Pregnancy may not have an impact on tumor recurrence in women with differentiated thyroid cancer

Hirsch D, Levy S, Tsvetov G, Weinstein R, Lifshitz A, Singer J, Shraga-Slutzky I, Grozinski-Glasberg S, Shimon I, Benbassat C. Impact of pregnancy on outcome and prognosis of survivors of papillary thyroid cancer. Thyroid 2010;20:1179-85. 10.1089/thy.2010.0081 [doi]

SUMMARY

BACKGROUND

Thyroid cancer affects women more often than men by a ratio of almost 3 to 1. Moreover, papillary thyroid cancer (PTC) is the most common form of differentiated thyroid cancer (DTC) among women of childbearing age, 10% of whom are either pregnant or are in the early postpartum period when thyroid cancer is diagnosed. Although the prevalence of thyroid cancer in pregnant women remains high, most are first identified after delivery. Still, the management of thyroid cancer during pregnancy poses serious diagnostic and therapeutic challenges to both the patient and the fetus. The thyroid gland may secrete more thyroid hormone than usual during early pregnancy, which some suggest may not only be the cause of this problem, but might also be responsible for the higher rate of DTC during pregnancy. There is concern about therapy for thyroid cancer during this period, mainly the timing of surgery, the use of levothyroxine, and the assessment of follow-up during gestation. The aim of this study was to determine whether pregnancy in thyroid cancer survivors poses a risk of progression or recurrence of thyroid cancer.

METHODS

This retrospective study comprises a group of consecutive women who had follow-up at the Endocrine Institute of Rabin Medical Center in Tel Aviv, Israel, for PTC from 1992 through 2009 who gave birth at least once after receiving thyroid cancer therapy. Medical records were reviewed for age at the time of thyroid cancer diagnosis and the age at delivery, tumor pathology, lymph-node metastases, and tumor–node–metastases (TNM) tumor staging according to the American Joint Committee on Cancer (6th edition) and the type of treatment, including thyroidectomy, lobectomy, and radioactive iodine (^{131}I); repeated surgeries and repeated ^{131}I treatments; levels of thyroglobulin (Tg) before and during pregnancy and 1 year after delivery; and thyrotropin (TSH) levels during pregnancy.

Thyroid cancer status before pregnancy was categorized as follows: free of disease, defined as a Tg level <0.9 ng/ml on levothyroxine (L-T_4) therapy with negative anti-Tg antibodies (TgAb) and negative neck ultrasonography; or persistent tumor defined by at least one of the following—Tg >0.9 ng/ml on L-T_4 therapy, neck mass on imaging studies with positive cytology for thyroid cancer metastases, or radioiodine uptake outside the thyroid bed and persistent TgAb that increased over time. The following features that were used to determine thyroid cancer progression or recurrence during pregnancy and postpregnancy within 1 year after delivery were Tg levels during L-T_4 therapy, neck ultrasonography, and TgAb titers during follow-up.

Progression of thyroid cancer during pregnancy was defined as one or more of the following: a 20% or larger increase in serum Tg from the prepregnancy level or a consistent increase of 20% or more in serum TgAb levels during pregnancy, new metastatic tumors on neck ultrasonography performed within 1 year after delivery, or an increase in size of a prepregnancy tumor on neck ultrasonography. Persistent disease before conception and the presence or absence of disease progression during pregnancy was analyzed against the demographic parameters, and disease-related indexes, such as TSH levels during pregnancy. All pregnancies were included in the analysis.

RESULTS

Clinical Characteristics (Figures 1 to 3)

A total of 63 women satisfied the inclusion criteria for the study. All were younger than 45 years of age at the time of diagnosis of thyroid cancer (Figure 1). Treatment comprised total thyroidectomy in 59 women, 58 of whom (98.3%) had thyroid remnant ablation (RRA), whereas hemithyroidectomy was performed in 4 women, none of whom had RRA. A total of 40 women gave birth to 90 children. The mean (±SD) duration from the time of treatment to the first delivery was 5.08±4.39 years (median, 3.20) and the mean duration of follow-up after the first delivery was 4.84±3.80 years (range, 3 to 17.3; median, 3.75). The demographic, clinical, histopathological, and biochemical features of the patients during the first pregnancy are shown in Figures 1, 2, and 3.

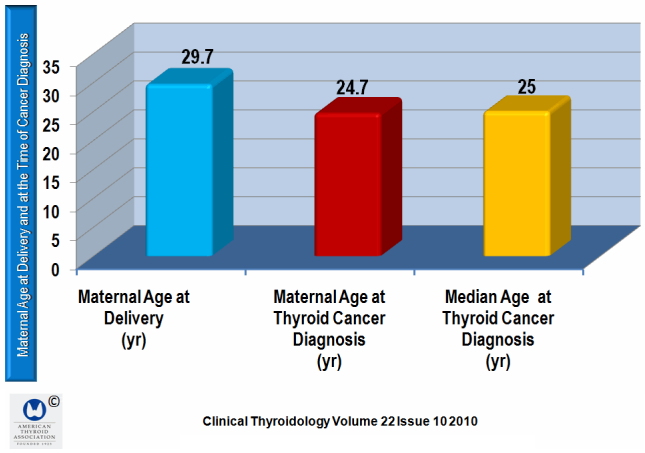

Figure 1. Figures 1, 2, and 3 show the demographic, clinical, histopathological, and biochemical features in 63 women who were thyroid cancer survivors. This figure shows the median age at the time of delivery, the maternal age at the time of diagnosis, and the median age at the time of cancer diagnosis. The first three figures were derived from data in Table 1 of Hirsch et al.

Persistent Tumor before the First Pregnancy (Figure 4)

Thirteen of the 63 women (20.6%) had persistent PTC before conception. Their serum Tg levels and imaging findings before and after pregnancy are shown in Figure 4. Five women had lymph-node dissection after initial surgery before conception, and 12 had persistent disease on the basis of a detectable serum Tg levels on L-T_4 therapy with or without imaging studies. One patient conceived 3 months after RRA and did not have neck ultrasonography or Tg measurements after delivery when lymph-node metastases were detected.

Serum Thyroglobulin Levels (Figure 4)

All serum Tg levels were measured during L-T_4 therapy. Excluded from this group were 4 patients treated with hemithyroidectomy, and 7 who were positive for serum TgAb. Also excluded were 5 women in whom pertinent study data were missing.

Among the remaining 47 women, the mean Tg level before the first pregnancy was 1.23±3.93 ng/ml (range, 0 to 23.9), and the mean postpartum Tg level was 1.18±3.54 ng/ml (range, 0 to 21.4). The difference was not statistically significant. In 39 of the 47 women (82.9%), a Tg level <0.9 ng/ml was documented before and after the first pregnancy. The data for the other 8 women are shown in Figure 4. In a group of 8 patients, there were no changes in serum Tg levels before pregnancy and after delivery with a mean suppressed serum Tg of 7.42±7.37 ng/ml, and 7.01±6.44 ng/ml, respectively, with a serum TSH suppression level before pregnancy of 0.1±0.13 mIU/L after delivery.

Tg was detectable before and after pregnancy in 7 of 8 women, whereas in 1 patient the serum Tg was undetectable before pregnancy but increased postpartum to detectable levels of 1.7 ng/ml, which was considered to indicate progression of cancer during pregnancy. Only 1 patient among those with detectable serum Tg levels had undetectable serum Tg levels before pregnancy that increased during pregnancy as the result of lymph-node metastases that were detected 5 months postpartum.

Structural Evidence of Tumor (Figure 3)

For 56 women in whom ultrasound data were available, 50 (89%) had negative ultrasound studies, whereas 4 of the remaining 6 women had fine-needle aspiration biopsy that revealed PTC cytology and 2 had ^{131}I uptake outside the thyroid bed. In 2 of the 6 women, the serum Tg level before pregnancy was <0.9 ng/ml on L-T_4 therapy, and in 1 patient the serum Tg levels were unavailable.

None of the patients with normal prepregnancy neck ultrasonography had new abnormal ultrasound findings after delivery. However, of the 6 women with abnormal prepregnancy neck ultrasound findings, 1 had new lymph-node metastases 5 months postpartum and another had growth of a preexisting malignant lymph node 3 months postpartum.

Serum TSH during the First Pregnancy

After the first diagnosis of DTC during pregnancy in 58 of 63 women (92%), 52 (89%) had their first TSH measurement performed in the first trimester; the remaining 6 had their first TSH measurement in the second trimester. In most of the women, the serum TSH level was measured a median of five times during pregnancy, during which the mean values were 2.65±4.14 mIU/L (median, 1.20), and only 8 (12.6%) had TSH levels <1 mIU/L throughout the first pregnancy. Still, there was no correlation between serum TSH levels and disease progression or Tg level during pregnancy.

Progression of Thyroid Cancer during Pregnancy (Figure 4)

Progression of thyroid cancer was considered to be present in 6 of 63 patients (9.5%) during their first pregnancy after diagnosis of thyroid cancer. In 4 patients, this was based on a new finding or worsening of a preexisting finding on neck ultrasonography within a year after delivery combined with a positive cytology for PTC, in another patient it was based on a postpartum elevation of serum Tg levels, and in another it was based on a consistent increase in serum TgAb levels throughout the follow-up period, including pregnancy (Figure 5).

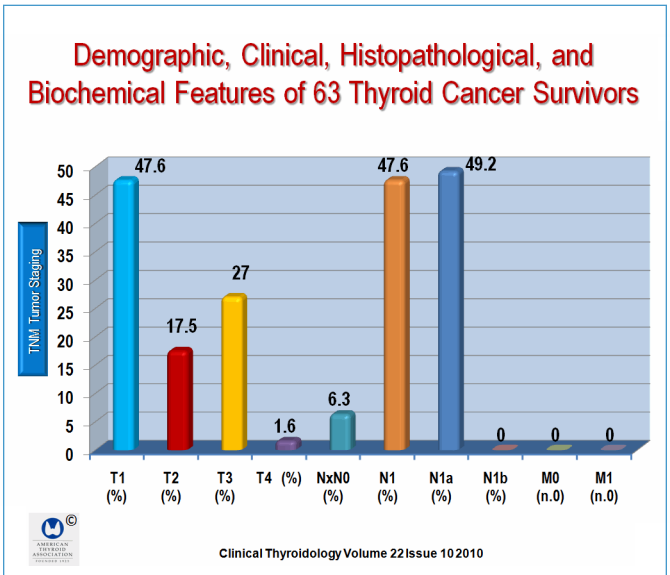

Figure 2. This figure shows the tumor–node–metastasis (TNM) features of the 63 pregnant patients with thyroid cancer.

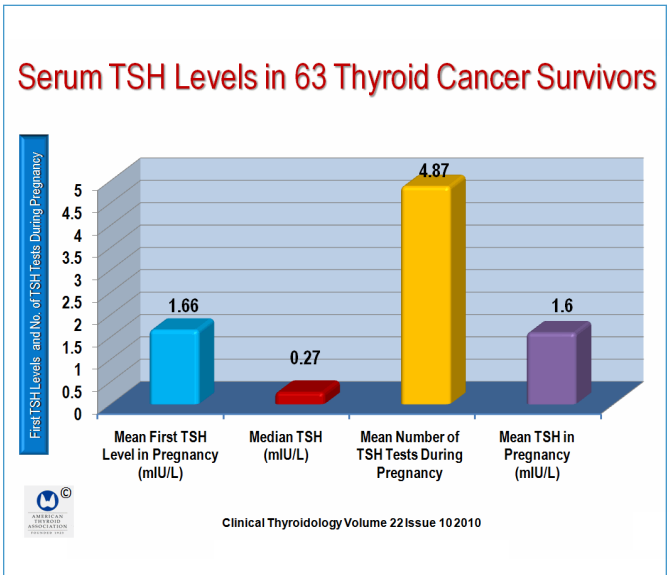

Figure 3. This figure shows the serum thyrotropin (TSH) levels in the 63 pregnant women who were thyroid cancer survivors.

Correlation of Clinical Factors with Disease Persistence during Pregnancy (Figures 4 and 5)

The persistence of thyroid cancer before pregnancy was correlated with tumor size, tumor extension, and TNM staging (P = 0.001, r = 0.345). It was also correlated with the total amount of ^{131}I administered until conception and during the follow-up period: women with persistent tumor before pregnancy were treated with 99.7±69.23.63 mCi; the mean total during the entire follow-up was 345.8±109 mCi in the women with persistent disease and 115.4±87 mCi in women with no prepregnancy evidence of disease (P<0.001, r = 0.729). In addition, disease persistence was also correlated with serum Tg levels before pregnancy (P<0.001, r = 0.606). No significant correlation was found between disease persistence and the other parameters measured.

There also was no correlation with patient age at diagnosis of thyroid cancer; patient age at delivery; interval from diagnosis of thyroid cancer to pregnancy; TNM staging; mean, median, or maximal TSH level during pregnancy; and Tg level before conception. However there was a strongly positive correlation between persistence of thyroid cancer before pregnancy and cancer progression during pregnancy (P<0.001). Every one of the 6 patients with progression of thyroid cancer during pregnancy had evidence of PTC persistence before conception. There also was a strong correlation between the total amounts of ^{131}I administered both until pregnancy and during the whole follow-up period with thyroid cancer progression during pregnancy. The total amount of ^{131}I administered until conception was 260±161.19 mCi in the women with PTC progression and 123±161 mCi in women without tumor progression (P = 0.003; r = 0.376). The total amount of ^{131}I during the whole follow-up period was 315.83±125.3 and 157.5±126.68 mCi, respectively (P = 0.005).

Progression of Thyroid Cancer during Second Pregnancy

A total of 23 women gave birth two times or more after thyroid cancer treatment, and thyroid cancer progressed during the second pregnancy in three women. These patients had persistent disease before both the first and the second pregnancies. Thyroid cancer progressed during both the first and second pregnancies in one woman, and only during the second pregnancy in two. Four women gave birth to three children after the diagnosis and treatment of PTC.

Current Patient Status

Of the 13 patients categorized as having persistent disease, 11 still had biochemical evidence of tumor with or without structural evidence of PTC at last follow-up and 6 were treated with additional therapy since giving birth. Two had dissection of lymph-node metastases, and another received an additional 150 mCi of ^{131}I and three others had surgery and received and additional 150 to 350 mCi of ^{131}I postpartum and have no evidence of disease.

CONCLUSION

Pregnancy may not have an impact on tumor recurrence in women with DTC.

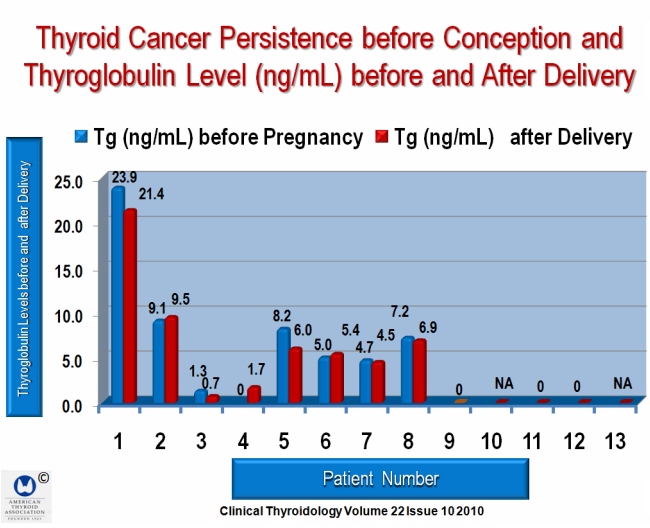

Figure 4. This figure shows the thyroid cancer persistence before conception and thyroglobulin levels before and after delivery. NA = not available.

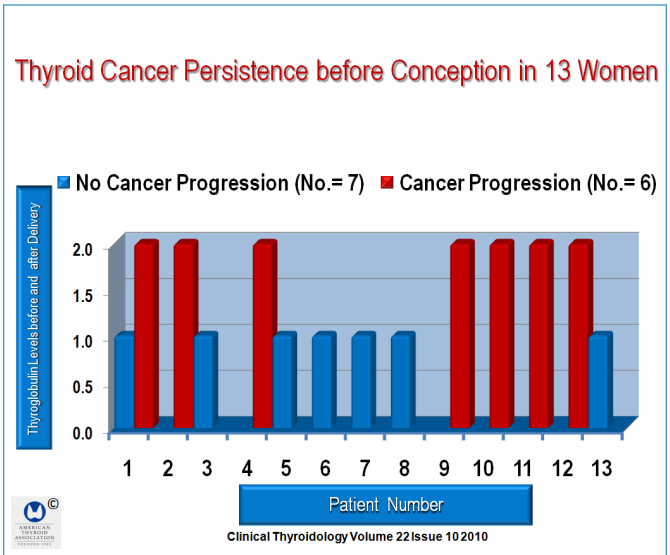

Figure 5. This figure shows thyroid cancer persistence before conception in 13 women, showing women with and without cancer progression

COMMENTARY

Thyroid cancer is a common problem in pregnant women. A study by Smith et al. (1) 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 whom 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 25% 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 some 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. Still, ionizing radiation remains the best-established risk factor for thyroid cancer (2), although 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 (3). 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 (4), 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 (5,6), and the effects tend to be small (7).

During normal pregnancy, the stimulatory effects of HCG and estrogen produce changes in serum TSH, free thyroxine (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 (8,9). There is a suggestion that estrogens may increase the expression of the Tg gene, increasing the potential production of Tg in DTC without stimulating the c-myc proto-oncogene and therefore not promoting rapid cell proliferation (10).

Hirsch report the serum Tg levels in pregnant women; however, 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, triiodothyronine (T_3) thyroid-binding globulin, and serum Tg. However, each of the studies has reached slightly differing conclusions.

One of the early studies of Tg during pregnancy was published in 1984 by Nakamura et al. (11), 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 women, the mean serum Tg levels were 8.4 ng/L in the first trimester, 9.2 in the second, 10.1 early in the third trimester, and 12.1 late in the third trimester, as compared with a mean serum Tg of 6.0 ng/L in nonpregnant women. Still, the authors concluded that Tg levels in pregnant women could be clinically interpreted without regard to the coexistence of pregnancy.

A study in 1986 by Hara et al. (12) 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 the first trimester and with values in healthy nonpregnant individuals ($P<0.01$); nonetheless, serum TSH levels were higher than normal in all stages of pregnancy, with a significant rise in the third trimester that the authors attributed to the presence of a subclinical hypothyroid state in the late stage of normal pregnancy.

A study by Soldin et al. (8) 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, whereas T_3 was significantly higher in the third trimester as compared with the second trimester, but T_4 was not significantly different among any of the trimesters. Lastly, a clinical study by Leboeuf found that serum Tg levels in pregnant women may be high without detectable tumor (13).

The main finding of the study by Hirsch et al. is that pregnancy does not have an impact on tumor recurrence in women with differentiated thyroid cancer. A study by Moosa and myself (14) of 61 pregnant women showed no increased risk for tumor recurrence, distant recurrence, and cancer mortality as compared with age-matched controls.

Not mentioned in the Hirsch study is the outcome of pregnancy and fetal survival in this group of women who were initially treated with relatively large amounts of ^{131}I. Managing thyroid cancer in pregnant women involves therapeutic decisions for both the mother and fetus, including decisions concerning breast-feeding, subsequent pregnancies, and outcome of the fetus.

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