Approach to the Pregnant Patient with Thyroid Cancer

Ernest L. Mazzaferri

Emeritus Professor of Medicine, The Ohio State University, Columbus, Ohio 43210

Thyroid cancer, the most common endocrine malignancy, increased progressively from 1972 through 2002 largely as the result of an increasing incidence of small papillary thyroid cancers, the majority of which are less than 2 cm and which increased almost 3-fold during the 30-yr study. During this time, thyroid cancer was found to affect women more often than men by a ratio of almost 3 to 1. Moreover, papillary thyroid cancer was found to be the most common form of differentiated thyroid cancer among women of childbearing age, 10% of whom were either pregnant or in the early postpartum period when thyroid cancer was diagnosed. Although the prevalence of thyroid cancer in pregnant women remains high, most are first identified after delivery. Nonetheless, the management of thyroid cancer during pregnancy poses serious diagnostic and therapeutic challenges to both the patient and fetus. The thyroid gland may secrete more thyroid hormone than usual during early pregnancy, which may not only be the cause of this problem but also may be responsible for the higher rate of differentiated thyroid cancer during pregnancy. There is concern about therapy for thyroid cancer during this period, including the timing of surgery, the use of levothyroxine, and the assessment of follow-up during gestation. **(*J Clin Endocrinol Metab* 96: 265–272, 2011)**

"There is almost always a conflict between maternal optimal therapy and fetal well-being." (1)

Ethical Issues

Thyroid cancer surgery for pregnant women with a viable fetus poses ethical issues that are entwined in the medical decisions for therapy. Oduncu *et al.* (1) wrote in a comprehensive editorial that "any choice of the best possible treatment option for pregnant women with thyroid cancer has to be based on precise medical facts." The authors went on to say, "There is almost always a conflict between optimal maternal therapy and fetal well-being." Oduncu *et al.* (1) discuss the issues that raise potential ethical conflicts in pregnant women with thyroid cancer and present a practical ethical approach that may help increase the clarity in maternal-fetal conflicts. The Oduncu editorial should be read by all who care for pregnant women with thyroid cancer.

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Learning Objectives
Upon completion of this educational activity, participants should be able to
- Describe current understanding of therapeutic outcomes of thyroid cancer in pregnant patients
- Discuss the utility of TSH and thyroglobulin measurements during pregnancy
- Effectively manage thyroid cancer in pregnant and postpartum women

Target Audience
This Journal-based CME activity should be of substantial interest to endocrinologists.
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Abbreviations: FT_4, Free T_4; HCG, human chorionic gonadotropin; NS, not significant; Tg, thyroglobulin.

The Scope of the Problem

A study by Smith *et al.* (2) of almost 5 million obstetric deliveries in California from 1991 through 1999 found that nearly 5000 were pregnant women with invasive malignancy, comprising approximately 1 in 1000 births. There were 23 different types of cancer in these pregnant women, most of which were diagnosed within a few months before or at the time of delivery. The two most common cancers were cancer of the breast (19 per 100,000) and thyroid cancer (14 per 100,000). About one fourth were thyroid cancers identified prenatally, 2% were found at the time of delivery, and 75% were discovered during the postpartum period. The timing of the cancer diagnosis thus affected the clinical outcomes. The most favorable perinatal cancer outcomes occurred in women whose cancer diagnosis was made 6 to 9 months after delivery, comprising 6% of the cases, whereas the most unfavorable perinatal cancer outcomes were associated with thyroid cancer diagnosed 0 to 3 months before delivery. For women whose cancer was diagnosed postpartum, perinatal outcomes were thus minimally affected by the presumed existence of occult cancer at the time of obstetric delivery. There has been concern that female hormones are the cause of the high rate of thyroid cancer during pregnancy, which in some cases may be more aggressive tumors.

The Case

A 24-yr-old gravida 2, para 1 woman was referred at 5 wk gestation to the Thyroid Cancer Clinic in Shands Hospital in Gainesville, Florida, for evaluation of a left-lobe thyroid nodule discovered by her gynecologist. The patient felt well but had been aware of a palpable neck nodule for approximately 1 yr, during which she believes the nodule had been slowly growing. There was no family history of thyroid disease, and she experienced no hoarseness, odynophagia, or dyspnea. Her physical examination was normal, except for a single palpable left-lobe thyroid nodule. Her serum TSH was 0.1 mIU/liter, within the range of normal healthy pregnant women in the first trimester, the serum free T_4 (FT_4) index was within the accepted reference range of 5.0 to 10.5, and serum thyroid peroxidase antibodies were negative. Neck ultrasonography identified a solid 2.6 × 2.4 × 2.3 cm (7.51 cm^3) thyroid nodule in an otherwise normal-appearing thyroid gland, with no abnormal lymph nodes in the lateral or central neck compartments. The thyroid nodule had irregular borders with small areas of calcification, with Doppler flow in several areas of the nodule consistent with thyroid cancer. After the suspicious ultrasound findings were discussed with the patient and her husband, the patient opted to have an ultrasound-guided fine-needle aspiration biopsy that yielded cytology consistent with papillary thyroid cancer. After the details of the cytology findings were explained, her therapy options were discussed in detail, including the potential risks and benefits to the patient and her fetus. She and her husband posed a number of questions concerning how the thyroid nodule might be managed if surgery was not performed immediately and asked about the potential risks of miscarriage, the use of medication such as thyroid hormone that might be helpful, and whether she could breastfeed her baby after delivery. She also raised the concern about radioactive iodine after delivery—mainly how it might interfere with breast feeding and future pregnancies. After a lengthy discussion about the fetus and herself, the patient decided to forgo immediate surgery and thyroid hormone therapy until delivery of the baby. Neck ultrasonography was performed at 12, 24, and 36 wk gestation, during which there was a small increase in nodule size to 2.8 × 2.6 × 2.4 cm (10.29 cm^3), and serum TSH remained within the acceptable ranges throughout pregnancy. Her gynecologist performed ultrasonography to monitor fetal growth, which appeared normal. The patient gave birth to a 7.5-pound healthy baby at 36 wk gestation. The patient nursed her baby for 3 months, after which she had a total thyroidectomy with left unilateral VI compartment dissection. The tumor histology was identified as classic papillary thyroid cancer that showed no extrathyroidal extension; however, there were two 9-mm lymph node metastases in the central lymph node compartment (level VI) and the lateral neck. Six weeks later her serum thyroglobulin (Tg) during thyroid hormone suppression of TSH was 2 ng/ml, and the patient opted not to be treated with ^{131}I for another 6 months, during which she breastfed her baby; afterward, she was treated with 50 mCi ^{131}I after preparation with recombinant human TSH. The posttreatment ^{131}I scan showed uptake only in the thyroid bed; 8 months later, her serum Tg was undetectable during TSH suppression and recombinant human TSH stimulation, and her neck ultrasonography was negative. She was informed that studies show she has nearly a 99% likelihood of being free of disease thereafter (3).

Background

Clinical studies of estrogen and thyroid disease in women

Although ionizing radiation remains the best-established risk factor for thyroid cancer (4), other factors may be responsible for the high rate of thyroid cancer in women, particularly the thyroid-stimulating effects of human chorionic gonadotropin (HCG) and estrogen

(5). Thyroid glands may secrete more thyroid hormone than usual during early pregnancy in response to HCG that overrides the normal operation of the hypothalamic-pituitary-thyroid-feedback axis (6), effects that might be responsible for the high rates of thyroid cancer in pregnant women. However, the data concerning the effect of estrogens on thyroid cancer are conflicting (7, 8), and the effects tend to be small (9). During normal pregnancy, the stimulatory effects of HCG and estrogen produce changes in serum TSH, FT_4, and FT_4 index and serum Tg concentrations during the third trimester that are substantially higher by approximately 25% than postpartum and second trimester concentrations (10, 11). There is a suggestion that estrogens may increase the expression of the Tg gene, increasing the potential production of Tg in differentiated thyroid cancer without stimulating the c-myc protooncogene and therefore not promoting rapid cell proliferation (12). Also, clinical studies suggest that serum Tg levels in pregnant women may be high without detectable tumor (13).

Therapeutic outcome of thyroid cancer in pregnant patients

Because of the high incidence of thyroid cancer in women that peaks in the reproductive years, another study (14) performed a matched case-controlled study of 292 pairs of women with thyroid cancer to examine the role of reproductive history and exogenous hormones in thyroid cancer. The study found that the use of oral contraceptives and other exogenous estrogens was not associated with thyroid cancer. However, the risk increased with the number of pregnancies in women using lactation suppression ($P = 0.03$), which decreased during breast feeding ($P = 0.04$). The authors concluded that these data provide only limited support for the hypothesis that reproductive and hormonal exposures are responsible for the high incidence of thyroid cancer in adult women.

A relatively recent study (15) of 123 women with differentiated thyroid cancer tested the hypothesis that pregnancy represents a favorable condition for the onset and growth of either benign or malignant thyroid nodules that are likely caused by several growth factors, especially high serum HCG levels and high estrogen levels that may lead to a rapid increase in thyroid tumor size during pregnancy and may stimulate the growth of benign and malignant thyroid lesions. To test this hypothesis, 123 women were divided into three groups according to the timing of tumor diagnosis: group 1, n = 47 (38%) with thyroid cancer diagnosed and treated 1 or more years after delivery; group 2, n = 14 (12%) with thyroid cancer diagnosed during pregnancy who were treated during the second trimester or in 2, 4, 5, or 11 months after delivery; and group 3, n = 61 (50%), patients who were nulliparous or had thyroid cancer that was treated before pregnancy. All patients had total thyroidectomy, and those with suspicion of lymph node metastases were treated with pretracheal and paratracheal lymph node dissection.

Thyroid cancer diagnosed during pregnancy (group 3) was associated with a poor prognosis as compared with tumors that developed in nongravid periods ($P < 0.001$). Stepwise logistic regression analysis found that the diagnosis of differentiated thyroid cancer during pregnancy or in the first year postpartum was the most significant indicator of persistent disease ($P = 0.001$). Estrogen receptor-α expression differed significantly among tumors in the three groups, being detected in 31% in group 1, 87.5% in group 2, and 0% in group 3. It is important to know that one patient in group 3 was considered twice in this analysis, once with follicular thyroid cancer, and 8 yr later with papillary thyroid cancer. Also, 15% of group 2 had follicular thyroid cancer, 15% had $BRAF^{V00600E}$ mutations, and 53% had extrathyroidal invasion, none of which were likely to have been the result of estrogen stimulation, based on the time frame under study. Moreover, the TNM (tumor, node, metastasis) staging system of the American Joint Commission on Cancer were not statistically different among the three study groups, suggesting that the tumors were not much different in the three study groups. Lastly, thyroid cancer was an incidental finding in many of the patients in groups 1 and 3, but not in those of group 2, suggesting that the two control groups (1 and 3) were clinically different as compared with group 2.

A retrospective study (16) that was published in the *JCEM* in 1997 compared outcomes of thyroid cancer in 61 pregnant women with 528 age-matched controls that were not pregnant. The mean ages of the participants were 26.3 ± 5.9 and 26 ± 5.9 yr, respectively [P = not significant (NS)]. Sixty-one women (30%) were pregnant when thyroid cancer was diagnosed, or when a thyroid nodule was recognized and later identified as thyroid cancer. The presenting manifestations were significantly different in the two study groups. Fewer pregnant women had symptoms referable to their thyroid nodule (74%), which was more often found unexpectedly during a routine prenatal neck examination, as compared with 43% of the controls who had a symptomatic neck mass with symptoms of dysphagia, hoarseness, or rapid nodule growth ($P < 0.001$). Five pregnant women (8%) and 31 controls (7%) had a history of head and neck radiation. Tumor stage ranged from 1 through 4 at the time of diagnosis and was not significantly different comparing the pregnant patients *vs.* controls (Table 1) (P = NS by Wilcoxon rank-sum test for tumor features by ANOVA for stage). Papillary thyroid

TABLE 1. Tumor stage at the time of diagnosis in pregnant and nonpregnant women

Tumor stage	Description
1	Primary tumor <1.5 cm diameter without metastases or local invasion of the thyroid capsule
2	Primary tumor 1.5 to 4.4 cm diameter of any size with lymph node metastases
3	Primary tumor ≥4.5 cm diameter or primary tumor of any size that is either multiple (more than three tumors) or is invading through the thyroid capsule
4	Distant metastases

NS, Not significant by Wilcoxon rank-sum test for tumor features and by ANOVA for stage. [Reproduced from Moosa and Mazzaferri (16).]

TABLE 2. Outcome

Outcome	Pregnant[a]	Not pregnant
Recurrence (yr)		
10	8 (15%)	85 (21%)
20	1 (17%)	13 (26%)
30	0 (17%)	8 (31%)
40	0 (17%)	1 (33%)
Distant recurrence (yr)[b]		
10	1 (2%)	9 (2%)
20	0	1 (3%)
30	0	2 (4%)
Cancer death (yr)		
10	0	0
20	0	2 (1%)
30	0	4 (3%)

Reproduced from Moosa and Mazzaferri (16).

[a] P = Not significant for all recurrences, distant recurrence, and cancer death comparing women who were and were not pregnant (log-rank test) for Kaplan Meier life-table events at 10, 20, and 30 yr.

[b] Distant recurrence sites: lungs, eight patients; bone, one patient; lungs and bone, two patients; lungs and brain, one patient.

cancer was found in 53 (87%) of the pregnant group and in 337 (81%) of the controls (P = NS).

At the time of diagnosis, 18 of the 61 pregnant women (30%) were in their first trimester, 26 (43%) were in their second trimester, and 17 (28%) were in their third trimester. None had therapeutic or spontaneous abortions. Time lapse from discovery of the tumor to initial therapy was similar in the pregnant and nonpregnant women [12.7 months (95% confidence interval, 7.9 to 17.4) *vs.* 10.8 months (95% confidence interval, 8.8 to 12.7)] in the two treatment groups, respectively (P = NS). Surgery was performed in the first trimester in one patient (2%), the second trimester in 12 (20%), and early in the third trimester in one patient (2%), but most of the patients (77%) had surgery 1 to 84 months after delivery. Some of these patients were treated before fine-needle aspiration and neck ultrasonography were widely used, accounting for the long delays in identifying malignant nodules in a few patients. Surgical therapy was near-total thyroidectomy in 43 (73%) pregnant women and 265 (59%) of the controls. Radioiodine was administered in the postpartum period to 18 (30%) of the pregnant and 119 (25%) of the nonpregnant women. Median follow-up was 22.4 *vs.* 19.5 yr for the pregnant women and controls, ranging from 20 to 40 yr in the two groups, respectively (P = NS).

There were nine (15%) cancer recurrences in the patient group and 107 (23%) in the controls (P = NS). Distant recurrences were found in one (2%) of the pregnant group and 12 of the controls (3%) (P = NS). Cancer deaths occurred in none of the patient group and six (1.2%) of the control group (P = NS). Outcomes were similar when surgery was performed during or after pregnancy (Table 2), despite a longer delay in treatment of the patient group (1.1 ± 1.0 *vs.* 16.1 ± 19.7 months in the controls; $P < 0.001$). This study suggests that the prognosis of differentiated thyroid cancer is the same in pregnant women and nonpregnant women of the same age and that the diagnosis and treatment of thyroid cancer occurring during pregnancy can be delayed until after delivery in most patients. Pregnant women now have access to earlier and more accurate diagnoses that can be performed much more safely with the improved understanding of when and how to perform therapy, giving women a greater range of treatment options.

Complications of surgery in pregnant women with thyroid cancer

Spontaneous abortion rates are relatively high during the first trimester when surgery is performed in pregnant women with thyroid cancer (17, 18). In addition, women with TSH levels greater than 2.5 mIU/liter during the end of gestation are at risk for breech presentation, and thus for obstetrical complications including fetal death (19).

A retrospective, cross-sectional study by Kuy *et al.* (20) compared age-matched nonpregnant and pregnant women who had thyroid and parathyroid procedures. A total of 201 pregnant women (mean age, 29 yr) had thyroid (n = 165) and parathyroid (n = 36) procedures that were examined together, 46% of whom had thyroid cancer. The 201 pregnant women had a higher rate of endocrine complications (15.9%) as compared with the 31,155 (8.2%) nonpregnant women ($P < 0.001$), a higher rate of general complications (22.4 *vs.* 3.6%), and higher hospital costs ($6873 *vs.* $5963; $P = 0.007$) in the two groups, respectfully. Multivariate analysis identified pregnancy as an independent predictor of higher combined surgical complications (odds ratio, 2.0; $P < 0.001$), longer length of hospital stay, and higher hospital costs. General anesthesia is complicated by important changes occurring during pregnancy, such as an increase in blood volume, which increases heart rate and cardiac output, and supine hypo-

tension resulting from aortic and venacaval compression of the enlarged uterus, which can cause hypoperfusion of the fetus and reduced functional residual capacity because of an elevated diaphragm (21–23), and special precautions should be taken to prevent aspiration.

The Endocrine Society Guidelines

The Endocrine Society Guidelines (21) recommend that when thyroid nodules discovered in the first or early second trimester are found to be malignant, pregnancy should not be interrupted, but surgery should be offered in the second trimester when fetal viability is a valid option. The guidelines also suggest that women found to have cytology indicative of papillary thyroid cancer or follicular neoplasm without evidence of advanced disease, who prefer to wait until the postpartum period for definitive surgery, may be reassured that most well-differentiated thyroid cancers are slow growing and that surgical treatment soon after delivery is unlikely to adversely affect prognosis. United States Preventive Service Task Force Recommendation level: B, Evidence-fair. The guidelines also suggest that there is no evidence that pregnancy worsens the prognosis of well-differentiated thyroid cancer (16, 22–24). If surgery is elected in pregnancy, these guidelines suggest that it is best that surgery be avoided in the first and third trimesters.

In a review of the pregnant thyroid cancer patient, Holt (25) wrote that "of the issues related to thyroid neoplasia for pregnancy for which The Endocrine Society provided guidelines, the most troubling for patients and physicians is the need for surgery for thyroid cancer during pregnancy." Holt wrote that the evidence upon which this guideline was based is limited, mainly because it is difficult to perform well-controlled surgical studies in pregnant women.

Thyroid Hormone, Thyroid Remnant Ablation, Breast Feeding, and Future Fertility

Pregnant women with thyroid cancer may require post-surgical ^{131}I remnant ablation, depending on the tumor stage, histology, and patient preferences. Women who are contemplating radioiodine therapy frequently express concern about breast feeding and future fertility. The U.S. Nuclear Regulatory Commission (NRC) recommends complete cessation of breast feeding in women being treated with ^{131}I. NRC Regulatory Guide 8.39 has regulations that provide advice for both mother and fetus. The decision concerning thyroid remnant ablation is, of course, within the purview of the mother to decline ^{131}I therapy. At present, there is no evidence that exposure to radioiodine affects the outcomes of subsequent pregnancies and offspring (26–28), providing the ^{131}I regulations are observed and the amounts of ^{131}I remain within the recommended treatment limits. See Table 3 in NRC Regulatory Guide 8.39 (http://www.nucmed.com/nucmed/ref/8_39.pdf).

Thyroid Hormone Replacement and Follow-Up of Initial L-T_4 Therapy

After a woman has been treated with thyroid surgery during pregnancy, L-T_4 therapy is necessary, with or without ^{131}I remnant ablation. This is a critical aspect of management, particularly during the first half of pregnancy, during which even mild hypothyroidism may be harmful to fetal development (29, 30), whereas subclinical hyperthyroidism does not carry the same risk for fetal development (31). Normally, there is an increased demand for L-T_4 during pregnancy (32) that occurs very early in gestation at 4 to 6 wk, which increases through midgestation (16 to 20 wk) and then is sustained until delivery (33).

Thus L-T_4 must be administered in a manner that replicates the normal pattern of TSH during pregnancy. During the first trimester in normal pregnant women, the upper TSH reference limit (95th percentile) is 2.5 mIU/liter, and the lower TSH limit is 0.1 mIU/liter (2.5th percentile) (34). This is critically important to the fetus because it is unable to produce and regulate T_4 before 20 wk gestation (35). If a pregnant woman is already taking L-T_4, then the normal gestational TSH patterns require a 20 to 40% increase in L-T_4 (32, 36, 37). Yet the TSH target changes dynamically during pregnancy and is somewhat difficult to maintain in a steady state (34). Moreover, the etiology of hypothyroidism influences the adjustment of L-T_4 (38). Most women first receive obstetrical care during their 8th to 12th week of pregnancy, at which time the majority of women taking L-T_4 already have an elevated serum TSH concentration, making it critical that the L-T_4 dose is swiftly adjusted.

Yassa *et al.* (33) recently found that a two-tablet increase in L-T_4 initiated when pregnancy has been confirmed significantly reduces the risk for maternal hypothyroidism during the first trimester to the time of delivery, thus mimicking the thyroid physiology of pregnancy. The study found that this protocol prevents maternal TSH elevations over 2.5 mIU/liter during the first trimester in 85% and over 5.0 mIU/liter in 100% of the patients. The authors recommend monitoring TSH every 4 wk through midgestation. Three factors identified the patients at greatest risk for an abnormally low TSH and should be monitored more closely, or perhaps required a more conservative initial adjustment of the L-T_4 dose. The three

factors were: athyreotic patients; patients with prepregnancy TSH levels below 1.5 mIU/liter; and lastly, patients receiving prepregnancy L-T_4 doses of at least 100 μg/d or more, who have a 3- to 7-fold risk for TSH suppression after an initial L-T_4 increase, although maternal subclinical hyperthyroidism does not have an adverse effect on the fetus (31).

Lastly, in the setting of pregnancy in women with thyroid cancer, the patient must be aware that a myriad drugs such as iron supplements, calcium, and antacids, and drinking coffee or ingesting food with levothyroxine can have a major impact on the fetus due to inadequate effectiveness of L-T_4 in a pregnant woman and her fetus.

The Utility of Tg Measurement during Pregnancy

The accuracy of serum Tg levels during pregnancy has been questioned in a number of studies, most of which have simultaneously evaluated serum thyroid hormone levels, FT_4, T_3 thyroid-binding globulin, and serum Tg. However, each of the studies has reached slightly differing conclusions.

For example, in 1984 Nakamura *et al.* (39) published one of the early studies concerning serum Tg levels in pregnant women, in which Tg levels in 52 women in various stages of pregnancy were compared with Tg in 15 age-matched nonpregnant women. Among the pregnant females, the mean serum Tg levels were 8.4 μg/liter in the first trimester, 9.2 μg/liter in the second, 10.1 μg/liter early in the third trimester, and 12.1 μg/liter late in the third trimester, as compared with a mean serum Tg of 6.0 μg/liter in nonpregnant women. Yet the authors still concluded that Tg levels in pregnant women could be clinically interpreted without regard to the coexistence of pregnancy.

A later study in 1986 by Hara *et al.* (39) found that serum T_3, T_4, FT_4, thyroid-binding globulin, TSH, and Tg levels were all decreased in the third trimester as compared with those of the first trimester and in normal nonpregnant individuals ($P < 0.01$); still, serum TSH levels were higher than normal in all stages of pregnancy, with a significant rise at the third trimester that the authors attributed to the presence of a subclinical hypothyroid state in the late stage of normal pregnancy.

A 2004 study by Soldin *et al.* (40) found that trimester-specific T_3, FT_4, TSH, and Tg concentrations were significantly different in the first and third trimesters ($P < 0.05$); however, in the second and third trimesters, FT_4, TSH, and Tg values were not significantly different ($P > 0.25$ for all), whereas T_3 was significantly higher in the third trimester, compared with T_3 levels in the second trimester. Also, T_4 was not significantly different among any of the trimesters (all $P > 0.80$). One exception was that T_3 and T_4 tended to be associated at all time points except the third trimester (all $P < 0.05$), and T_4 and FT_4 concentrations tended to correlate positively during pregnancy ($P < 0.05$) but not in the postpartum period ($P < 0.05$). The authors suggested that the trends in this study suggest that T_3, FT_4, Tg, and possibly TSH trimester-specific measurements are warranted for this situation in pregnancy.

In a study by Eltom *et al.* (41), serum Tg, TSH, and urinary iodine concentrations were measured in 27 healthy pregnant Swedish women and in 21 Sudanese women. The median Tg levels in the pregnant Swedish women were 15.5 in the first, 10.5 in the second, and 18.0 μg/liter in the third trimester. However, the median Tg in the third trimester was higher than that in the first and second trimesters ($P < 0.0001$).

Median Tg levels in the pregnant Sudanese women were 27.5 in the first, 25.0 in the second, and 30.0 μg/liter in the third trimester. However, there were no significant differences between these concentrations, as compared with the control group. The Sudanese pregnant women had a significantly higher median Tg level in the third trimester ($P < 0.01$), and the Sudanese pregnant women also had significantly higher median Tg levels as compared with the pregnant Swedish women in all three trimesters of pregnancy ($P < 0.05$, $P < 0.001$, and $P < 0.01$, respectively). However, there were no significant differences between the two nonpregnant controls. Among the Swedish pregnant women, 40, 23, and 30% of the subjects had serum Tg levels greater than 20 μg/liter during the three trimesters, respectively. Corresponding Tg figures for the Sudanese pregnant women were 55, 61, and 64% greater than 20 μg/liter in the three trimesters, respectively. A significant negative correlation was shown between serum Tg and urinary iodine concentrations during the second and third trimesters in the Swedish women ($r = -0.8$, $P = 0.01$; and $r = -0.5$, $P = 0.03$, respectively) and in the third trimester in Sudanese women ($r = -0.6$; $P = 0.03$, respectively). No such correlation was observed between TSH and urinary iodine concentration in either the Swedish or the Sudanese pregnant women. The authors concluded that serum Tg is a more sensitive indicator of iodine deficiency than serum TSH during pregnancy.

There are three main points concerning serum Tg measurements in pregnant women. The first is that serum Tg levels may be altered on the basis of thyroid hormone and TSH levels during pregnancy. Second,, unstimulated serum Tg measurements during pregnancy are not likely to provide enough diagnostic information to make safe, clinically relevant decisions concerning the management strategy of thyroid cancer that may be unfavorable for the mother and fetus. Third, neck ultrasonography and repeated analyses of thyroid hormone and TSH concentra-

tion are by far a more sensitive and specific means of follow-up during pregnancy.

The Author's Opinion

Thyroid cancer during pregnancy requires the combined efforts of endocrinologists, surgeons, nuclear medicine physicians, and the patient's primary care physician. Together, this group must reach a consensus concerning the optimal treatment for the patient and fetus that must be presented to the patient in a lucid fashion that provides a spectrum of reasonable and medically sound options for both the patient and fetus, from which the patient can make the final decision.

In my opinion, the safest treatment for most women and the fetus is usually to perform the initial thyroid cancer surgery after the baby has been born, providing that there is careful predelivery ultrasound follow-up of the patients' tumor during each trimester and regular measurement of serum TSH and FT_4 concentrations every 4 wk as described by Yassa *et al.* (33), while the patient's gynecologist tracks the development of the fetus. If the patient experiences rapid tumor growth of 50% or more or develops ultrasound evidence of extracapsular tumor invasion or lymph node metastases 1 cm or larger, then surgery during the second trimester should be considered, although there is greater risk for the fetus.

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Address all correspondence and requests for reprints to: Ernest L. Mazzaferri, M.D., MACP, University of Florida, 4020 SW 93rd Drive, Gainesville, Florida 32608. E-mail: Ernest.Mazzaferri@gmail.com.

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