that unlike anti-Tg autoantibody interference, HAB immunoassay interferences were not well recognized as a Tg assay problem. They noted that when HAB interference does occur, it usually results in false positive Tg test results. They provided the caveat that some patients with thyroid cancer may be treated with ^{131}I on the basis of an elevated serum Tg result alone, which has the potential of administering unnecessary therapy. The study evaluated the prevalence of HAB interference in a commonly used automated immunoassay in 1106 consecutive specimens with Tg values >1 ng/ml. All Tg measurements were repeated after the samples were incubated in heterophile-blocking tubes, which showed a >3 SD percentage difference from the original result, which was considered to be HAB interference. Tg levels fell to <1 ng/ml in 32 specimens after HABBT treatment, 20 of which fell to <0.1 ng/ml. Of these 20 specimens, 17 were TgAb-negative. All 32 specimens had a fall of >3 SD percentage points (>56.91%) as compared with the original result. There also were two samples that showed a significant increase of greater than 56.91% after HABBT treatment. The authors concluded that HAB interference is relatively prevalent (1.5 to 3.0%) in a commonly used automated Tg assay and can lead to clinically significant artifacts. The authors suggested that unless a Tg assay is confirmed to be free of HAB interference or uses additional blocking steps, HAB interference should be suspected if Tg results do not fit the clinical picture. Verburg found that HAB interference results mostly in falsely elevated Tg or TgAb levels.

A study by Persoon et al. (3) identified HAB interference in Tg measurements in only 1 of 127 patients with the Nichols Advantage chemiluminometric assay, but the study did not use HABBT and identified HAB influence, instead identifying an HAB effect through an elevated Tg recovery rate.

Verburg et al. express concern about using HABBT in their study (and in others), as the exact formulation of these tubes in this study is considered a trade secret by the manufacturer, which leaves the possibility that the tubes contain substances that might interfere with the Tg measurement. The authors opine that the rare cases in which HAB interference can be seen are thus of no clinical consequence. They offer the caveat that this may not hold true for other assays and other populations.

Most authors who have studied this problem have concluded that this is a difficult situation that must be left to the discretion of the attending physician. This is true. In my view, one of the most important concepts in the treatment of patients with DTC is that serum Tg and TgAb concentrations are not static phenomena and that thyroglobulin and TgAb are best observed and evaluated over time, during which the direction of these markers must be carefully assessed. A serum Tg level clearly rising over time is usually the most likely signal of increasing tumor volume. Also, serious conclusions for repeated therapy also evolve around sensitive imaging studies such as ultrasonography, computed tomography–positron-emission tomography, or other imaging studies, depending on the potential location of the residual or recurrent tumor. Such fastidious evaluations almost always will avoid unnecessary ^{131}I therapy when HAB interference is a factor.

— Ernest L. Mazzaferri, MD, MACP

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Hypothyroxinemia is not harmless in preterm infants

Delahunty C, Falconer S, Hume R, Jackson L, Midgley P, Mirfield M, Ogston S, Perra O, Simpson J, Watson J, Willatts P, Williams F. Levels of neonatal thyroid hormone in preterm infants and neurodevelopmental outcome at 5½ years: Millennium Cohort Study. J Clin Endocrinol Metab 2010. jc.2010-0743 [pii];10.1210/jc.2010-0743 [doi]

SUMMARY

BACKGROUND

Transient hypothyroxinemia is the most common thyroid dysfunction of premature infants, leading to adverse fetal neurodevelopment. However, the validity of these associations is uncertain because studies have been adjusted for a different range of factors likely to affect neurodevelopment. The aim of this study was to describe the association of transient hypothyroxinemia with neurodevelopment at 5.5 years of corrected age. Although transient hypothyroxinemia was previously thought to be without clinical significance, more recent studies have found adverse associations between transient hypothyroxinemia and neurodevelopment. Transient hypothyroxinemia is characterized by temporary postnatal reductions in whole blood levels of thyroxine (FT_4) with normal levels of thyrotropin (TSH)

STUDY GROUP AND METHODS

The Study Cohort

The children in this study are from a cohort of infants recruited from January 1998 through August 2001, (Millennium study). The infants were born at ≤34 weeks' gestation (n = 666) or at least 37 weeks (n = 135), from November 1999 through August 2001. Term infants were included to validate the McCarthy scales with a Scottish population. The children were assessed at a mean (±SD) of 5 years 6 months (±2 months) (corrected for gestation). The majority of assessments were performed in the child's hospital of birth (47%) or school (27%), but if the children had moved, testing was performed in the child's general practitioner's premises (17%) or at home (8%).

The McCarthy Scales

For this study, the McCarthy scales provided information on fine and gross motor skills and cognitive development. The scales contain 18 tests, grouped into six scales: verbal, perceptual performance, quantitative, general cognitive, memory, and motor function. Each assessment lasted about 90 minutes and was performed by one of three psychologists trained to use the McCarthy scales, and their performance was audited regularly. The population mean is 100 for the general cognitive scale and 50 for the other scales. The child and the person bringing the child in for assessment each completed a British Picture Vocabulary Scales assessment (BPVSII), which provided an indication of their verbal IQ. The person bringing the child also completed a questionnaire recording significant illnesses or events that had occurred between discharge from the neonatal unit and the child's 5.5-year assessment.

Hypothyroxinemia

Transient hypothyroxinemia was defined as a serum thyroxine (T_4) on day 7, 14, or 28 that was no greater than the 10th percentile for cord serum corrected for gestational age. To classify the hypothyroxinemic status of an infant on postnatal day 7 who was born at 26 weeks' gestation, the cutoff level of T_4 was a value less than or equal to the 10th percentile of cord serum measured in all infants in the Millennium cohort born at 27 weeks' gestation; day 14 levels were compared with 28-week gestation, and day 28 levels were compared with 30-week gestation. This was based on the notion that brain growth follows a predefined pattern, whether in utero or ex utero, in which the T_4 levels in the premature infant should ideally be within the range of T_4 levels of an infant of the equivalent gestational age, while current cord levels are the best proxy for in utero levels. Euthyroid status was defined as a serum T_4 on day 7, 14, or 28 that was greater than the 10th percentile and less than the 90th percentile of cord serum, corrected for gestational age. Transient hyperthyroxinemia was defined as a serum T_4 level on day 7, 14, or 28 that was ≥90th percentile.

Factors Associated with Neurodevelopment

Twenty-six factors identified from the literature that were potentially associated with neurodevelopment, and for which the authors had information collected either during the Millennium study or from the British Association of Perinatal Medicine (BAPM) score that was used as a proxy for severity of illness. The BAPM scoring system was devised to quantify resources required by UK neonatal intensive care units, in which severity of illness is related to the amount of resources required, decreasing from levels 1, 2, and 3 to normal care, with 1 being severe illness.

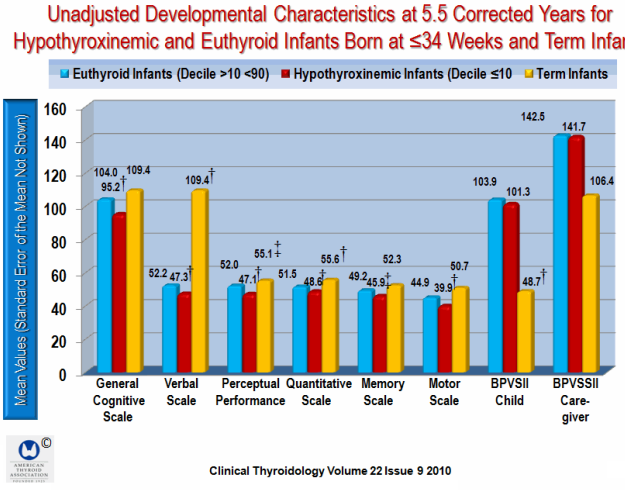

Figure 1. This figure shows the unadjusted developmental characteristics at 5.5 corrected years for infants with hypothyroxinemia and euthyroid infants born at ≤34 weeks' gestation and for term infants. For both the groups of infants, the percentage below 2 SD of the population mean is displayed. The figure shows the significant effect on the general cognitive scale, on the verbal scale, the perceptual performance, quantitative scale, memory scale motor scale, and BPVSII for both the child and the child's caregiver. †P<0.001. ǂ P< 0.05. The data in this figure are derived from Table 2 of Delahunty et al.

The 26 potential independent confounding variables for the evaluation of neurodevelopment were maternal characteristics (smoking history, marital status, BPVSII, maternal age, treated maternal thyroid disease), intrapartum outcomes (use of epidural, spinal or general anesthesia; opiates; or Entonox (during labor), sex of the infant, BWR (ratio of the actual birth weight and the mean Scottish birth weight for the appropriate gestational age), multiple births, mode of delivery, gestation, hospital of birth, BAPM score of level 1 or a level 2 to 3 score at day 7 with or without day 24 or day 28, thyrotoxinemic status, parental lifestyle (maternal postnatal depression or maternal depression), birth order, number of months breast-feeding, attendance at nursery group, fostering of a child, death of close family member, or moving home.

RESULTS

Of the 666 infants recruited at ≤34 weeks' gestation, hypothyroxinemic status could be categorized for 528. The authors assessed 442 infants, 120 (3%) of whom were categorized as hypothyroxinemic; their data were excluded for the present analysis. A total of 100 term infants (≥37 weeks' gestation) were assessed. From the group followed and reported on by the authors, 89 of 442 infants at ≤34 weeks' gestation (20%) were classified as hypothyroxinemic; 31 of 82 at 23 to 27 weeks' gestation (38%), 38 of 166)at 28 to 30 weeks' gestation (23%), and 20 of 194 at 31 to 34 weeks' gestation (10%).

Factors That Identify Children with Hypothyroxinemia

Two factors distinguished the children classified as hypothyroxinemic: a lower gestational age at birth (28 vs. 30 weeks; P<0.0001) and a higher proportion of infants with level 1 BAPM scores on day 7 and day 14 or 28 (56 vs. 14%; P<0.0001). Infants with hypothyroxinemia scored significantly worse than euthyroid infants on all McCarthy scales except for the quantitative subscale.

Adjusting for the Main Confounders of Neurodevelopment

The unadjusted differences were general cognitive scale (9 points), its three subscales (5, 5, and 3 points), memory (3 points), and motor scales (5 points).There was no difference in BPVSII scores of the person bringing the child for assessment. For all tests, a significantly higher proportion of infants with hypothyroxinemia as compared with euthyroid infants scored <2 SD values of the population mean. *(Figure 1)*. After adjustment for the main confounders of neurodevelopment, infants with hypothyroxinemia still scored worse than euthyroid infants on the McCarthy scales, although the magnitude of the difference was attenuated as compared with the unadjusted scores. Infants with hypothyroxinemia scored significantly lower than euthyroid infants on the general cognitive score (7 points) and its verbal subscale (5 points). The adjusted difference for the quantitative (1 point) and perceptual performance (3 points) subscales, motor scale (2 points), and memory scale (3 points) were not significantly lower **(Figures 2 and 3)**.

McCarthy Scales and Subscales versus BAPM Scores

The authors opine that the BAPM scores were the most persistent and detrimental influence on the McCarthy scales. Moreover, the BAPM level 1 infants (the sickest) scored significantly worse on all scales and subscales, ranging from 12 points lower on the general cognitive scale to 5 points lower on the quantitative subscale *(Figure 4)*. Infants of mothers with treated thyroid disease scored significantly higher than infants with euthyroid mothers on the general cognitive scale (19 points) and its subscale (19 points) and the subscale of perceptual performance (12 points). Small increments were

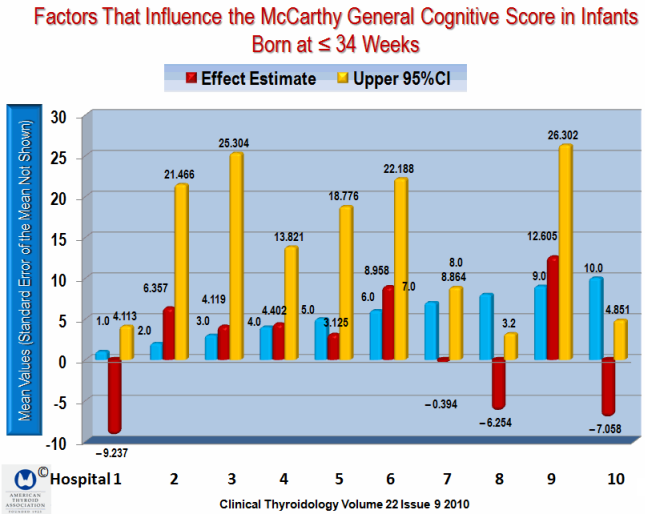

Figure 2. This figure shows the estimates for factors that significantly influence the McCarthy general cognitive score in infants born at ≤34 weeks. The figure shows the estimated and the upper 95% confidence intervals (CI) of the effects of different birth hospitals, maternal thyroid disease, infant hypothyroxinemia, BAPM scores (level 1 and levels 2 and 3), and caregiver BPVSII evaluation. The differences in Table 2 are all statistically significant. The data are derived from Table 3 of Delahunty et al. Nonsignificant factors not shown were smoking, marital status, anesthesia during labor, Entonox or opiates given during labor, emergency cesarean section, vaginal breech, spontaneous vaginal delivery, sex of infant, multiple births, and several other factors.

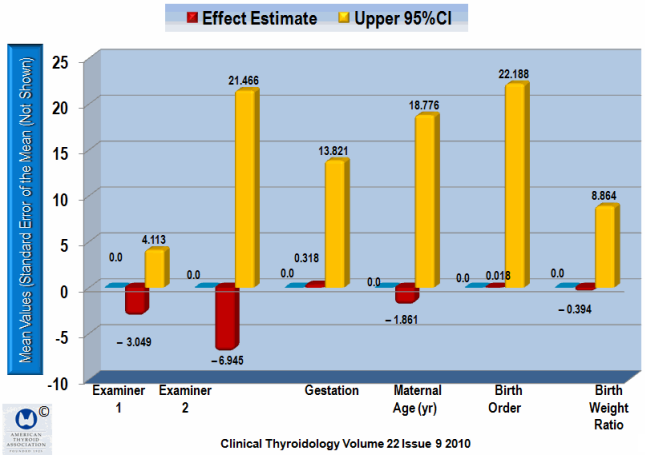

Figure 3. This figure is an extension of *Figure 2*, showing the effects of examiners, gestation, maternal age, birth order, and birth weight ratio.

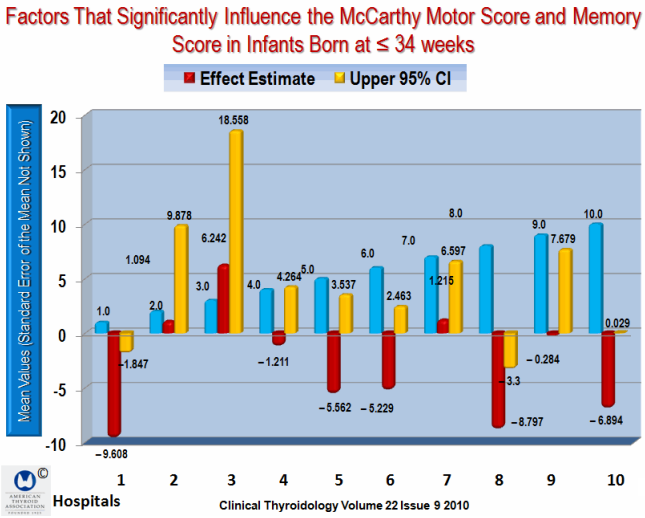

Figure 4. This figure shows the factors that significantly influence the McCarthy Motor Score and memory score in infants born at ≤34 weeks. This figure also shows the effect of the birth hospital, delivery, emergency cesarean section

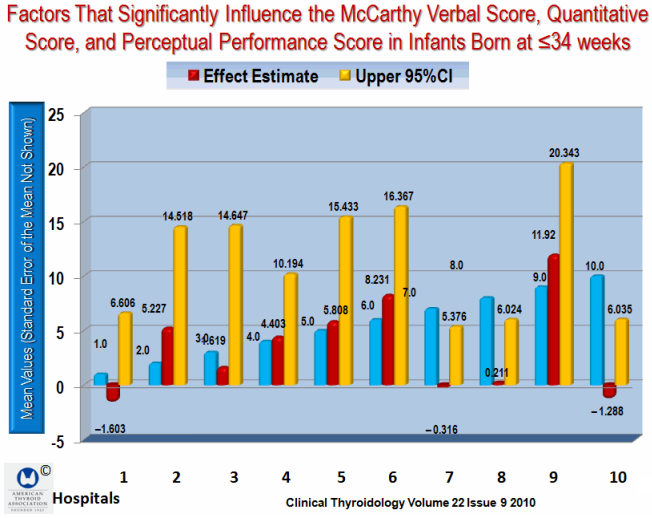

Figure 5. This figure shows the factors that significantly influence the McCarthy verbal score, and perceptual performance score in infants born ≤34 weeks. This figure also shows the estimated effects of birth hospitals, examiners, BAMP score on d 7,14, or 28 and in Level 1 (seriously ill) level 2/3). Not shown in the figures is the McCarthy quantitative score and McCarthy perceptual performance score and generally the same features as mentioned in figures 1 to 4. The data in this figure are derived from Table 5 of Delahunty et al.

found between BPVSII of the person bringing the child for testing and the general cognitive score, its three subscales, and the memory scale. In all, 100 term infants were assessed *(Figure 5)*. The group's mean score on the general cognitive scale was 109, which is significantly higher than the general population norm (P<0.001). The differences in test scores between euthyroid and term infants were generally less marked than the differences between infants with hypothyroxinemia and euthyroid infants.

CONCLUSION

The findings in this study do not support the notion that the hypothyroxinemic state is harmless in preterm infants.

COMMENTARY

Transient hypothyroxinemia is a common finding in premature infants that has been thought not to have long-term sequelae or to require treatment. Reuss et al.(1) investigated whether hypothyroxinemia in premature infants is a cause of subsequent motor and cognitive abnormalities. In this study, the authors retrieved blood thyroxine values during routine screening in the first week of life in children who weighed ≤2000 g at birth and were born at ≤33 weeks' gestation who were enrolled in a population-based study of the late sequelae of neonatal brain hemorrhage. The effects of severe hypothyroxinemia, defined as a blood thyroxine value >2.6 SD below the mean for New Jersey newborns, were assessed before and after adjustment for gestational age and potentially confounding variables. After adjusting for gestational age and multiple prenatal, perinatal, and early and late neonatal variables, severe hypothyroxinemia was found to be associated with an increased risk of disabling cerebral palsy (odds ratio, 4.4; 95% confidence interval [CI], 1.0 to 18.6) and a reduction of nearly 7 points (95% CI, 0.3 to 13.2) in the mental-development score. The authors concluded that severe hypothyroxinemia in preterm infants may be an important cause of problems in neurologic and mental development detected at the age of 2 years.

In a study by Meijer et al. (2) of 563 preterm children born at <32 weeks' gestation with a very low birth weight (<1500 g), the relationship between neonatal thyroxine concentration and psychomotor development was assessed at 2 years of age. The study found a significant association between low neonatal thyroxine concentration and a negative score on the three milestones of development (three developmental milestones chosen for analysis were obtained by direct observation of the child: builds tower by direct observation [coordination] walks without support [gross motor function], and puts a ball in a box by request [passive language]). The authors concluded that their findings do not support the view that transient hypothyroxinemia in preterm infants is harmless.

More recently, Simic et al. (3) studied 64 infants born at 24 to 35 weeks' gestation who were stratified into four gestational age groups: group A, 23 to 26 weeks (n = 10); group B, 27 to 29 weeks (n = 23); group C, 30 to 32 weeks (n = 20); and group D, 33 to 35 weeks (n = 11). The controls were 33 full-term healthy infants (group E).

Free thyroxine (FT_4), triiodothyronine (T_3,) and TSH were measured at 2 and 4 weeks of life and at 40 weeks' postconceptional

age. At 3 months corrected age, all infants were assessed with the Bayley Scales of Infant Development-Second Edition (BSID-II), from which both mental development index (MDI) and psychomotor development index (PDI) scores and four indexes of attention were evaluated: sustained attention, selective attention, attention shift, and total attention. The gestational age-stratified preterm groups differed significantly in T_3 and FT_4 levels at 2 and 4 weeks of life in infants born at <27 weeks' gestation. Preterm infants scored significantly below full-term infants on BSID-II, MDI, and PDI and selective, sustained, and total attention scales. In the preterm group, FT_4 levels were positively associated with PDI and selective, sustained, and total attention. The conclusion was that reduced levels of thyroid hormone in the neonatal period in preterm infants are associated with a reduced neurocognitive outcome in the attention domain at 3 months corrected age.

Lastly, van Wassenaer et al. (4) conducted a randomized, controlled trial with T_4 supplementation in infants born at <30 weeks' gestation and with the last neurodevelopmental follow-up at the age of 5.5 years. T_4 supplementation was associated with an improved outcome of infants born at <28 weeks' gestation and a worse outcome of infants born at 29 weeks' gestation. The authors studied gestational age–dependent effects of T_4 supplementation at the mean age of 10.5 years in children participating in this randomized, controlled trial. Questionnaires regarding school outcome, behavior, quality of life, motor problems, and parental stress were sent to the parents and children and their teachers at the same time point for all surviving children 9 to 12 years of age. A total of 72% of the families responded to the questionnaires. Nonrespondents had more sociodemographic risk factors and worse development until 5.5 years. At the mean age of 10.5 years, T_4 supplementation was associated with a better school outcome in those who were born at <27 weeks' gestation and a better motor outcome in those who were born at <28 weeks' gestation, whereas the reverse was true for those who were born at 29 weeks' gestation. No other gestational age–dependent outcomes were found. The authors concluded that gestation-dependent effects of T_4 supplementation remain stable over time. These effects do not prove beneficial effects of T_4 in infants born at <28 weeks, but the authors suggest that this should be the background for a new randomized, controlled trial with thyroid hormone in this age group.

Delahunty et al. conducted an important study of 442 infants born at ≤34 weeks' gestation who had a serum T_4 measurement on postnatal day 7, 14, or 28 that was compared with 100 term infants who had serum T_4 measurements in cord blood and follow-up at 5.5 years. The infants with hypothyroxinemia, defined as a T_4 level ≤10th percentile on day 7, 14, or 28 corrected for gestational stage, had scores that were significantly lower on McCarthy scale testing than those of euthyroid infants with a T_4 level greater than the 10th percentile and less than the 90th percentile on all days on all McCarthy scales except the quantitative scales. After adjusting the McCarthy scales for 26 confounders of neurodevelopment, the scores of infants with hypothyroxinemia were significantly lower than on the general cognitive and verbal scales as compared with euthyroid infants.

This study found that the most persistent and detrimental influence on the McCarthy scales was the BAPM scores. The British Association of Perinatal Medicine (BAPM), founded in 1976, is an association of professionals who have a special interest in the care of fetuses and newborn babies. Using the available evidence, a working group of BAPM, in consultation with the membership, the Royal Colleges, and the Neonatal Nurses Association, prepared the first edition of this document.

Compared with preterm euthyroid infants, the preterm infants with hypothyroxinemia were born earlier and were more often categorized as sicker (BAPM level 1) during the first 28 postnatal days. The authors of this study indicated that the consistent detrimental association between BAPM 1 and all aspects of developmental assessment were anticipated. The authors previously had shown that the BAPM score, while just a management tool to determine the level of nursing support required, is a very good proxy for severity of infant illness.

Delahunty et al. concluded that how the changing demographic pattern affects hypothyroxinemia is not clear, but it is possible that the hypothyroxinemia observed in their cohort is still no more than a consequence of other, as yet unidentified confounders. However, in the context of this analysis, the authors suggest that their findings do not support the view that the transient hypothyroxinemic state in preterm infants in entirely harmless.

This appears to be the consensus of most studies, and it seems reasonably certain that randomized, prospective studies will be necessary to fully understand the pathophysiology of this problem.

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Men with low normal TSH levels are more likely than usual to have lower bone mineral density

Kim BJ, Lee SH, Bae SJ, Kim HK, Choe JW, Kim HY, Koh JM, Kim GS. The association between serum thyrotropin (TSH) levels and bone mineral density in healthy euthyroid men. Clin Endocrinol (Oxf) 2010;73:396-403. doi.1111/j.1365-2265.2010.03818.x

SUMMARY

BACKGROUND

Although osteoporosis is mainly a disease of postmenopausal women, men account for up to 35% of all femoral fractures and approximately 50% of all vertebral fractures. In addition, the mortality rates are twofold to threefold greater in men with osteoporosis as compared with women with osteoporosis. The causes of osteoporosis in men are wide, including a number of diseases such as Cushing's disease, renal disease, hypogonadism, and hyperthyroidism, all of which have been linked to osteoporosis. Because thyroid hormone has a profound effect on bone metabolism, the question raised by Kim et al. is whether there is an association of bone metabolism and thyroid function in euthyroid men.

Methods and Study Subjects

The study population comprised 2000 Korean participants in a routine health screening program at the Health Promotion Center of the Asan Medical Center (AMC) in Seoul, South Korea. The study subjects were screened from January 1 through December 31, 2006; all the subjects were interviewed and examined by physicians in the health-promotion center, who elicited information on medication and a history of previous medical or surgical diseases. The height (in cm), weight (in kg) and body-mass index (the weight in kilograms divided by the square of the height in meters; BMI) was measured in each man. Smoking and drinking habits were categorized into three levels: never, past, or current smokers, and alcohol drinkers labelled as none, or moderate, 2 to 3 times per week or heavy, ≥4 times per week.

Subjects Excluded from the Study

Excluded from the study were men with abnormal serum thyrotropin (TSH) (>5.0 mIU/L) with or without free thyroxine (FT_4; <0.10.3 or >2.5 pmol/L), and those with a history of thyroid surgery or the use of thyroid hormone or antithyroid drugs. Also excluded were men who did not have blood taken in the fasting state or for whom anthropometric measurements were not taken; those who had any diseases that might affect bone metabolism, such as diabetes mellitus, cancer, hyperparathyroidism, or rheumatoid arthritis; and those who had a stroke or dementia (the last was because of concern about their limited physical activity). Also excluded were subjects with any abnormal results on liver- or renal-function tests, which might have caused thyroid hormone assay results or changes in bone metabolism. After these exclusions, 1478 men were eligible for the study.

Blood Measurements

After overnight fasting, early morning blood samples were analyzed at a central laboratory at AMC. Serum FT_4 concentrations were measured by radioimmunoassay. The intraassay and interassay coefficients of variation (CVs) were ≤8.3% and ≤7.5%, respectively, and the lower limit of detection was 0.5 pmol/L.

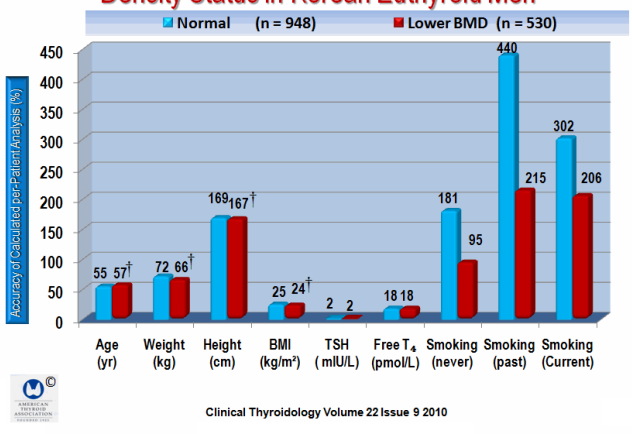

Figure 1. This figure shows baseline characteristics of the euthyroid Korean men by bone mineral density status. The values are means (±SD) . BMI = body-mass index (weight in kilograms divided by the square of the height in meters). The data for Figure 1 are derived from Table 1 of Kim et al.

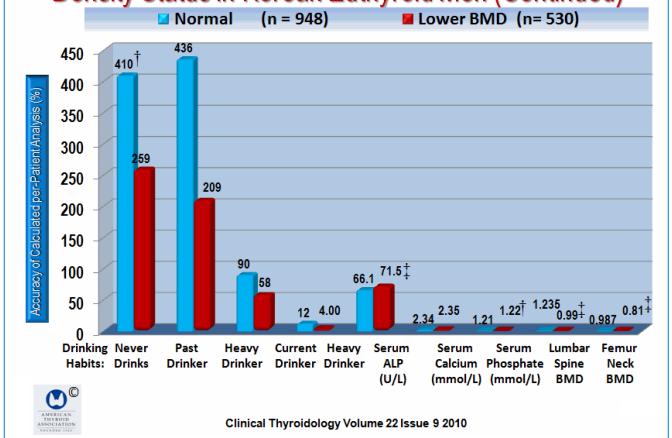

Figure 2. This is a continuation of Figure 1. The number of subjects with osteoporosis (n = 63) was too small for a separate analysis. As a consequence, subjects who met the criteria for at least osteopenia (T-score less than –1.0) at either the lumbar spine or femoral neck were classified as "lower BMD").

Serum TSH was measured by an immunoradiometric assay with a sensitivity of 0.04 mIU/L. Reference ranges for serum FT_4 were 10.3 to 24.5 pmol/L and for serum TSH 0.4 to 5.0 mIU/L. Euthyroidism was defined as a normal serum TSH while not taking thyroid hormone or antithyroid drugs. Serum calcium was measured by an autoanalyzer with intraassay and interassay CVs of 1.24% and 2.06%, respectively, and the reference range was 2.07 to 2.5 mmol/L after correction for serum albumin levels. The intraassay and interassay CVs for serum phosphate were 1.28% and 2.54%, respectively, and for serum alkaline phosphatase (ALP) concentrations 0.7% and 1.3%, respectively; the reference range was 40 to 120 U/L.

Bone Mineral Density (BMD) Measurements

BMD (g/cm2) at the lumbar spine (L2 to L4) and femoral neck was measured by dual-energy x-ray absorptiometry in 910 men using Hologic equipment. In the other 568 men, BMD was estimated using Lunar equipment. The intraassay and interassay CVs were 0.85% and 0.82% for the lumbar spine and 1.20% and 1.12% for the femoral neck, respectively. These values were obtained by scanning 17 volunteers who were not participating in the study, each of which had five scans on the same day, getting on and off the table between examinations to determine the cross-calibrations.

BMD measurements provided absolute values for each anatomic site and were then compared with those of healthy young Korean men (T-score). The reference populations were 245 and 274 men age 20 to 39 years for the Hologic and Lunar equipment, respectively. According to the World Health Organization definition, osteoporosis was diagnosed at a T-score of –25 SD or less at either the lumbar spine or femoral neck. Cutoff values of calibrated BMDs corresponding to osteopenia and osteoporosis were 1.068 and 0.879 g/cm2 for the lumbar spine, respectively, and 0.854 and 0.662 g/cm2 for the femoral neck, in the Korean population. Men who met the criteria for at least osteopenia (T-score less then –1.0) at either site were classified as having lower BMD.

RESULTS

Baseline Characteristics of Study Subjects (Figures 1 and 2)

The mean (±SD) ages of subjects with normal and lower BMD were 55±8.9 years (range, 22 to 84) and 57.2 ±9.2 years (range, 26 to 85), respectively. Weight, height, BMI, and serum TSH concentrations were significantly higher in normal men as compared with men who had lower BMD levels *(Figure 1)*. There were no significant differences in serum FT_4, calcium, and phosphate between the two groups. The serum ALP level was significantly higher in men with lower BMD *(Figure 2)*. About 32% of normal men and 39% with lower BMD levels were current smokers. The percentage of heavy drinkers was slightly higher in men with lower BMD (10.9%) as compared with normal men *(Figure 2)*.

Univariate Analysis (Figure 3)

Using BMD values as a continuous variable, weight and height were positively correlated with both lumber spine and femoral neck BMD, whereas age was only inversely related with the femoral neck BMD. Lumbar spine and femoral neck BMD were both significantly different according to smoking and drinking status. Univariate analysis by Pearson correlation analysis showed that age (P<0.001), weight (P<0.001), height (P<0.001), smoking (P = 0.041, and drinking habits (P = 0.005) were all statistically significant variables *(Figure 3)*.

Multivariate Analysis (Figure 4)

Multivariate analysis examined the independent effect of each variable on BMD. Weight was independently related to BMD at both the lumbar spine and femoral neck. Although current smoking showed an inverse relationship with BMD at both sites, past smoking was associated with only lumbar spine BMD *(Figure 4)*.

Weight was independently related to BMD at both the lumbar spine and the femoral neck. Although current smoking showed an inverse relationship with BMD at both lumbar sites, past smoking was associated only with lumbar spine BMD. Age was

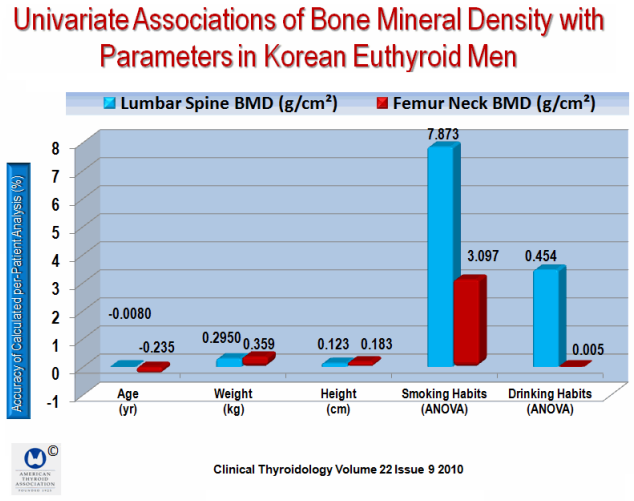

Figure 3. This figure shows the univariate associations of bone mineral density with parameters in Korean euthyroid men. ANOVA = analysis of variance. The data for this figure are derived from Table 2 of Kim et al.

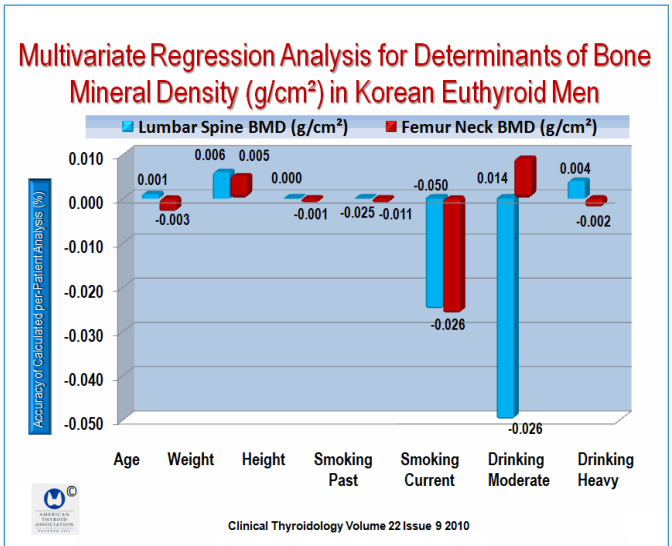

Figure 4. This figure shows the results of multiple regression analysis for determinant of bone mineral density (g/cm2) in Korean euthyroid men. This figure is derived from Table 3 of Kim et al.

inversely associated with femoral neck BMD after considering other independent variables, but it bore no relationship to lumbar spine BMD *(Figure 4)*.

Bone Mineral Density According to TSH Quintile Categories (Figure 5)

Pearson correlation analysis for continuous variables (age, weight, and height) and analysis of variance for categorical variables (smoking and drinking habits) showed mild associations of serum TSH concentration as a continuous variable with BMD values at the lumbar spine and femoral neck. To assess whether the relationships of TSH levels with BMD might have a threshold, subjects were categorized into five groups according to the serum TSH concentration *(Figure 5)*.

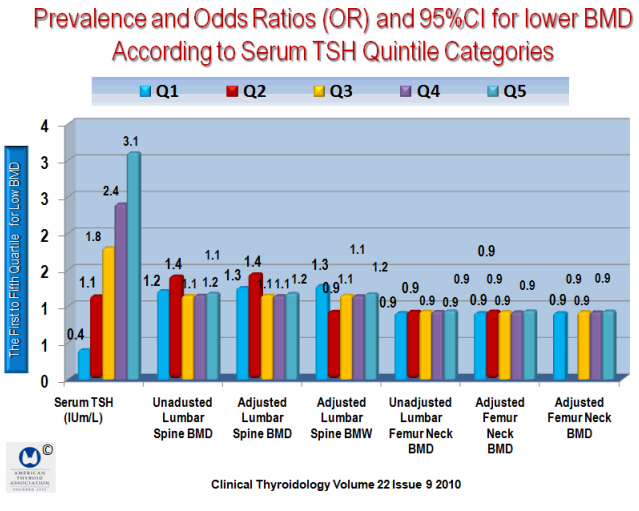

Figure 5. This figure shows bone mineral density according to TSH and the first to fifth quintile category before and after adjustment for confounding variables. The data shown are mean 95% CIs. For lumbar spine and femoral neck BMD according to serum quintile categories estimated by analysis of covariance. BMD = bone mineral density; CI = confidence interval; OR = odds ratio. These data are derived from Table 5 in Kim et al.

There were no differences in height and drinking habits among the groups; however, current smoking and serum ALP concentration showed inverse associations with serum TSH quintile categories, while age and weight increased linearly. BMD values at both the lumbar spine and the femoral neck also increased in a dose-response fashion across increasing TSH quintile categories, before adjustment for age, weight, and height *(Figure 5)*. However, in contrast to results for lumbar spine BMD, the trend for femoral neck BMD was no longer statistically significant after additional control for smoking and drinking habits. Lastly, when ALP concentration was added as a confounding variable, the relationship between lumbar spinal BMD and TSH quintile categories was still significant (P for trend = 0.016). Especially as compared with those in the highest TSH quintile category (Q5), men in the lowest TSH quintile category (Q1) had significantly lower lumbar spine BMD both before and after adjustment for confounding factors *(Figure 5)*.

The overall proportion of subjects in the first Quintile1 and fifth Quintile who met the criteria for osteopenia and osteoporosis were 31.6% and 4.3%, respectively. The prevalence of lower BMD among subjects in Q1 was 42.1%, while only 31.5% of subjects in Q5 met criteria for osteopenia or osteoporosis. After adjusting for age, weight, and height, the odds of lower BMD was 55% higher among subjects in Q1 than it was among subjects in Q5, and the odds ratio (OR) remained statistically significant after additional adjustment for smoking and drinking habits (Table 6 of the article by Kim et al.) When the serum ALP was added as a confounding variable in this model, statistical significant persisted (OR, 1.45 , 95% confidence interval, 1.02 to 2.10) *(Figure 5)*.

CONCLUSION

There is an increased likelihood of lower bone mineral density in men with low normal TSH levels.

COMMENTARY

This study shows that serum TSH concentrations were positively associated with lumbar spine BMD but not femoral neck BMD in healthy euthyroid men after adjusting for several potentially confounding factors. The main finding was that men with low-normal serum TSH concentrations had significantly greater odds of having a lower BMD as compared with men with high-normal TSH concentrations. The authors suggest that these findings are consistent with findings previously reported in women (1;2). The study by Morris et al. (1) also found that low-normal TSH levels were associated with low bone mineral density and an increased risk for osteoporosis in healthy postmenopausal women, even in the euthyroid state. Morris et al. also found that American women with low-normal TSH were levels were 3.4- to 2.2-fold as likely to have osteoporosis and osteopenia, as compared with women with high-normal TSH levels.

Kim et al. identified only one study of BMD in healthy men; Grimnes et al. (3) evaluated the relationship between TSH and BMD in healthy men. The Grimnes study comprised 993 postmenopausal women and 968 men with valid BMD measurements at the hip and forearm in the fifth Tromsø study conducted in 2001. The study subjects were divided into six groups based on the 2.5th and 97.5th percentiles of serum TSH and the quartiles between them. Multiple linear regression analyses adjusting for age, weight, height, and smoking status and for physical activity level and the use of hormone-replacement therapy in women was used in the analyses. After multivariate adjustment, 28 men and 18 women with serum TSH levels less than the 2.5th percentile had significantly lower BMD at the ultradistal forearm (women) and the distal forearm (both men and women), as compared with 921 men and 950 women with serum TSH in the normal range. Also, the 25 postmenopausal women with a serum TSH

above the 97.5th percentile had significantly higher BMD at the femoral neck as compared with women who had a serum TSH level in the normal range. Across the normal range of serum TSH, there was no association between TSH and BMD, and serum TSH as a continuous variable had no effect on BMD in the multiple linear regression model. The authors concluded that TSH within the normal range was not associated with BMD. The small groups of men and women with serum TSH consistent with hyperthyroidism had lower BMD at the forearm than those with serum TSH in the normal range.

In summary, Kim et al. found that serum TSH concentrations within the reference range showed a clear trend of increasing lumbar spine BMD with increasing TSH levels after multivariate adjustment. They also found a lower BMD in association with low-normal TSH, as compared with high-normal TSH concentrations. The authors suggest that longitudinal studies are necessary to document that low-normal serum TSH concentrations are associated with accelerated bone loss, and more importantly, increased risk for fracture.

— Ernest L. Mazzaferri, MD, MACP

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Median maternal serum TSH concentration is increased and FT_4 is decreased in pregnancies resulting in miscarriage or fetal death during the second and third trimesters

Ashoor G, Maiz N, Rotas M, Jawdat F, Nicolaides KH. Maternal thyroid function at 11 to 13 weeks of gestation and subsequent fetal death. Thyroid 2010. doi:10.1089/thy.2010.0058

SUMMARY

BACKGROUND

Hypothyroidism is associated with a substantial risk for miscarriage. However, whether subclinical hypothyroidism has the same effect and is mediated by antithyroid antibodies is in question. This study is based on the hypothesis that maternal thyroid function in the first trimester is altered in pregnancies ending in miscarriage or fetal death

METHODS AND STUDY PATIENTS

This is a prospective screening study of adverse obstetric outcomes in women attending their first routine hospital visit during the 11th to 13th weeks of gestation. During this visit, maternal age, ethnic origin (white, black, South Asian, East Asian, and mixed) were recorded, including cigarette smoking during pregnancy, the method of conception (spontaneous or assisted), parity (parous or nulliparous if no delivery beyond 23 weeks), weight, height, and body-mass index (BMI). Ultrasonography was performed to confirm gestational age by measurement of the crown-to-rump length, to diagnose any major fetal abnormalities, and to measure fetal nuchal translucency thickness (a measurement of the size of the translucent space behind the neck of the fetus using ultrasound between 10 and 14 weeks of pregnancy), reflecting the amount of fluid that has accumulated under the skin of the fetus.

Nuchal translucency tends to be increased in chromosome disorders such as Turner syndrome and Down syndrome; however, this is strictly a screening test that provides information that requires further testing). Also measured were the maternal serum free beta subunit of human chorionic gonadotropin and pregnancy-associated plasma protein A as part of screening for chromosomal abnormalities by a combination of measurement of fetal nuchal translucency thickness and serum biochemistry, as well as serum concentrations of free triiodothyronine (FT_3), free thyroxine (FT_4), thyrotropin (TSH), antithyroperoxidase antibody (anti-TPOAb), and antithyroglobulin antibody (anti-TgAb) at 11 to 13 weeks' gestation. A total of 202 singleton pregnancies that subsequently resulted in miscarriage or fetal death comprise the fetal loss group.

These data were compared with the results of the authors' previous study of 4318 singleton pregnancies with no history of thyroid disease and without the development of preeclampsia that resulted in live birth after 34 weeks of phenotypically normal neonates with birth weight above the 5th centile. The study comprised 726 (16.8%) pregnancies in which the concentration of one or both antithyroid antibodies was ≥60 U/ml. Normal ranges for TSH, FT_3, and FT_4 were derived from the study of the 3592 pregnancies with no antithyroid antibodies. The minimum detectable concentrations were 0.3 pmol/L for FT_3, 1.3 pmol/L for FT_4, 0.003 mIU/L for TSH, and 15 U/ml 30 U/ml for anti-TPOAb. A serum concentration <60 U/ml for anti-TPOAb and anti TgAb was considered normal.

RESULTS

TSH, FT_3, and FT_4 Values in the Fetal Loss and Unaffected Groups (Figures 1 and 2)

The patients in this study were examined from December 2005 through May 2006. The gestational age distribution at the time of miscarriage or the diagnosis of fetal death in the fetal loss group is shown in *Figure 1*. The patient characteristics of the fetal loss and unaffected groups are compared in *Figure 2*. The median BMI was higher in the fetal loss group, as compared with the unaffected group, and there was a higher prevalence of black women, and women who conceived after receiving ovulation induction drugs in the fetal loss group.

Univariate Analysis (Figure 3)

This study converted the serum FT_3, FT_4, and TSH to multiples of the normal medians (MoMs) corrected for gestational age, maternal age, ethnic origin, and BMI.

Univariate analysis found that the TSH MoM was increased in the fetal loss group as compared with the unaffected group

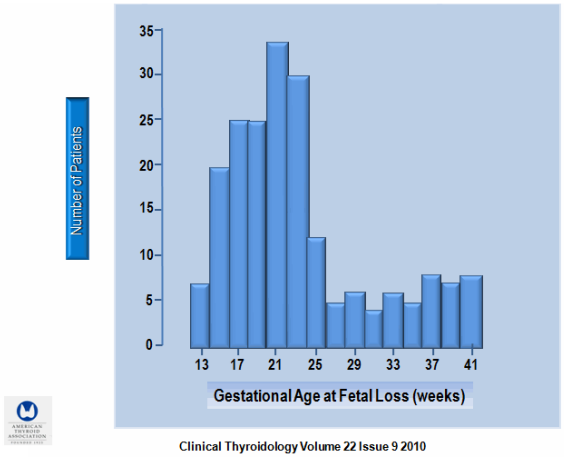

Figure 1. This figure shows the number of patients expressed as gestational age distribution of miscarriage or fetal death. This figure is adapted from Figure 1 of Ashoor et al.

and that the FT_3 MoM and FT_4 MoM were decreased. Linear regression analysis of the fetal loss group found that there was no significant association between the gestational age at fetal loss and TSH MoM (P = 0.654), FT_3 MoM (P = 0.411), and FT_4 MoM (P = 0.917). In the fetal loss group, TSH was above the 97th centile of the normal range in 12 cases (5.9%) and the serum FT_4 was below the 2.5th centile in 10 (5%). In 5 of the 10 cases with low FT_4, serum TSH was high.

Multiple Logistic-Regression Analysis (Figures 4 and 5)

Multiple logistic-regression analysis showed significant contributions to the prediction of fetal loss from the following factors: black ethnic origin (odds ratio [OR], 4.102; 95% confidence interval [CI], 3.003 to 5.603; P<0.001); use of ovulation drugs (OR, 8.238; 95% CI, 5.210 to 13.028; P<0.001); BMI (OR, 1.028; 95% CI, 1.000 to1.057; P = 0.05); and log FT_4 MoM (OR, 0.011; 95% CI, 1.000 to 1.057; P<0.001); but not TSH MoM (P = 0.208). However, if FT_4 MoM is not included, then TSH MoM becomes statistically significant. The authors suggest that this is the result of the good correlation between FT_4 MoM and TSH MoM. The associations between TSH and FT_3, TSH, and FT_4 are shown in *Figures 4 and 5*.

Prevalence of Antithyroid Antibodies (Figure 6)

In a previous screening study by the authors, 726 of the 4318 pregnancies (16.8%), were positive for both antithyroid antibodies, but in this study of pregnancies complicated by fetal loss, the prevalence of antithyroid antibody positivity was not significant *(Figure 6)*.

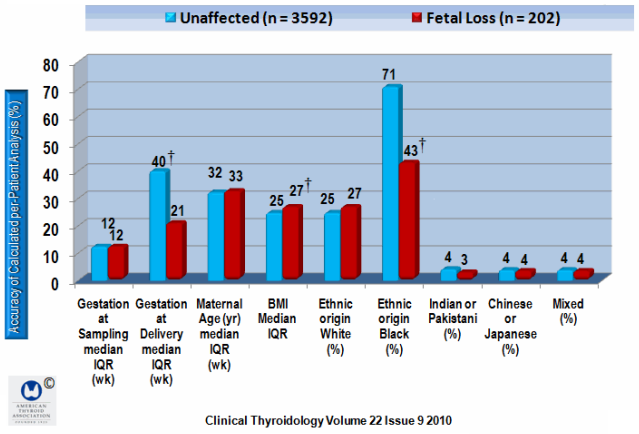

Figure 2. This figure shows the comparison the fetal loss group and the unaffected group. †P<0.001 comparing the two groups. IQR = interquartile range; MoM = multiple of the median. The data for this figure are derived from Table 1 of Ashoor et al.

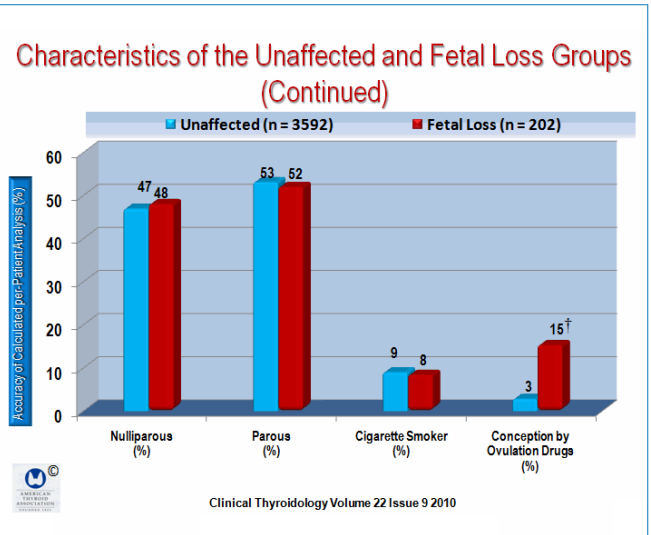

Figure 3. This is a continuation of *Figure 2*, showing the effects of ethnic origin, Parity, cigarette smoking, and the effect of conception by ovulation drugs (%)

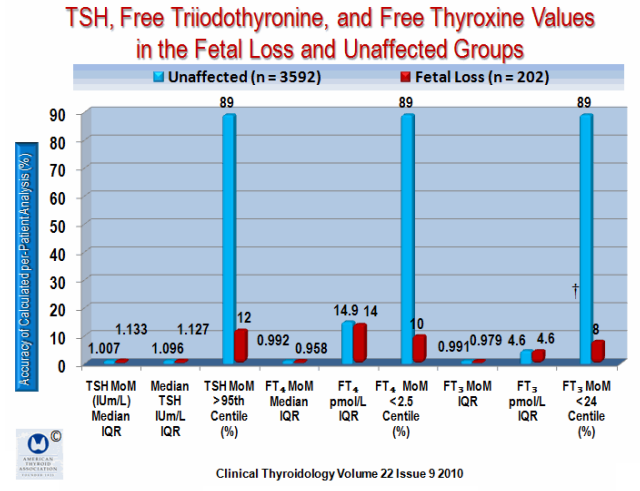

Figure 4. This figure shows TSH, FT_4, and FT_3 values in the fetal loss and unaffected groups. †P<0.05 and ‡P<0.0001, comparing the unaffected (n = 3592) and fetal loss groups (n = 202). The data for this figure are derived from Table 2 of Ashoor et al.

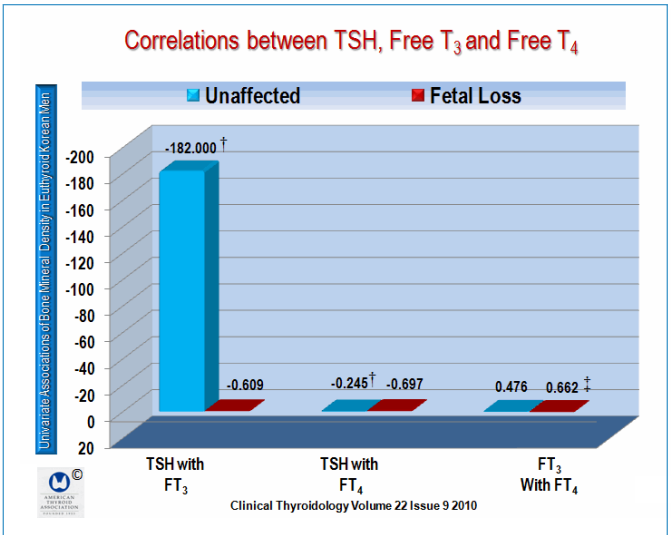

Figure 5. This figure shows the correlation between TSH, FT_3, and FT_4, in the unaffected and fetal loss groups. ‡P<0.01 and †P<0.0001 comparing TSH with FT_3, TSH with FT_4 and FT_3 with FT_4 in the unaffected and fetal loss groups. The data for this figure are derived from Table 4 of Ashoor et al.

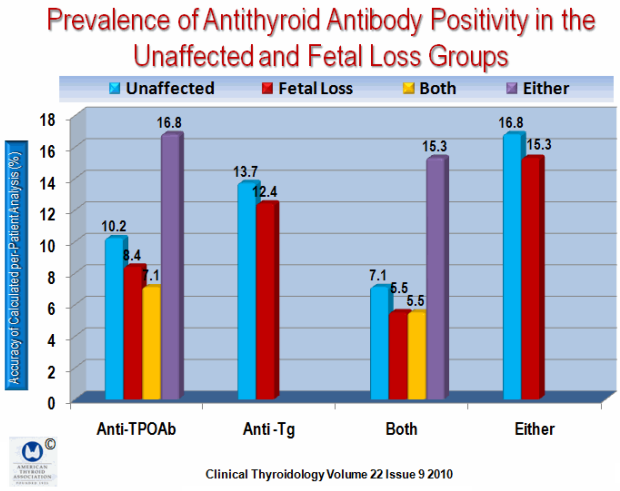

Figure 6. This figure shows the prevalence of antithyroid antibody positivity in the unaffected and fetal loss groups. The data for this figure are derived from Table 4 of Ashoor et al.

CONCLUSION

Median maternal serum TSH concentration is increased and FT_4 is decreased in pregnancies resulting in miscarriage or fetal death during the second and third trimesters, whereas there are no significant differences in FT_3 or the prevalence of antithyroid antibody positivity. Moreover, the fetal loss group had more women of black ethnic origin, a higher median maternal BMI, and more pregnancies conceived after ovulation as compared with the normal outcome group.

COMMENTARY

This study demonstrated that the median TSH MoM was increased, and the median FT_3 and FT_4 MoMs were decreased in the fetal loss group, as compared with the unaffected groups. Linear regression analysis in the fetal loss group found no significant association between the gestation at fetal loss and the TSH MoM and the FT_3 and FT_4 MoMs. In the fetal loss group, serum TSH was above the 97.5th centile of the normal range in 12 cases (5.9%) and the serum FT_4 was below the 2.5th centile in 10 (5%) with low serum FT_4 and high TSH.

Multiple logistic-regression analysis showed that there were significant contributions to fetal loss, including black ethnic origin, use of ovulation drugs, BMI, and log FT_4 MoM but not TSH MoM. However if the regression of FT_4 MoM was not included, the TSH MoM became statistically significant. Thus, more women of black ethnic origin, median maternal BMI, and pregnancies conceived after ovulation all were contributors to fetal loss as compared with the normal outcome group.

Ashoor et al. identified a study by Willinger et al. (1) that reached comparable conclusions. The Willinger study comprised 5,138,122 singleton gestations from the National Center of Health Statistics perinatal mortality and birth files, from 2001 through 2002. The main results were that black women have a 2.2-fold increased risk of stillbirth as compared with white women. The disparity between black and white women in the stillbirth hazard at 20 to 23 weeks was 2.75, decreasing to 1.57 at 39 to 40 weeks. Higher education reduced the hazard for whites more than for blacks and Hispanics. Medical, pregnancy, and labor complications accounted for 30% of the hazard in blacks and 20% in whites and Hispanics. The study found that congenital anomalies and small size for gestational age contributed more to preterm stillbirth risk among whites than blacks. Moreover, pregnancy and labor conditions contributed more to preterm stillbirth risk among blacks than among whites. The authors concluded that the excess stillbirth risk for blacks was greatest in preterm deliveries and that factors contributing to stillbirth risk vary by race and gestational age.

Another finding of the Ashoor study was that BMI was higher in the fetal loss group. Metwally et al. (2) performed a systematic review of all the relevant articles on MEDLINE from 1964 through 2006 and in EMBASE from 1974 through September 2006. The main outcomes were pregnancy loss at <20 weeks of gestation. Sixteen studies were included in the meta-analysis. Patients with a BMI (the weight in kilograms divided by the square of the height in meters) ≥25 had significantly higher odds of a miscarriage, regardless of the method of conception (odds ratio [OR], 1.67; 95% confidence interval [CI], 1.25 to 2.25). Subgroup analysis from a limited number of studies suggested that this group of women may also have greater odds of miscarriage after oocyte donation (OR, 1.52; 95% CI, 1.10 to 2.09) and ovulation induction (OR, 5.11; 95% CI, 1.76 to 14.83). There was no evidence for increased odds of miscarriage after in vitro fertilization–intracytoplasmic sperm injection. The authors concluded that although there is evidence that obesity increases the general risk of miscarriage, there is insufficient evidence to describe the effect of obesity on miscarriage in specific groups such as those conceiving after assisted conception.

Ashoor et al. also noted that there is a scarcity of studies on the outcome of pregnancies conceived after the use of ovulation-induction drugs without in vitro fertilization. The authors question whether pregnancies conceived through assisted reproductive technology (ART) are at increased risk for fetal loss; is the results are inconclusive and studies on maternal-age ART-type and gestational age-specific risk are limited.

One study that Ashoor cites is by Farr et al. (3), who mention that approximately 30% of pregnancies in the United States end in

miscarriage or stillbirth. Farr et al. question whether the notion that pregnancies conceived through ART are at an increased risk of fetal loss is conclusive, and that data on maternal age, the type of ART, and gestational age-specific risk of loss are limited. Farr et al. studied 148,494 ART pregnancies conceived from 1999 through 2002 and found that the Kaplan–Meier estimate of total risk of pregnancy loss was 29% but ranged from 22% to 63% depending on patient age and the ART procedure. The study found that by 6 weeks' gestation, almost 60% of the pregnancy losses had occurred. The risk of pregnancy loss ranged from 10% to 45% at 6 weeks' gestation and from 2% to 7% at the first trimester and was <2% after 20 weeks' gestation.

Ashoor emphasizes that there are multiple causes of miscarriage and fetal death during the second and third trimesters, but their study demonstrates that previously undiagnosed hypothyroidism at 11 to 13 weeks' gestation may be a contributing factor to approximately 5% of fetal losses. They question whether subclinical hypothyroidism and appropriate therapy can prevent fetal loss and the cost-effectiveness of this strategy remains to be determined.

— Ernest L. Mazzaferri, MD, MACP

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.

AMERICAN THYROID ASSOCIATION

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Call for Applications

Editor-in-Chief of *Clinical Thyroidology*

The Publications Committee of the American Thyroid Association (ATA) is soliciting applications for the position of Editor-in-Chief of *Clinical Thyroidology*. The new Editor-in-Chief (EIC) will officially assume responsibility for the journal on January 1, 2011 but should be willing to assume some responsibilities by November/December 2010. The Committee seeks an individual who will continue the growth, quality, reputation, and scholarship of this important ATA publication. The applicant should be a respected thyroid clinician or investigator who is well organized, innovative, energetic and dedicated to making *Clinical Thyroidology* indispensable to clinicians and scientists interested in thyroid diseases. She/he should have experience as a writer and as an editor, associate editor, or editorial board member of a peer-reviewed journal. The initial appointment will be for a three-year term renewable by mutual agreement between the EIC and the ATA.

Applicants should submit a cover letter, their curriculum vitae, and a general statement outlining their vision and aims for *Clinical Thyroidology* to Dr. James Fagin, Chair of the ATA Publications Committee, by email to Ms. Bobbi Smith, CAE, ATA Executive Director (bsmith@thyroid.org).

The applications will be reviewed during August/September, and candidates should be available to be interviewed in person at the 14th International Thyroid Congress (ITC) in Paris, France. Questions regarding this position may be directed to Dr. James Fagin, Search Committee Chair [Phone 646-888-2136 Email faginj@mskcc.org].

American Thyroid Association, Inc.
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Falls Church, VA 22041
(703) 998-8890
www.thyroid.org

Call for Proposals – American Thyroid Association (ATA) Research Grants
Deadline: January 31, 2011

Electronic Submission: Proposals should be submitted electronically through the research grant application feature on the ATA website, www.thyroid.org.

The American Thyroid Association (ATA) is pleased to announce the availability of funds to support new investigator initiated research projects in the area of thyroid function and disease. Topics may include, but are not limited to, clinical thyroidology, thyroid autoimmunity, thyroid and the brain, thyroid hormone action and metabolism, and thyroid cell biology. Research awards are intended to assist new investigators in obtaining preliminary data for submission of a more substantial application (i.e., to the NIH). Research grants, up to $25,000 annually, will be awarded for two year terms based on receipt and review of a satisfactory progress report from funded investigators in the fourth quarter of the first year of funding.

Guidelines for All Research Grant Proposals: As mentioned above, research awards are targeted for funding of new investigators to obtain preliminary data for submission of a more substantial application (i.e., to the NIH).

Eligibility of Applicant and Use of Funds Guidelines:

1. New investigators are individuals who are less than 6 years from completion of their post-doctoral fellowship and have never been a PI on an NIH RO1 or equivalent grant (recipients of NIH R29, R21 and KO8 awards are eligible).
2. Faculty members (MD and PhD) are eligible.
3. Postdoctoral fellows are eligible if their department provides written confirmation that at the time of the award the applicant will have a junior faculty position. Students working towards a PhD are not eligible.
4. Investigators and individuals who have previously received ATA, ThyCa or THANC awards are not eligible. In general, investigators who have achieved the rank of associate professor or higher are not eligible.
5. Applications are limited to one per individual researcher.
6. The funds can be used for direct costs associated with the proposal, including technician's salary, supplies or equipment but not for PI's salary.
7. Recipients of ATA grants should be ATA members or must apply to become ATA members. For new members, membership dues for the first year will be waived.

Proposal Requirements: Interested investigators should submit a brief description of the proposed research by January 31, 2010. Each proposal must include the following:

1. Name and affiliation of applicant with complete work and home contact information
2. Title of proposed study
3. Short proposal that should be no longer than 900 words or three double-spaced pages in 12 point type. These space requirements are absolute and nonconformance will preclude review. This short proposal should include:
   - Background to the project
   - Hypothesis and/or outline of proposed studies
   - Outline of methodology
   - Anticipated results and implications
   - A short statement of how the grant will aid the applicant
   - References (selected)
4. An NIH-style CV (no longer than two pages) including evidence that the applicant is a new investigator (see above), namely date of completion of postdoctoral training and current grant support (if any). In the case of postdoctoral fellows, written confirmation from the department chair must be provided that the applicant will have a junior faculty position at the time of the award. **Note: Without a suitable CV, applications will not be considered.**

Grant Review: The ATA Research Committee will rank proposals according to their scientific merit. Authors of selected proposals will be notified in March 2011 and invited to submit a complete grant application.

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