

A summary of the abundant data on the growing literature on the management of thyroid cancer during pregnancy

Holt EH. Care of the pregnant thyroid cancer patient. *Curr Opin Oncol* 2010;22:1-5.

SUMMARY

BACKGROUND

The incidence of differentiated thyroid cancer, especially papillary thyroid cancer in women, has been steadily increasing for the past three decades, peaking in women during their mid-40s. As a consequence, thyroid cancer and thyroid nodules are an especially important problem during the reproductive years in women. In fact, about 10% of thyroid cancers occurring during the reproductive years are diagnosed during pregnancy or the first year after delivery. A study by Vannuchi et al. that is highlighted in this issue of *Clinical Thyroidology* shows that pregnancy has a negative impact on the outcome of thyroid cancer, and is associated with especially high levels of estrogen receptor α (ER α) during pregnancy as compared with the levels before and after pregnancy. ER α appears to have an important impact on follicular cell growth, and numerous studies have documented its neoplastic tendencies in thyroid tissues.

The main finding of the Vannuchi study is that pregnancy has a negative impact on the outcome of thyroid cancer, almost all of which were papillary thyroid cancers. This leads to a number of new and important questions concerning the clinical management of thyroid cancer in pregnant women. Holt's review of the current care of pregnant women with thyroid cancer is propitious, considering the timing of events linking pregnant women with more aggressive papillary thyroid cancers. This set of events is important to obstetricians, internists, and endocrinologists.

METHODS

Holt summarized the recommendations of the Endocrine Society in late 2007 and the data in a symposium on thyroid dysfunction and pregnancy hosted by the American Thyroid Association (ATA) in April 2009. In addition to the problem of thyroid cancer, hypothyroidism was addressed by the ATA and the Endocrine Society. Moreover, recent studies have addressed the consequences of thyroid cancer and hypothyroidism on the fetus and the impact of surgery, radioiodine, and levothyroxine therapy in both mother and fetus.

RESULTS

Guidelines for Thyroid Cancer during Pregnancy

The Holt study summarizes the Endocrine Society's guidelines for the care of pregnant patients with thyroid nodules or thyroid cancer, highlighting the following six features: [1] Thyroid nodules ≥ 1 cm should be evaluated with fine-needle aspiration biopsy. [2] Women with malignant or rapidly growing thyroid nodules should be offered surgery in the second trimester. [3] As thyroid nodules and thyroid cancer are not expected to progress rapidly, the risk of surgery might outweigh the benefits of immediate surgery, and it thus might be appropriate for women to wait until postpartum for thyroidectomy. This latter recommendation will have to be regarded in light of the Vannuchi study. [4] Women with

thyroid cancer should have a consistently low but measurable levothyroxine (L-T₄) level during pregnancy. [5] Women who are breast-feeding should wait 6 to 12 months before becoming pregnant. [6] Women should wait 6 to 12 months after ¹³¹I therapy before becoming pregnant.

Guidelines for Hypothyroidism

[1] During pregnancy, women who have had lobectomy should be screened for hypothyroidism. [2] As a consequence of physiologic changes on thyroid function during pregnancy, the Endocrine Society recommends that the interpretation of thyroid-function tests should be as follows: for the total thyroxine (TT₄), multiply the upper and lower limits of the laboratory-specific adult normal range for TT₄ by 1.5 to bring it into the normal range during the second and third trimester; keep the free T₄ (FT₄) results in the laboratory-specific normal range during pregnancy; keep the thyrotropin (TSH) below 2.5 mU/L; and keep TSH in the trimester-specific normal range as determined by the laboratory determining the TSH concentration.

Thyroid Surgery during Pregnancy

[3] The Endocrine Society guidelines recommend that patients found to have thyroid cancer during pregnancy be considered for thyroidectomy during the second trimester, when the fetus is viable but after organogenesis is complete. Holt indicates that that this guideline was based on limited evidence.

Perhaps the most important study is a retrospective one by Kuy et al. (1) that was aimed at performing the first population-based measurement of clinical and economic outcomes in pregnant women who had thyroid and parathyroid surgery and to identify the characteristics of this population in the Health Care Utilization Project Nationwide Inpatient Sample (HCUP-NIS), a 20% sample of nonfederal U.S. hospitals. All pregnant women were compared with age-matched nonpregnant women who had thyroid and parathyroid procedures from 1999 through 2005. A total of 201 pregnant women had thyroid (165 patients) and parathyroid (36 patients) surgery and were examined together. The study subjects' mean age was 29 years; 60% were white and 46% had thyroid cancer. As compared with 31,155 nonpregnant women, pregnant patients had a higher rate of endocrine complications (15.9% vs. 8.1%, $P < 0.001$) and general complications (11.4 vs. 3.6%, $P < 0.001$), longer unadjusted lengths of stay (2 days vs. 1 day, $P < 0.001$), and higher unadjusted hospital costs (\$6,873 vs. \$5,963, $P = 0.007$). Fetal and maternal complication rates were 5.5% and 4.5%, respectively. On multivariate regression analysis, pregnancy was an independent predictor of higher combined surgical complications (odds ratio, 2; $P < 0.001$), longer adjusted length of stay (0.3 day longer, $P < 0.001$), and higher adjusted hospital costs (\$300, $P < 0.001$). Other independent predictors of outcome were surgery volume, patient race or ethnicity, and insurance status. Pregnant women thus had worse clinical and economic outcomes following thyroid and parathyroid surgery

than nonpregnant women, with disparities in outcomes based on race, insurance, and access to high-volume surgeons. These data will help physicians and patients to deal with thyroid cancer during pregnancy, particularly for women who are advised to wait until the postpartum period for surgery.

Hypothyroidism or Hyperthyroidism during Pregnancy

A study by Cleary-Goldman et al. (2) was aimed at estimating whether maternal thyroid hypofunction is associated with complications. The study subjects were 10,990 patients who had first- and second-trimester serum assayed for TSH, FT₄, and antithyroglobulin antibodies (TgAb) and antithyroperoxidase antibodies (TPOAb). Subclinical hypothyroidism was defined as TSH levels above the 97.5th percentile, and FT₄ between the 2.5th and 97.5th percentiles. Hypothyroxinemia was defined as a TSH between the 2.5th and 97.5th percentiles and FT₄ below the 2.5th percentile. Patients with subclinical hypothyroidism were compared with euthyroid patients who had TSH and free FT₄ between the 2.5th and 97.5th percentiles. Also, patients with and without antibodies were compared. Subclinical hypothyroidism was found in 240 of 10,990 (2.2%) women in the first trimester and in 243 of 10,990 women (2.2%) in the second trimester. Hypothyroxinemia was found in 232 of 10,990 women (2.1%) in the first trimester and in 247 of 10,990 women (2.3%) in the second trimester. Subclinical hypothyroidism was not associated with adverse outcomes. Hypothyroxinemia was associated with preterm labor in the first trimester, (adjusted odds ratio [aOR], 1.62; 95% confidence interval [CI], 1.00 to 2.62) and macrosomia (aOR, 1.97; 95% CI, 1.37 to 2.83). In the second trimester, hypothyroxinemia was associated with gestational diabetes (aOR, 1.7; 95% CI, 1.02 to 2.84). A total of 1585 of 10,990 women (15%) in the

first trimester and 1491 of 10,990 women (14%) in the second trimester had TgAb. When both TPOAb and TgAb were positive in either trimester, there was an increased risk for preterm premature rupture of membranes (P = 0.002 and P<0.001, respectively). The authors concluded that maternal thyroid hypofunction is not associated with a consistent pattern of adverse outcomes.

Thyroid Function Testing in Pregnancy

Although there are a number of studies describing normal ranges for serum TSH and T₄, the largest is from the National Health and Nutrition Examination Survey (NHANES III) from 1988 through 1995. Soldin et al. (3) used the NHANES III data to determine trimester-specific levels of serum T₄ and TSH in the U.S. population and compared these data with published trimester-specific T₄ and TSH means and medians obtained in other countries. The mean serum T₄ levels for the U.S. population were 141.35 mIU/L in the first trimester, 152.95 in the second, and 142.65 in the third, whereas mean serum TSH levels were 0.91, 1.03, and 1.32 mIU/L, respectively. The study concluded that gestation-specific mean T₄ and TSH levels for the representative U.S. population are well within the trimester-specific reference intervals. T₄ and TSH measured during pregnancy in longitudinal and cross-sectional studies of populations worldwide demonstrate that, in some populations, serum T₄ and TSH levels are outside the normal trimester-specific reference intervals.

CONCLUSION

There is a growing literature on the management of thyroid cancer during pregnancy, and this study is a major contribution that summarizes the abundant data on this problem.

COMMENTARY

This review by Dr. Holt was placed in *Clinical Thyroidology* adjacent to the study by Vennuchi et al., which reported that a diagnosis of differentiated thyroid cancer during pregnancy or in the first year postpartum is a harbinger of persistent disease. This is an even greater problem than usual, given the fact that the rate of papillary thyroid cancer in women has been steadily rising over the past three decades. Thyroid cancer poses a wide spectrum of problems for pregnant women with thyroid cancer. In addition to the problems summarized in this issue of *Clinical Thyroidology*, a pregnant woman must make important decisions not only about the timing and extent of initial surgery, she must maintain euthyroidism to protect the fetus from serious developmental defects and must make important decisions

concerning radioiodine and its effect on gonadal function and follow-up to mention a few.

This is a unique problem in which endocrinologists, surgeons, gynecologists, and primary care physicians often are involved, and all these providers must be cognizant of the myriad issues to properly advise the patient in making a decision that is best for her and the fetus. The short summary of the Holt study in this issue of *Clinical Thyroidology* does not fully cover the wide spectrum of information that is found in the study. This is a powerful source of information that will help physicians assist in the treatment and education of patients with this serious problem. The Holt article should be read in its entirety.

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References

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