

CLINICAL THYROIDOLOGY

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EDITORS' COMMENTS

This is the seventh 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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Hypothyroxinemia predicts a higher risk for verbal and nonverbal cognitive delay in early childhood

Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, Visser W, Steegers EA, Verhulst FC, de Rijke YB, Tiemeier H. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study. *J Clin Endocrinol Metab* 2010; jc.2010-0415 [pii];10.1210/jc.2010-0415 [doi]

SUMMARY

BACKGROUND

Thyroid hormones play a critical role in fetal neurodevelopment from early pregnancy onward. Still, population-based data on the association between maternal thyroid function in early pregnancy and a child's cognitive development are sparse. The objective of this study was to review the associations of maternal hypothyroxinemia, thyrotropin (TSH), and free thyroxine (FT₄) levels during early pregnancy across the entire range of cognitive functioning during early childhood.

SUBJECTS AND METHODS

This study was derived from the Generation R Study, a population-based cohort from fetal life onward in Rotterdam, The Netherlands that has been reported previously. The children in this study were born from April 2002 through January 2006. Data concerning thyroid function were complete in 4892 pregnant women. Excluded from the study were women being treated with levothyroxine (n = 36), leaving 4856 women for the study cohort. Of this group, 1147 mothers did not provide information on cognitive outcome in the children, and 50 children who were assessed outside the age range of the cognitive measures were excluded from the study, leaving 3659 children (75.3%) of the 4856 eligible subjects. Analysis of language functioning was performed at 18 months after birth on 2819 observations and on nonverbal cognitive functioning at 30 months on 2748 observations.

THYROID MEASUREMENTS

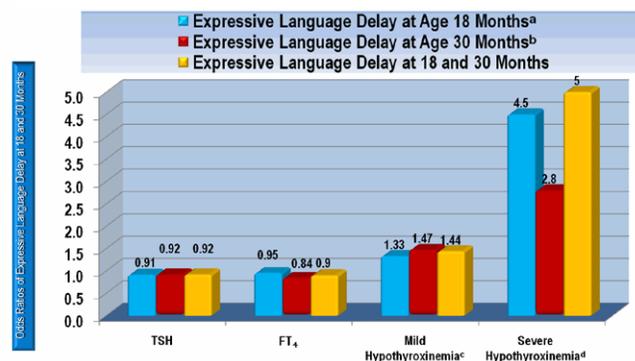
Maternal blood samples were collected in early pregnancy (mean [±SD], 13.3±1.7 wk). In 2295 neonates, cord blood was also obtained and promptly stored at -80°C for TSH and FT₄ concentrations. The normal range of FT₄ was 11 to 25 pmol/L during early pregnancy, and the normal range for maternal TSH was 0.3 to 2.5 µIU/ml. Maternal mild and severe hypothyroxinemia were defined as normal TSH levels and FT₄ concentrations in early pregnancy below the 10th percentile (FT₄, <11.76 pmol/L) and the 5th percentile (FT₄, <10.96 pmol/L), respectively. The following cutoffs were used to define high TSH levels (TSH, >1 SD) above the gestational age-specific mean, and low FT₄ concentrations (FT₄ <1SD) below the gestational age-specific mean at birth. Neonates were categorized as having hypothyroidism when they had high TSH and low FT₄ levels at birth. Maternal hypothyroidism (TSH >2.5 µIU/ml and FT₄ <11 pmol/L) and hyperthyroidism were not studied as determinants because of the small number of at-risk children (54 and 29, respectively).

The interassay coefficients of variation for maternal TSH and FT₄ were 2.5 to 4.1% and 4.7 to 5.4%, respectively, and the intraassay coefficients of variation for maternal TSH and FT₄ were 1.0 to 1.2% and 2.6 to 2.7%, respectively.

VERBAL AND NONVERBAL COGNITIVE DEVELOPMENT

At 18 and 30 months after birth, verbal and nonverbal cognitive development was assessed using three reports mailed by parents. Expressive vocabulary was assessed by the MacArthur Communicative Development Inventory (MCDI), consisting of 680 words. Expressive vocabulary sum scores were converted to age- and gender-specific scores as described in the MCDI manual. At 30 months, mothers completed the Language Development Survey (LDS), which is a 310-word vocabulary

Maternal Thyroid Function in Early Pregnancy and Expressive Language Delay at 18 and 30 Months



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Figure 1. This figure shows maternal thyroid function in early pregnancy and expressive language delay at 18 and 30 months. Models were adjusted for maternal age, maternal educational level, maternal smoking during pregnancy, maternal prenatal distress, gestational age at blood sampling, birth weight, and child ethnicity. The sample size of the respective analysis is represented by a number. a Expressive language delay at 18 months was defined as an expressive vocabulary score below the 15th age- and gender-specific percentile. b Expressive language delay at 30 months was defined as an expressive vocabulary score below the 15th age- and gender-specific percentile or no word combinations. c Mild maternal hypothyroxinemia was defined as normal TSH levels and FT₄ concentrations below the 10th percentile. d Severe maternal hypothyroxinemia was defined as normal TSH levels and FT₄ concentrations below the 5th percentile. Mothers with abnormal TSH levels during early pregnancy were excluded.

checklist. An expressive language delay at 30 months was categorized as LDS vocabulary scores below the 15th percentile or no word combinations. At 30 months, nonverbal cognitive development was assessed using the parent-administered and parent-report part of the Parent Report of Children's Abilities (PARCA) scores, which were calculated by summing the 22 parent-administered items and the 26 parent-report questions. Nonverbal cognitive delay was defined as nonverbal cognitive scores below the 15th age- and gender-specific percentile. Furthermore, with a population-based sample, PARCA and MCDI scores predicted language problems later in childhood.

General nonoptimal neurodevelopment was significantly correlated with word production scores at 18 and 30 months ($r = -0.11$; $P < 0.010$), indicating that low cognitive scores as reported by parents are correlated with observed neuromotor problems.

RESULTS

Almost 66% of the children were Dutch, and 16% of the mothers had a primary education. On average, children were born at term (mean, 39.9 ± 1.1 wk). Based on the criteria described, 1.5% of the mothers had hypothyroidism, 0.8% had hyperthyroidism, 8.5% had mild hypothyroxinemia, and 4.3% had severe hypothyroxinemia. A subgroup of 1815 children was tested to determine whether thyroid status differed among neonates of mothers with and without hypothyroxinemia. Neonates of mothers with severe hypothyroxinemia were not more likely to be hypothyroid (1.3 vs. 1.2%, $\chi^2 = 0.02$, $P = 0.964$) or to have higher FT_4 levels (mean, 12.9 ± 12.6 vs. 12.0 ± 8.1 pmol/L; $P = 0.317$), but they were more likely to have lower FT_4 levels (mean, 19.9 ± 3.39 vs. 21.0 ± 3.39 ; $P = 0.017$) than neonates of mothers with normal prenatal thyroid function.

A similar pattern of results was observed when comparing the status of neonates of mothers with or without mild hypothyroxinemia. Figure 1 shows the adjusted associations of maternal thyroid function in early pregnancy with expressive language delay at 18 months, 30 months, and across ages. Maternal TSH and FT_4 levels were not related to different measures of language functioning, with one exception: higher FT_4 predicted a lower risk for expressive language delay at 30 months. In keeping with this pattern, mild hypothyroxinemia was associated with language delay at 18 and 30 months, although this was not statistically significant (odds ratio [OR], 1.33; 95% confidence interval [CI], 0.91 to 1.94; $P = 0.143$; and OR, 1.47; 95% CI, 1.00 to 2.17; $P = 0.051$, respectively). However, in an analysis across ages, mild hypothyroxinemia was significantly related to expressive language delay (OR, 1.44; 95% CI, 1.09 to 1.91; $P = 0.010$). Severe hypothyroxinemia predicted a higher likelihood of expressive language delay at both 18 and 30 months and across ages (OR, 1.80; 95% CI, 1.24 to 2.61; $P = 0.002$). The maternal thyroid function in early pregnancy and expressive language delay at 18 and 30 months is shown in Figure 1.

Once more, severe maternal hypothyroxinemia predicted a higher risk for nonverbal cognitive delay at 30 months (OR, 2.03; 95% CI, 1.22 to 3.39; $P = 0.007$). There also was a dose-response relationship in the lower range of the FT_4 distribution with verbal and nonverbal cognitive delay in early childhood. In addition, there was a dose-response relationship of maternal FT_4 categories with expressive language delay (OR per category, 1.30; 95% CI, 1.09 to 1.55; P for trend = 0.003). Thyroid function in early pregnancy and nonverbal cognitive delay at 30 months is shown in Figure 2. There were dose-response relations in the lower range of the FT_4 distribution with verbal and nonverbal cognitive delay in early childhood. There was a dose-response relationship of maternal FT_4 categories with expressive language delay (OR per category, 1.30, 95% CI, 1.09 to 1.55, P for trend = 0.003).

CONCLUSION

Models were adjusted for maternal age, maternal educational level, maternal smoking during pregnancy, maternal prenatal distress, gestational age at blood sampling, birth weight, and child ethnicity. The sample size of the respective analysis is represented by n. a Nonverbal cognitive delay was defined as a score below the 15th age- and gender-specific percentile Mild maternal hypothyroxinemia was defined as normal TSH levels and FT_4 concentrations below the 10th percentile. c Severe maternal hypothyroxinemia was defined as normal TSH levels and FT_4 concentrations below the 5th percentile. d Mothers with abnormal TSH levels during early pregnancy were excluded. The data for this figure are derived from Table 2 in Henrichs et.al Maternal hypothyroxinemia predicts a higher risk for verbal and nonverbal cognitive delay in early childhood. The results support the main hypothesis of this study that hypothyroxinemia is associated with poor cognitive function in early childhood,

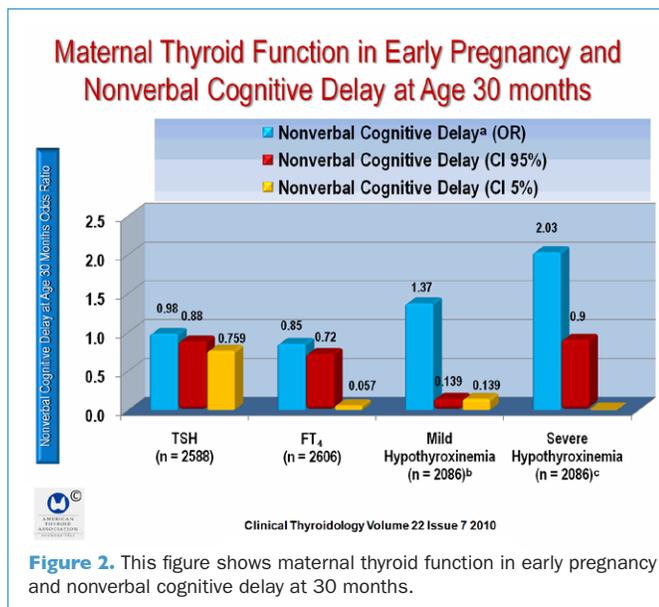


Figure 2. This figure shows maternal thyroid function in early pregnancy and nonverbal cognitive delay at 30 months.

COMMENTARY

This study demonstrates that maternal hypothyroxinemia predicts a higher risk for verbal and nonverbal cognitive delay in early childhood, whereas TSH levels across the entire range did not predict cognitive outcomes. TSH levels >98th percentile during pregnancy accompanied by low T₄ levels (maternal clinical hypothyroidism) resulted in neurodevelopmental deficits. Nonetheless, maternal gestational hypothyroidism should not be disregarded, as neuropsychological outcomes have been reported by Haddow et al. (1). Henrichs et al. suggest that the structure of cognitive abilities in early childhood is far from being clear. However, the study found that severe maternal hypothyroxinemia predicted a higher risk for both verbal and nonverbal cognitive delay, suggesting that maternal hypothyroxinemia below a certain threshold has a consistent effect on cognition. The authors suggest that low levels of FT₄ availability to early embryonic tissues may account for the study findings. A study by Morreale de Escobar et al. (2) suggested that the first trimester of pregnancy constitutes a critical

period in which subtle FT₄ levels may affect brain development. Also, Henrichs et al. suggest that low FT₄ levels can indicate suboptimal placental function during early pregnancy (3). Another possibility, according to Henrichs et al. is that thyroid peroxidase antibodies and autoimmunity can cause hypothyroxinemia (4).

The authors point out that before 2 years of age, it is difficult to measure a child's cognitive development. However, a review of 23 studies that relate to parent-report measures with standard tester-administered assessments supports the validity of measurements by parents (5).

This is a large study that clearly shows how low FT₄ concentrations affect fetal brain development and put children at risk for subsequent neurodevelopmental deficits. The authors opine that T₄ screening and levothyroxine supplements early in pregnancy are needed in patients with hypothyroxinemia.

— Ernest L. Mazzaferri, MD, MACP

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TSH levels between 2.5 and 5.0 in first-trimester thyroid antibody-negative women are associated with a significant increase in the rate of spontaneous miscarriage

Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. *J Clin Endocrinol Metab.* June 9, 2010. doi:10.1210/jc.2010-0340

SUMMARY

BACKGROUND

The definition of what comprises a normal thyrotropin (TSH) during pregnancy has been changing. Although thyrotropin (TSH) values of 4.0 to 5.0 mIU/L were considered normal in the past, more recent opinions suggest that first-trimester TSH values >2.5 mIU/L, and second- and third-trimester values >3.0 μIU/ml are outside the normal range. This is reflected in the Endocrine Society's 2007 guidelines on thyroid and pregnancy, which recommend that TSH values in pregnant women on levothyroxine therapy should be <2.5 mIU/L in the first trimester and <3.0 mIU/L after the first trimester. The TSH in the first trimester is largely driven by human chorionic gonadotropin, which cross-reacts at the TSH receptor, thus creating a decline in first-trimester TSH levels. The objective in this study was to assess the pregnancy loss and preterm delivery rate in first-trimester thyroid peroxidase antibody-negative women with TSH values between 2.5 and 5.0 mIU/L.

Current normative data support a revised normal range for TSH in pregnancy, although the precise upper limit of normal varies somewhat among studies. The authors began with the notion that in order to accurately identify the normal range for TSH during pregnancy, it is of vital importance to define the clinical implications, starting with pregnancy loss and preterm delivery, of an untreated first-trimester TSH in a range that had previously been considered normal.

SUBJECTS AND METHODS

The current study is a component of a prospective study of 4657 women who were screened for TSH and thyroid peroxidase antibody within the first 11 weeks of gestation in southern Italy. To be eligible for the study, women had to have no history of a thyroid disorder and a spontaneous singleton pregnancy. The women were randomly assigned to a universal screening group or a case-finding group and stratified as high risk or low risk for thyroid disease. Both the high- and low-risk women in the universal screening group and the high-risk women in the case-finding group had their serum TSH and thyroid peroxidase antibody levels tested immediately. During pregnancy, the women who were antibody-positive with a TSH >2.5 μIU/ml were treated with levothyroxine and the women with a suppressed TSH and an elevated free thyroxine (FT₄) were classified as hyperthyroid and were referred to an endocrinologist. Maternal and neonatal outcomes were assessed.

All of the women in the study who were thyroid antibody-negative, not classified as hyperthyroid, and had a serum TSH of ≤5.0

mIU/L were evaluated, but none of these women were treated during pregnancy. Women were stratified into two groups: group A had a serum TSH <2.5 mIU/L and was classified as euthyroid; group B had a serum TSH between 2.5 and 5.0 μIU/ml and was classified as having subclinical hypothyroidism. The study outcome was based on the percentage of pregnancy loss, which included miscarriage before 20 weeks, stillbirth after 20 weeks, preterm delivery at 34 to 37 weeks, and very preterm delivery at <34 weeks, in each group.

RESULTS

Stratification of Serum TSH and FT₄ Levels in Group A and Group B (Figure 1)

A total of 4123 women were thyroid antibody-negative, with a TSH of 5.0 mIU/L or lower, and were not hyperthyroid. Group A comprised 3481 women (84.4%), and group B comprised 642 women (15.6%). According to the study design, the median TSH in group A was significantly lower than the TSH in group B (0.82 vs. 3.14 mIU/L; P<0.001). Mean FT₄ levels were significantly higher in group A as compared with group B (12.2 vs. 10.6 pmol/L, P<0.01) (Figure 1). The rate of spontaneous pregnancy loss was 127 of 3481 women in group A (3.6%), which was significantly lower than that in group B, which was 39 of 642 women (6.1%; P<0.006).

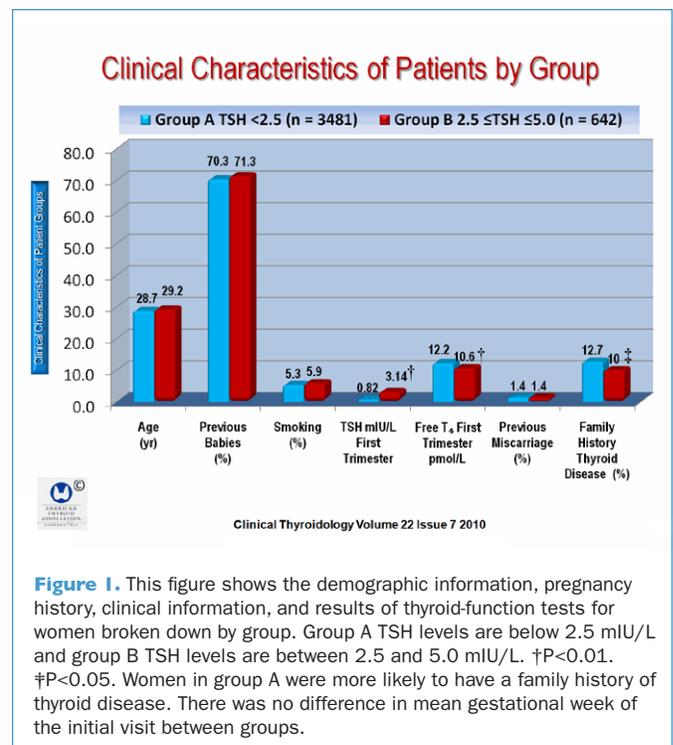


Figure 1. This figure shows the demographic information, pregnancy history, clinical information, and results of thyroid-function tests for women broken down by group. Group A TSH levels are below 2.5 mIU/L and group B TSH levels are between 2.5 and 5.0 mIU/L. †P<0.01. ‡P<0.05. Women in group A were more likely to have a family history of thyroid disease. There was no difference in mean gestational week of the initial visit between groups.

Rate of Spontaneous Pregnancy Loss (Figure 2)

The rate of spontaneous pregnancy loss in Group A (3.6%, n = 127 of 3481) was significantly lower than the rate of spontaneous pregnancy loss in group B (6.1%, n = 39 of 652 (P = 0.006). (Figure 2). There was no difference between groups

in the rates of preterm delivery in group A (1.85%, vs. 0.93% in group B; P = not significant).

The FT₄ was significantly higher in group A as compared with group B; however, the rate of spontaneous pregnancy loss, preterm delivery, or very preterm delivery was not related to FT₄ levels (Figure 2). There were no differences in maternal age, pregnancy history, or thyroid function tests in women who had a miscarriage in each group versus those who did not miscarry. There was a slight but statistically significant increase in smoking rates in women who did not miscarry in group A. The mean gestational age at the time of the first obstetrical visit and mean gestational age at the time of pregnancy loss were essentially identical in all groups.

To further assess the impact of TSH levels, a simple logistic-regression analysis was performed to predict miscarriage from TSH level and smoking status. The odds ratio (OR) for each point of TSH was 1.157; 95% confidence interval [CI], 1.002 to 1.336; P = 0.047), suggesting a continuous relationship between TSH and miscarriage, controlling for smoking. The odds were lower for smokers than nonsmokers (OR, 0.120; 95% CI, 0.014, 0.732, controlling for the TSH level).

Clinical Characteristics of Patients by Group and Miscarriage History

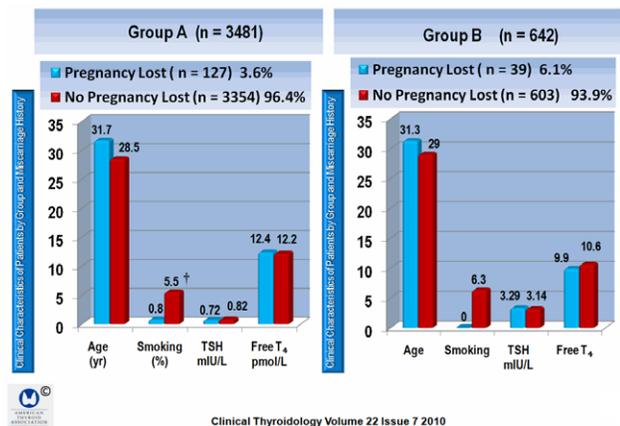


Figure 2. This figure presents age, obstetrical history, clinical data from thyroid-function tests, and mean gestational age of pregnancy loss in groups A and B broken down by the presence or absence of pregnancy loss. There was a slight but statistically significant increase in smoking rates in women who did not have a miscarriage (P<0.05).

CONCLUSION

TSH levels between 2.5 and 5.0 in first-trimester thyroid antibody-negative women is associated with a significant increase in the rate of spontaneous pregnancy loss as compared with the first-trimester thyroid antibody-negative women with TSH levels <2.5 µIU/ml, excluding women with hyperthyroidism.

COMMENTARY

This study shows for the first time that serum TSH levels between 2.5 and 5.0 in thyroid antibody-negative women in the first trimester is associated with a significant increase in the rate of spontaneous fetal loss as compared with first-trimester thyroid antibody-negative women with TSH levels <2.5 mIU/L, except for women with hyperthyroidism. However, there were no differences in the rates of preterm delivery or very preterm delivery. The authors conclude that the increased rates of spontaneous fetal loss in women with TSH levels between 2.5 and 5.0 mIU/L provides strong support to redefine the normal TSH during pregnancy, especially in the first trimester.

Negro et al. summarized the changing opinions concerning the normal range for TSH levels during pregnancy, especially during the first trimester, which has been investigated in a number of studies. For example, over the past decade, the normal TSH range has been studied by Panesar et al. (1), who performed a prospective study of 343 Chinese women and found that the normative range for first-trimester TSH levels were 0.03 to 2.3 mIU/L. Pearce et al. (2) found in a study of 585 antibody-negative women in Boston that before 14 weeks of gestation, TSH levels ranged between 0.04 and 3.6 mIU/L. Another study, by Stricker et al. (3) found that the interpretation of thyroid-function tests in pregnant women using nonpregnancy reference intervals could potentially result in misclassification of a significant percentage of the results, including TSH and thyroid peroxidase autoantibody (anti-TPOAb). Negro et al. found

that the overall consistency in the TSH ranges reported for the first-trimester antibody-negative women reached a consensus centering on the lower limit of TSH of 0.04 and an upper range of normal of 2.5 mIU/L.

A recent study from the Netherlands by Benhadi et al. (4) found in a cohort of pregnant women without overt thyroid dysfunction that the risk of child loss increased with higher levels of maternal TSH and that maternal FT₄ concentrations and child loss were not associated. The authors concluded that pregnancy outcome might be improved by treating women with mildly elevated TSH, or even with normal TSH if TPOAb is present.

Negro et al. concluded that recent normative studies confirm that a redefinition of the TSH is required, resulting in a shift to a range of approximately 0.03 to 2.5 mIU/L, and that a TSH >2.5 mIU/L not only exceeds the 97.5th percentile for the first trimester of pregnancy but also is associated with serious physiologic consequences. Negro et al. (5) recently reported in a prospective, randomized trial that treating thyroid TPOAb-positive women with TSH levels ≥2.5 mIU/L results in a significant decrease in maternal and neonatal complications.

The authors propose that a similar study is now needed for thyroid antibody-negative women with a TSH >2.5 mIU/L, which seems warranted, based on the current findings.

— Ernest L. Mazzaferri, MD, MACP

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Growth pattern and metastatic behavior of papillary thyroid cancer are similar in prepubertal children and adolescents

Machens A, Lorenz K, Thanh PN, Brauckhoff M, Dralle H. Papillary Thyroid cancer in children and adolescents does not differ in growth pattern and metastatic behavior. *J Pediatr* 2010. S0022-3476(10)00326-4 [pii];10.1016/j.jpeds.2010.04.026 [doi]

SUMMARY

BACKGROUND

Although uncommon, thyroid cancer is not unusual in adolescents and in the young adult population. Between 1975 and 2000, thyroid cancer represented approximately 7.8% of all cancers diagnosed in the 15- to 19-year age group according to data in the Surveillance Epidemiology and End Results (SEER) database (1). The yearly incidence of differentiated thyroid cancer (papillary and follicular thyroid cancer) in the United States in patients from 5 to 20 years of age ranged from 0.7 to 14 cases per year per million in patients 5 to 20 years of age (SEER 1975 to 2000) (1). The objective of the study by Machens et al. was to provide comprehensive clinicopathologic data, comparing the growth pattern and metastatic behavior of papillary thyroid cancer between children and adolescents.

PATIENTS AND METHODS

A total of 83 consecutive patients 18 years of age or younger had surgery for papillary thyroid cancer (PTC) from November 1994 through December 2009. A total of 36 patients had initial surgery and 47 had reoperations for suspected or confirmed locoregional disease, mainly lymph-node metastases. Of the 83 patients, 57 (69%) were women and 26 (31%) were men, comprising 9% of the 921 patients treated at the Martin Luther University, Halle (Saale), Germany, for papillary thyroid cancer during this period.

Five (6%) of the 83 patients, 9, 12, 14, and 15, and 16 years of age, had a history of external radiation for inoperable intrathoracic neuroblastoma, nephroblastoma (Wilms' tumor), Hodgkin's lymphoma, acute lymphocytic leukemia, and medulloblastoma 5 to 10 years earlier.

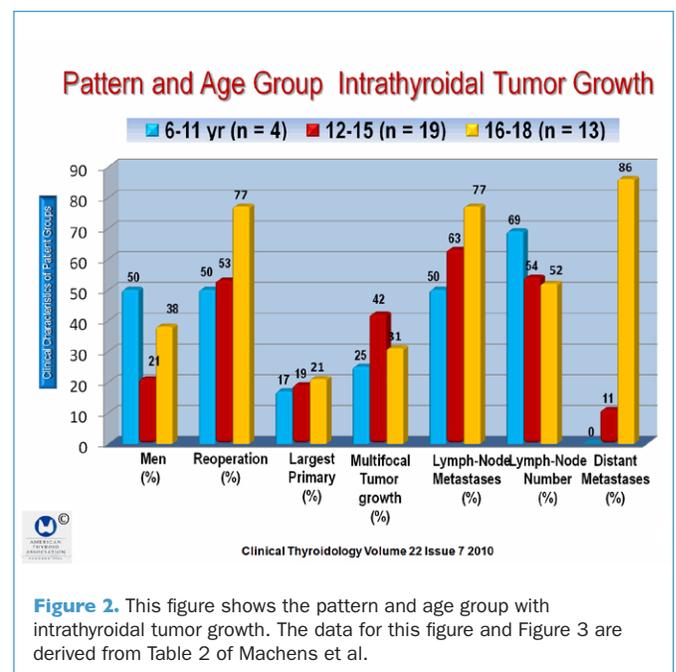
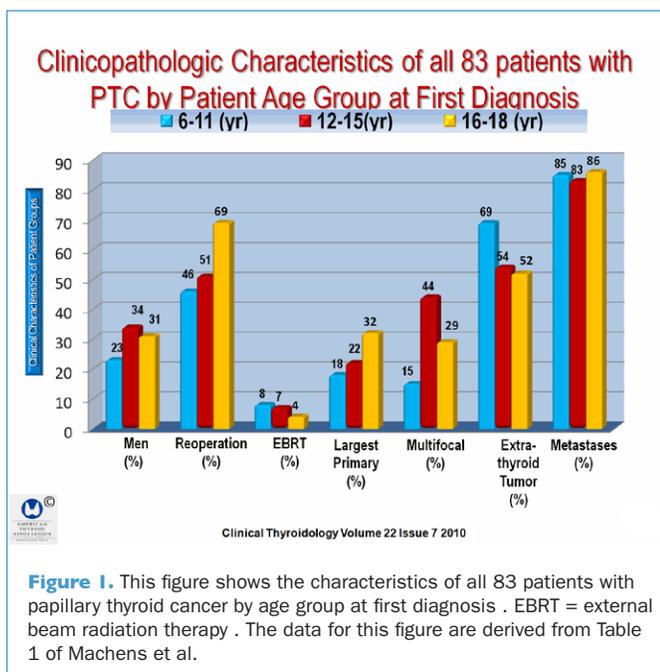
All 83 patients had total thyroidectomy, 80 of whom (96%) also had systematic lymph-node dissection, and 57 (69%) had lateral neck compartment dissection. In addition, the upper anterior mediastinum was dissected in 7 (8%) of the 83 patients. Three children did not have lymph-node dissection because they were incidentally found to have 4-, 6-, and 10-mm solitary PTCs, confined to the thyroid gland.

RESULTS

Clinicopathologic Patient Characteristics by Age Groups and Tumor Growth Pattern (Figures 1 to 4)

Among the 83 patients with PTC, there were no age-related difference in sex distribution, reoperation rate, history of external radiation, multifocal tumor growth, number of thyroid cancers, extrathyroidal tumor growth, lymph-node metastases, number of involved and removed lymph-node metastases, number of involved and dissected lymph-node metastases, or distant metastases (Figure 1).

After stratifying the tumor growth pattern, patients with extrathyroidal tumor growth were found to have larger tumors,



especially in the highest age group, but this difference was not significant (Figures 2 and 3).

When stratified by increments of 10 lymph nodes, significant relationships were found with the intensity of lymph-node metastases and multifocal tumor growth, the number of thyroid cancers, and extrathyroidal tumor growth. However, all

other clinicopathologic variables, including patient age at first diagnosis, did not differ significantly when grouped by the number of lymph-node metastases (Figure 4).

CONCLUSION

This study suggests that there is a similar growth pattern and metastatic behavior of PTC in prepubertal children and adolescents.

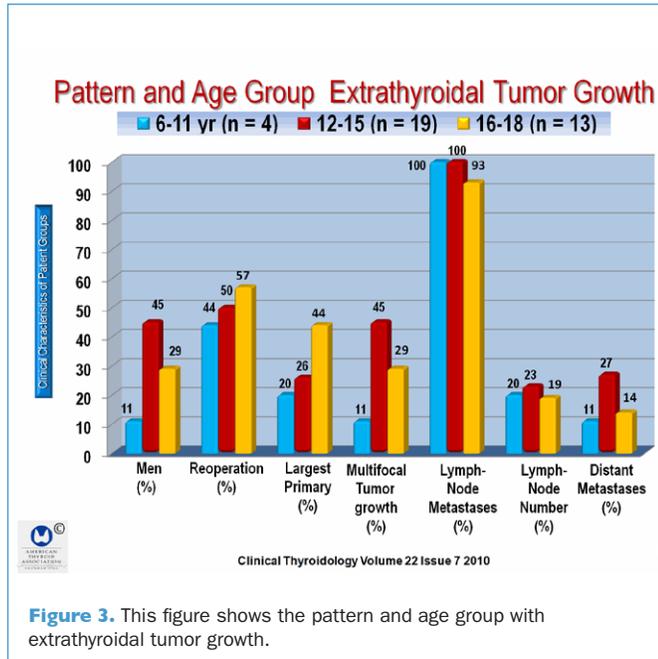


Figure 3. This figure shows the pattern and age group with extrathyroidal tumor growth.

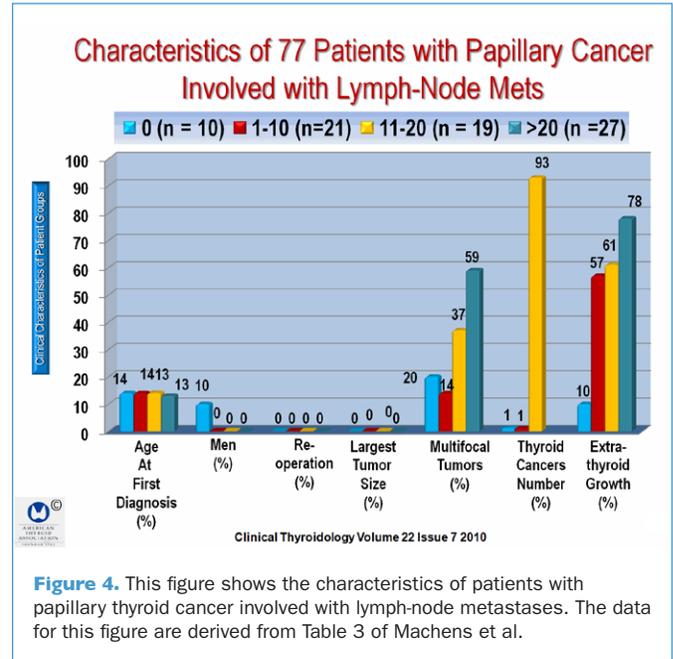


Figure 4. This figure shows the characteristics of patients with papillary thyroid cancer involved with lymph-node metastases. The data for this figure are derived from Table 3 of Machens et al.

COMMENTARY

Almost all the young patients in this study had lymph-node metastases and extrathyroidal tumor growth without a significant difference between prepubertal children and adolescents. The authors suggest that typically, children and adolescents with locoregional metastases trigger a workup for thyroid cancer and prompt referral for specialist surgical care, introducing referral and age bias in studies (2,3). The authors make the point that if children had more extensive disease as compared with adolescents, the children should have been overrepresented among the pediatric patients in this study, which apparently is not the case. However, this is a relatively small study that may not have been large enough to uncover minor age-related differences among the two study groups. The authors conclude that having comparable extent of disease, children should not receive less extensive neck surgery as compared with adolescents, which may result in a higher rate of locoregional recurrence in young children. A study of 19 patients by Robie et al. (3) found a strong trend toward locoregional recurrence among those with metastatic disease to more than five cervical nodes (P<0.08); however, the primary operations on the thyroid and regional nodes were not significant predictors of neck recurrence. Although there have been no deaths among these patients, 25% had persistent disease at a mean follow-up of 12.6 years, leading the authors to conclude that the incidence of surgical morbidity

does increase with more extensive surgery, and that outcome is predicted primarily by the initial extent of disease. Likewise, Machens et al. also suggest that the extent of the initial operation is what influences locoregional recurrence rates rather than the child's age; however, they provide the caveat that with surgery in children and adolescents, and especially in younger children, there is more of a risk than in older patients, and thus should be treated by dedicated surgical centers that have experience with pediatric neck surgery.

SEER Database Information on the Incidence Rates and Mortality Rates in Children and Adolescents, and Young Adults (Figures 5, 6, and 7)

A SEER monograph (1) of cancer epidemiology in older adolescents and young adults (15 to 29 years of age) provides important insight into the epidemiology of thyroid cancer in children. The SEER data show that in the United States, from 1975 through 2000, thyroid cancer accounted for about 10% of all malignancies diagnosed in individuals 15 to 29 years of age, and thyroid cancer was the fourth most common cancer in this age group. The incidence of thyroid cancer increased rapidly between 15 and 29 years of age, reaching a plateau by the 5th and 6th decades (Figure 5).

In 2000, the estimated incidence rates of thyroid cancer per million in persons younger than age 30 years were 0 for age

<5 years, 1.0 for ages 5 to 9, 4.3 for ages 10 to 14, 17.6 for ages 15 to 19, 43.3 for ages 20 to 24, and 63.0 for ages 25 to 29 (Figure 6). Moreover, the estimated numbers of persons diagnosed with thyroid cancer in 2000 were 0, 20, 89, 335, 820, and 1222, respectively.

Based on incidence data collected from 1975 through 2000 in the U.S., approximately 2,400 persons between 19 and 29 years of age had a diagnosis of thyroid cancer. More than half these patients were 25 to 29 years of age. Over this same period, more than 350 older adolescents in the 5 to 19 year age group had a diagnosis of thyroid cancer. (4)

The estimated incidence rates of thyroid cancer in year 1975 through 2000 per million in persons younger than age 44 years, was 0 for age <5 years, to 78% in patients age 40 to 44 years. (Figure 6).

The mortality rate of thyroid cancer increased above the age of 10 years, and continued to rise as a function of age.

It is difficult to dismiss the effect of age on the outcome of papillary and follicular thyroid cancer, including that of prepubertal, pubertal and adolescent patients.

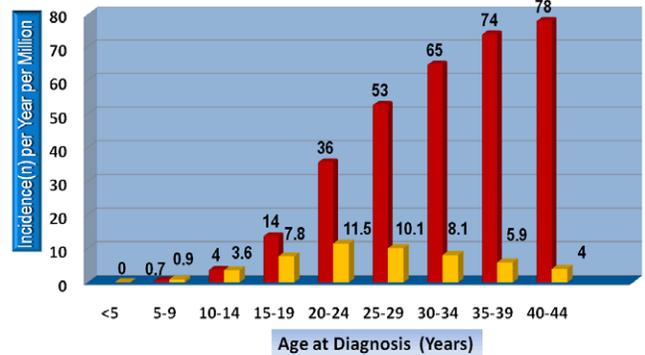
The mortality rate of thyroid cancer increased at greater than 10 years of age and continued to rise as a function of age (Figure 7). Mortality from thyroid cancer has not declined in the 15-

to 29-year age group during the past quarter century, probably because of the high survival rates (1).

It is difficult to dismiss the effect of age on the outcome of PTC.

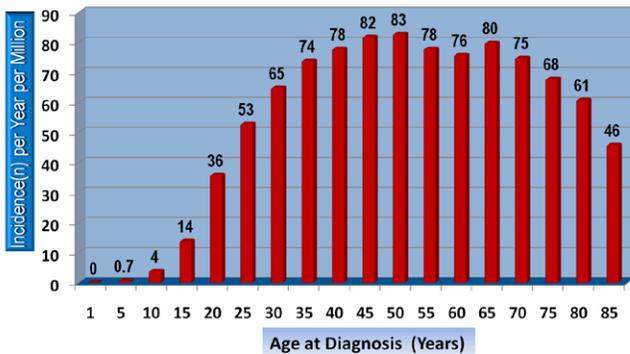
— Ernest L. Mazzaferri, MD, MACP

SEER Incidence of Thyroid Cancer Relative to all Cancer



Clinical Thyroidology Volume 22 Issue 7 2010
Figure 6. This figure shows the incidence rate per year per million of thyroid cancer relative to all other cancers by age (yr) at the time of diagnosis. The data for this figure are derived from SEER figure in chapter 12, figure 12.1, chapter 12, page 146. (4)

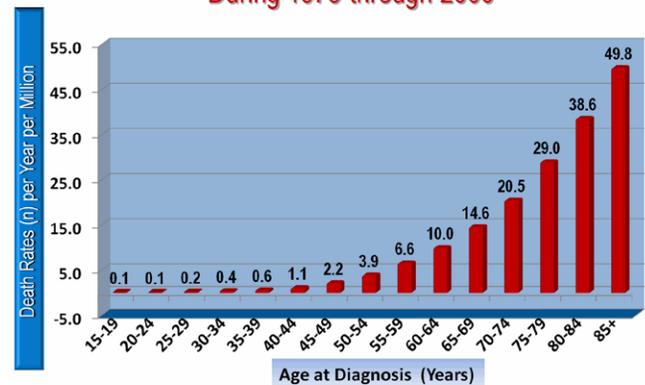
SEER Incidence of Papillary and Follicular Thyroid Cancer



Clinical Thyroidology Volume 22 Issue 7 2010

Figure 5. This figure shows the incidence rate per year per million, by age at the time of diagnosis of differentiated thyroid cancer (papillary and follicular thyroid cancer) from 1975 through 2000. The data for this figure are derived figure 12.3 in Chapter 12, page 147 in the SEER Monograph (1)

SEER Thyroid Cancer Deaths per Year per Million During 1975 through 2000



Clinical Thyroidology Volume 22 Issue 7 2010

Figure 7. Mortality from thyroid cancer has not declined in the 15 to 29-year age group during the past quarter century, probably because of the high survival rates (1). The data for this figure are derived from SEER figure 12.13 in chapter 12, chapter 12, page 150 (4).

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Rituximab appears to have a significant effect on thyroid eye disease that requires further randomized controlled studies

Silkiss RZ, Reier A, Coleman M, Lauer SA. Rituximab for Thyroid Eye Disease. *Ophthalm Plast Reconstr Surg* 2010. DOI: 10.1097/IOP.0b013e3181c4dfde

SUMMARY

BACKGROUND

The medical treatment of thyroid eye disease (TED) continues to be problematic. Glucocorticoid therapy provides acute control of periocular inflammation and long-term or high-dose glucocorticoid therapy is effective but associated with systemic side effects. Regional external beam radiotherapy may improve extraocular motility impairment, but efficacy in the improvement of diplopia, proptosis, eyelid fissure height, and eyelid swelling has not been established as the best therapy for this disorder. If at all possible, medical therapy should prevent progression of the disease or control acute and long term inflammation, with a favorable safety profile. Immunobiologic therapy that targets specific components of the immune system with genetically engineered monoclonal antibodies may provide acute and long-term efficacy and a safe form of therapy. Rituximab is an intravenously administered chimeric mouse-human monoclonal antibody that targets the CD20 antigen on pre-B and mature B lymphocytes. Hematopoietic stem cells, pro-B cells and normal plasma cells do not express the CD20 antigen, thus rituximab does not induce significant immunosuppression. The Food and Drug Administration approved rituximab in 1997 for the treatment of B-cell non-Hodgkin lymphoma, and in 2006 it was approved for the treatment of rheumatoid arthritis and is now being studied as a possible treatment for a number of other autoimmune diseases. Limited information has suggested that rituximab results in B cell depletion in the thyroid gland of patients with Graves' disease, and a study of the decline in production of specific thyroid stimulating autoantibodies has been reported.

This is a prospective, open-label, interventional clinical trial study that reports the results of a phase I/II safety and efficacy trial of 12 patients treated with rituximab for TED and their 1-year posttreatment clinical course.

PATIENTS AND METHODS

This is a 2-center study registered as Clinicaltrials.gov number NCT00424151, which recruited patients 18 years of age or older with relevant orbitopathy and Clinical Activity Scores (CAS) of 4 or greater. The demographic data that were collected comprised patient sex, age laterality of the orbitopathy (1 or 2 eyes), ethnicity, and smoking status at the time of presentation, with serum autoantibody levels including thyroid stimulating immunoglobulin (TSI) >125, thyrotropin (TSH) receptor antibody, or antithyroid peroxidase antibodies. Patients were required to have active ophthalmopathy not reversible with short-term glucocorticoid therapy and were offered rituximab as an alternative to long-term glucocorticoid therapy, radiation therapy, or surgery, and were required to have negative serology for hepatitis B, and C, and HIV. The exclusion criteria were hematologic abnormalities, a history of malignancy, psychiatric disorders, cardiac or pulmonary disease, pregnancy, or active

lactation. Patients had pretreatment ophthalmic and systemic evaluation exophthalmometer examination. The severity of disease activity or thyroid-associated ophthalmopathy was evaluated by CAS and the Thyroid Associated Ophthalmopathy Scale (TAOS). The CAS scale used a scale of 0 to 8, based on 5 items: orbital pain, chemosis, edema, conjunctival and eyelid injection. The TAOS scoring was also used to quantify the effect of treatment. This scoring system assesses orbital pain, chemosis, eyelid edema, conjunctival injection, and eyelid injection on a scale of 0 to 2, and total scores from these 5 items range from 10 to 10). Hematologic and serologic data were collected at week 0 (pretreatment baseline, 4, 8, 16, 24, 36, and 52 weeks after the second infusion of rituximab.

RESULTS

The mean age of the 12 patients that entered into the study was 52.1 years (range 34 to 80), 5 (41.7%) were men and 7 (58.3%) were women, 7 (58.3%) were white, 5 (41.7%) were Hispanic, 4 (33%) were smokers, 1 (8%) had unilateral and 11 (91.7%) had bilateral orbitopathy. Hyperthyroidism was present for 1 year or less in 7 patients, 2 to 3 years in 2 patients, and 4 years in 1 patient, and 1 was euthyroid. Seven were treated with oral thyroid suppression (propylthiouracil, methimazole, or Cytomel, and 2 patients did not require treatment for hyperthyroidism, and none had pretibial myxedema.

Twelve patients with active TED were treated with 2 courses of rituximab over a 2-week period, and there were no adverse effects of the rituximab infusions and no reported side effects during the 1-year post infusion observation period.

The mean exophthalmometer reading was 20.16 mm (range 15 to 31), palpable fissure was 11 mm (range 8 to 16), and the degree of diplopia was none in 7 patients (58.3%), minimal in 1 (8.3%), moderate in none, and severe in 4 patients (33%). Symptomatic keratopathy was present in 5 patients (41.7%) and absent in 7 (58.3) patients. Visual acuity based on a Snellen chart was 20/20 in 14 patients (58.3%), 20/25 to 20/30 in 7 (29%), 20/40 to 20/60 in 2 (8.3%) and one patient had CF (count fingers). The mean Hertel reading was 20.16 mm, (range 8 to 16).

The mean CAS score was 5.5, with a median baseline score of 5.3, and there were statistically significant decreases from baseline for weeks 4,8,16, 24, 36, and 52 ($P<0.01$). The mean decreases ranged from -2.3 to -4.7, and the median decreases ranged from -2.5 to -4.5, (Figure 1).

The mean baseline TAOS score was 10.4, (median baseline score 9.0), and there were statistically significant decreases from baseline for weeks 4,8,16, 24, 36, and 52 ($P<0.05$). The mean decreases ranged from -3.3 to -8.0, with a median range of -3.0 to -6.5 (Figure 2).

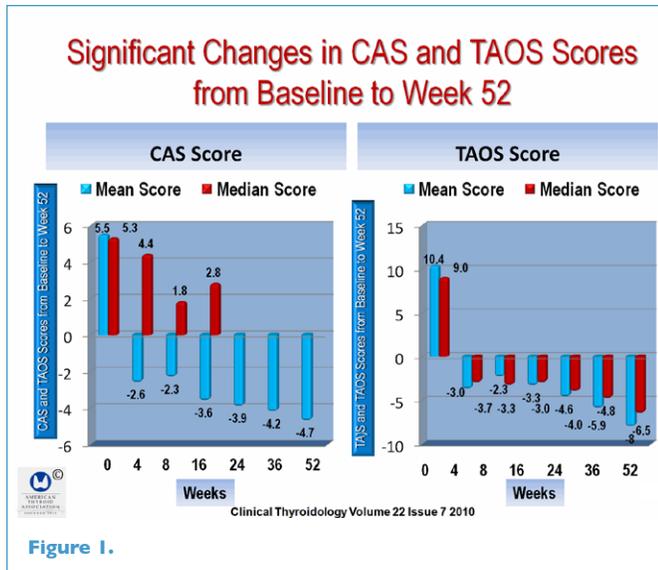


Figure 1.

The mean baseline TSI score was 251.3%, with a median score of 214.0% but there were no statistically significant changes from baseline at any of the follow-up visits

The mean baseline TSH score was 3.45 IU/mL with a median baseline score of 1.11 IU/mL. There were no statistically significant changes from baseline at any of the follow-up visits ($P > 0.05$) CD 19 levels started to increase 36 weeks post infusion. CD19 levels started to increase 36 weeks post infusion, but the changes were minimal.

CONCLUSION

Twelve patients with active TED were treated with 2 courses of rituximab over a 2-week period. There were no adverse effects of the rituximab infusions and no reported side effects during 1 year after the infusion of the drug. There was a significant improvement in CAS scores that was observed 1 month after infusion of rituximab that was sustained throughout the 12-month observation period.

COMMENTARY

This is a relatively small study that suggests rituximab, an anti-CD20 monoclonal antibody, given over a 2-week period has no obvious adverse effects during 1-year post-perfusion period, and CAS scores that were observed within a month of rituximab infusions that appears to persist for 1-year.

Several studies support research on rituximab for Graves' disease. A prospective controlled, nonrandomized study by El Fassi et al (1) that was published in 2007 studied 20 patients with newly diagnosed Graves' disease, 10 of which received 375 mg of rituximab, and 10 did not receive the drug. Four patients in the rituximab group remained in remission with a median follow-up of 705 d (range, 435-904 d), whereas all the patients not in the rituximab group had relapsed by d 393 ($P < 0.05$). All of the patients in remission had initial TRAb levels below 5 IU/liter (normal, < 0.7 IU/liter); whereas none of the five patients not treated with rituximab had correspondingly low TRAb levels were in remission ($P < 0.01$). The group that was treated with rituximab did not have an affect on autoantibody levels to a greater extent than did MMI monotherapy. The conclusion of the study was that rituximab therapy may induce sustained remission in patients with Graves' disease with low TRAb levels. However, the fact that the rituximab did not affect autoantibody levels seemed to suggest the drug is ineffective in patients with high TRAb levels. The concluded that at present, high cost, low efficacy, and potential side effects do not support use of rituximab in uncomplicated Graves' disease

Hasselbalch et al (2) suggested that B-cell depletion with rituximab may be a targeted therapy for Graves' disease and autoimmune thyroiditis. Salvi (3) studied a patient with Graves' disease with hyperthyroidism and ophthalmopathy that was unresponsive to steroid and was thus treated with rituximab. The ophthalmopathy responded to rituximab therapy by

ameliorating the eye signs with a decrease in the CAS score from 5 to 2 in 3 months, while the patient had peripheral B-cell depletion. However hyperthyroidism did not improve during the 6 months of B-cell depletion and serum TSH-receptor antibodies (TRAb) levels did not significantly change after rituximab therapy. They concluded that the persistence of Graves' hyperthyroidism suggests that a single cycle of rituximab does not result in complete lymphocyte depletion in thyroid tissue and this no decline in serum TRAb was observed.

A prospective, 26-week phase II study by Heemstra et al (4) of 13 patients with relapsing Graves' disease (9 females and 4 males, age 39.5 ± 9.5 years, received 2 dosages of rituximab, 1000 mg intravenously with a 2-week interval. Before administration and on several periods after the administration of TSH, free thyroxine (FT4), thyrotropin binding inhibitory immunoglobulins (TBII) and the proportion of CD19 and MS4A1-positive peripheral blood mononuclear cells were measured. The proportion of MS4A1-positive lymphocytes decreased in all the patients from 5.8% at baseline to 1.4% at 26 weeks ($P = 0.007$). Four patients with high initial FT4 levels did not respond to treatment. The remaining patients all had a decrease in FT4 levels at 26 weeks ($P = 0.001$) and an increase in TSH levels ($P = 0.011$). Thyroid binding immunoglobulin (TBII) decreased in all the remaining patients ($P = 0.003$). At a 14 to 27 month follow-up, nine of the patients were still euthyroid with normal FT4 ($P < 0.001$) and TSH levels ($P = 0.008$). The authors concluded that the study results suggest a beneficial role of rituximab in mild relapsing Graves' disease. A subsequent randomized controlled trial with rituximab was recommended.

In conclusion, rituximab appears to be a drug with promise, but requires larger prospective randomized studies to settle the differences reported in the literature.

— Ernest L. Mazzaferri, MD, MACP

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A 50% decrease of serum calcitonin concentrations within 30 minutes after surgery indicates that all the calcitonin-producing tumor tissue has been removed, whereas a calcitonin decline <50% suggests persistent residual tumor

Faggiano A, Milone F, Ramundo V, Chiofalo MG, Ventre I, Giannattasio R, Severino R, Lombardi G, Colao A, Pezzullo L. A decrease of calcitonin serum concentrations less than 50 percent 30 minutes after thyroid surgery suggests incomplete C-cell tumor tissue removal. *J Clin Endocrinol Metab* 2010. 0-0045 [pjc.2011ii];10.1210/jc.2010-0045[doi]

SUMMARY

BACKGROUND

The prognosis of medullary thyroid carcinoma (MTC) depends greatly on the completeness of the first surgical treatment. However, whether central lymph-node compartment dissection should be performed with total thyroidectomy is a matter of debate unless there is preoperative or intraoperative evidence revealing the presence of lymph-node metastases. Without this information, there is relatively little information that can indicate to the surgeon whether the tumor has been completely removed after total thyroidectomy. The aim of this study was to evaluate the reliability of intraoperative calcitonin as an effective predictor of residual tumor and the final outcome of surgery in patients with MTC.

PATIENTS AND METHODS

Patients

The study subjects comprise 20 patients, 9 men and 11 women, 25 to 70 years of age (mean (\pm SD) 50 ± 2.3), who were candidates for thyroid surgery on the basis of abnormally elevated serum calcitonin levels, without preoperative evidence of lymph-node metastases or distant metastases. All of the patients had thyroid surgery on the basis of elevated basal calcitonin levels or pentagastrin (PG)-stimulated calcitonin levels above 100 ng/L. Five patients had basal serum calcitonin concentrations above 100 ng/L, and 15 others had basal calcitonin concentrations ranging from 18 to 68 ng/L that increased to over 100 ng/L with PG stimulation.

Neck ultrasonography identified thyroid nodules on all of the patients; 8 patients had a single nodule and 12 had two or more nodules, but none had lymph-node metastases identified on the preoperative ultrasound. Ultrasound-guided fine-needle aspiration biopsy was performed on thyroid nodules with features suspicious for malignancy. None of the patients tested positive for a RET mutation.

All patients had total thyroidectomy and central compartment lymph-node dissection with removal of bilateral pretracheal and paratracheal compartments. As none of the patients had lymph-node metastases on the preoperative ultrasound examination or the intraoperative surgical exploration, an extensive neck dissection comprising both central and bilateral cervical lymph-node dissection was not performed in any patient. MTC was found on the histologic examination in 10 patients, and 10 others had C-cell hyperplasia.

Outcome

After surgery, calcitonin was measured every 3 months, and then was measured every 6 months. A PG test was performed 6 months after surgery in patients with a histologic diagnosis of MTC. Mean follow-up after surgery was 14.6 ± 1.7 months (range, 6 to 30). In 16 of the 20 patients, there was no evidence of persistent disease or relapse, and 4 patients had persistent disease, 2 of whom had both basal and PG-stimulated abnormally high calcitonin levels, and 2 others had basal calcitonin levels of 5 ng/L or less, with a progressive increase of calcitonin during follow-up and a positive PG-stimulated calcitonin level. This group of patients had a radiologic workup and periodic ultrasound follow-up with Doppler, contrast-enhanced computed tomography and magnetic resonance imaging, and ^{18}F -deoxy-d-glucose positron-emission tomography. One of the four patients with persistent disease after surgery had ultrasound evidence of tumor remnant in the neck lymph nodes. The other 3 patients with elevated postoperative calcitonin levels did not have signs of tumor at the last radiologic examination, 12, 16, or 22 months after surgery.

Calcitonin Assay

Serum calcitonin was determined by a commercially available two-site immunometric assay with normal values of 0.4 to 18.9 ng/L and an analytic sensitivity of 1 ng/L or less. No hook effect was observed until a calcitonin concentration increased to 500,000 ng/L. A PG-plus-calcium test was performed as follows: calcium was first injected intravenously in 1 minute at a dose of 2 $\mu\text{g}/\text{kg}$ of body weight. PG was injected in 15 seconds at a dose of 0.5 $\mu\text{g}/\text{kg}$ in 5 ml of NaCl solution 0.9%. Blood samples were collected at 0, 1, 2, 3, 5, and 10 minutes after the injection, and the assay run time was 15 minutes. According to Costante et al. (1), the calcitonin peak greater than 100 pg/ml after a PG test is considered as positive for MTC.

RESULTS

The Outcome of Patients Who Had Surgery and Calcitonin Measurement at 10 Minutes and 30 Minutes after Surgery (Figures 1 and 2)

Histologic examination identified 10 patients with MTC and 10 with C-cell hyperplasia. Among patients with MTC, the tumor stage was T1N0 in six, T2N0 in two, and T2N1 in two (Figure 1). Among the entire patient population, preexcision serum calcitonin values were 908 ± 695 ng/L (range, 11 to 9160) and postexcision values were 319 ± 202 ng/L (range, 9 to 2845) at 10 minutes after the surgical excision and 146 ± 75 ng/L (range, 7 to 10656) at 30 minutes after the surgical excision. The mean

calcitonin decrease was $44 \pm 4.6\%$ (range, 13 to 76) 10 minutes after surgery and $61 \pm 2.9\%$ (range, 39 to 80) 30 minutes after surgery (Figure 2).

A receiver operating characteristic curve identified a decrease of serum calcitonin concentrations greater than 50% at 30 minutes after surgery, which was able to significantly distinguish with 100% sensitivity and specificity between patients who were cured and those who had disease persistence during the follow-up ($P < 0.005$) (Figure 2). No statistical significance was found in predicting the patient outcome when considering calcitonin concentrations at 10 minutes after surgery. However, an intraoperative calcitonin decrease greater than 50% at 30 minutes after surgery was achieved in all 16 patients who had

complete remission during follow-up ($66 \pm 2.4\%$), whereas the calcitonin decrease at 30 minutes after surgery was 16, 39, 40, and 44% in the four patients, who had persistent disease after surgery, as compared with patients who had a 50% or more decline in calcitonin in patients who were free of MTC (Figure 2).

Conclusion

The main finding in this study is that an intraoperative calcitonin that decreases 50% or more 10 minutes after surgery is a reliable indicator that a patient with MTC is free of disease after surgery limited to total thyroidectomy and central compartment lymph-node dissection, whereas a calcitonin 30 minutes after surgery that fails to decline 50% or more suggests that the surgeon should extend the operation to other lymph-node compartments.

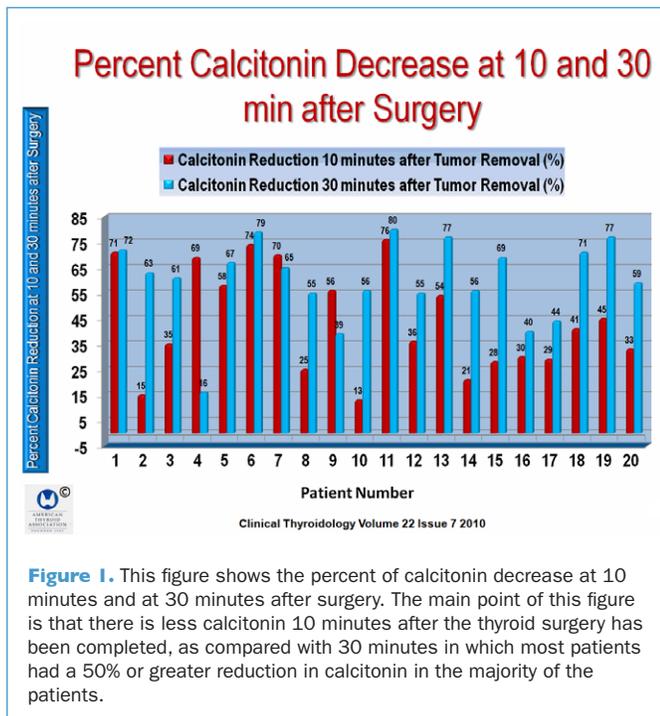
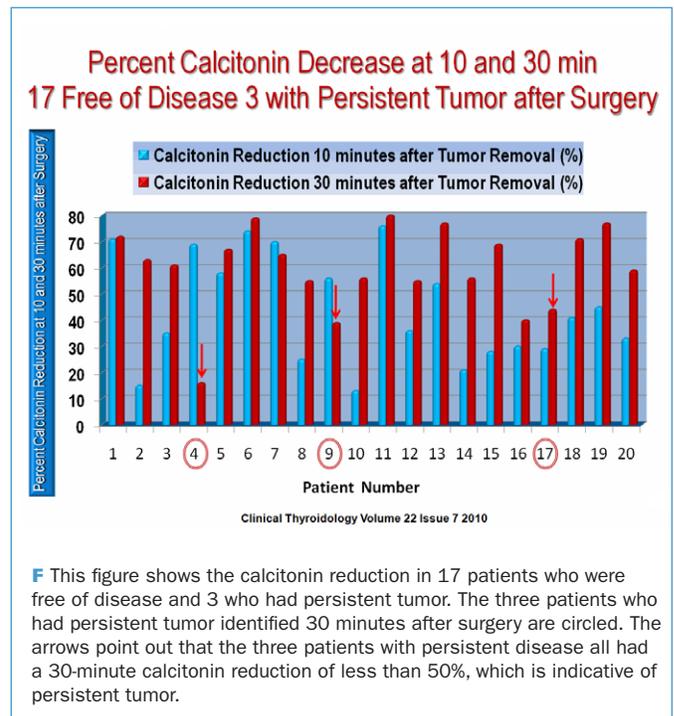


Figure I. This figure shows the percent of calcitonin decrease at 10 minutes and at 30 minutes after surgery. The main point of this figure is that there is less calcitonin 10 minutes after the thyroid surgery has been completed, as compared with 30 minutes in which most patients had a 50% or greater reduction in calcitonin in the majority of the patients.



F This figure shows the calcitonin reduction in 17 patients who were free of disease and 3 who had persistent tumor. The three patients who had persistent tumor identified 30 minutes after surgery are circled. The arrows point out that the three patients with persistent disease all had a 30-minute calcitonin reduction of less than 50%, which is indicative of persistent tumor.

COMMENTARY

MTC is a tumor with a 10-year relative survival rate of 75%, which is approximately fourfold that of papillary thyroid cancer, underscoring the gravity of this disease (2). Surgery is the mainstay of therapy for the initial treatment. If the primary surgery is incomplete, the initial treatment is ineffective in achieving disease remission (3). Although preoperative calcitonin concentrations have been reported to predict the postoperative calcitonin levels of patients with MTC (1), no clinical parameters clearly predict the postoperative outcome of patients with this disease (3).

The study by Faggiano et al. demonstrates that intraoperative monitoring of calcitonin 10 minutes after surgery is a reliable way to determine whether a patient can be considered free of disease after surgery. The authors suggest that intraoperative calcitonin monitoring seems to be more cost-effective than intraoperative PG testing in the recognition of patients with incomplete surgery. The study shows that the main difference

is that the sensitivity and negative predictive value of the intraoperative calcitonin monitoring was 100% with no false negative results, whereas the sensitivity of intraoperative PG testing was 80% and had a negative predictive value of 91%, meaning that PG testing did not recognize 20% of the patients who had persistent disease after surgery.

The results of this study clearly demonstrate that a decrease of calcitonin serum concentrations greater than 50% 30 minutes after surgery indicates that all the calcitonin-producing tumor tissues have been removed, while a calcitonin decrease of less than 50% suggests that an incomplete surgery has been performed, giving the surgeon an opportunity to perform another lymph-node compartment dissection.

This is an important study that should be read in its entirety to obtain its full impact.

— Ernest L. Mazzaferri, MD, MACP

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HOT ARTICLES

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DISCLOSURE

Dr. Mazzaferri is a consultant to Genzyme.

Dr. Sipos Lectures for Abbott Pharmaceutical and Genzyme.



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].

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