THYROID
Volume 28, Number 1, 2018

DOI: 10.1089/thy.2017.0496

Recent Pregnancy Is Not Associated with High-Risk Pathological Features of Well-Differentiated Thyroid Cancer

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Background: Thyroid cancer is commonly diagnosed in the first postpartum year, supporting the theory that high levels of estrogen may stimulate progression of hormone-mediated thyroid cancer. The aim of this study was to assess the effect of recent pregnancy on histopathologic disease characteristics of well-differentiated thyroid cancer (WDTC).

Methods: Cases of WDTC (1999–2012) were identified from the California Cancer Registry and linked to data from the Office of Statewide Health Planning and Development. Using a matched control design, recently pregnant women (pregnancy up to five years before and nine months after a thyroid cancer diagnosis) were compared with non-pregnant controls matched by age and race/ethnicity. The main outcome measures were histopathologic tumor characteristics (tumor size, extrathyroidal extension, and nodal metastases), disease status at last follow-up, and five-year disease-specific survival.

Results: The study sample of 1204 women ($M_{age} \pm$ standard deviation $= 30.9 \pm 5.5$ years; 46.5% Caucasian and 40.0% Hispanic) included 301 recently pregnant women matched against 903 non-pregnant controls. Comparing recently pregnant versus non-pregnant women, no significant differences were observed with respect to tumor size ($M = 2.2 \pm 1.6$ vs. 2.3 ± 3.9 cm; $p = 0.39$), extrathyroidal extension (12.0% vs. 14.1%; $p = 0.46$), stage at diagnosis (localized disease: 67.4% vs. 62.8%; regional metastases: 30.6% vs. 33.4%; distant metastases: 2.0% vs. 3.8%; $p = 0.17$), disease status at last follow-up (free of tumor vs. not free of tumor; $p = 0.48$), and five-year disease-specific survival (99.5% vs. 99.5%). In multivariate analyses, after controlling for patient age and ethnicity, recent pregnancy was not a significant predictor of tumor size, extrathyroidal extension, nodal metastases, or distant metastases.

Conclusions: In this cohort, recent pregnancy was not associated with high-risk pathological features of differentiated thyroid cancer. These findings provide reassurance with regards to the concern that pregnancy may act as a potential stimulus for thyroid cancer growth.

Keywords: pregnancy, postpartum, thyroid cancer, childbearing, women

Introduction

Thyroid cancer is the most common endocrine malignancy, with an incidence that is increasing by 3.8% each year (1). More than one third of diagnoses occur in patients <45 years old, of which 75% occur in women with peak onset during the reproductive years (2,3). Pregnancy stimulates an increase in both the number and size of thyroid nodules (4). Furthermore, well-differentiated thyroid cancer (WDTC) is one of the two most commonly diagnosed cancers in the first postpartum year (5). This has prompted the concern that pregnancy may stimulate thyroid cancer cell growth (4,5).

In 2017, the American Thyroid Association (ATA) released updated guidelines on the management of thyroid nodules and thyroid cancer in pregnant and postpartum women (6). These guidelines acknowledge that the prognosis of women with WDTC during pregnancy is largely similar to that of non-pregnant patients, and recommend deferral of surgery during pregnancy in the setting of low-risk disease.

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However, two studies suggest that pregnant women may have more aggressive disease with higher relapse rates (7,8). The ATA recommendations are influenced by limited data supporting a poorer prognosis of thyroid cancer in pregnancy, as large-scale studies with consistent results are lacking.

Utilizing a large comprehensive statewide cancer database, differences in the histopathologic characteristics and disease outcomes of women with WDTC following recent pregnancy matched against non-pregnant controls were assessed.

Materials and Methods

This was a matched-control study of recently pregnant women compared to non-pregnant controls. Women were matched 1:3 on the basis of age at thyroid cancer diagnosis (within one year) and race/ethnicity (white vs. non-white). Inclusion criteria for the recently pregnant cases were women with pregnancy up to five years before and nine months after a WDTC diagnosis within the California Cancer Registry (CCR) from 1999 to 2012. A period of five years before thyroid cancer diagnosis was chosen as a reasonable time frame before which an insult (pregnancy) might impact the development of thyroid cancer, as suggested by the substantial increase in incidence of thyroid cancer at this time point following the Chernobyl nuclear accident (9). Because the available codes within the CCR database capture birth and delivery events, a pregnancy that was coded within nine months after cancer diagnosis indicated that the diagnosis was made while the patient was still pregnant. Therefore, extending the study time frame to nine months after the diagnosis of thyroid cancer allowed patients who were diagnosed during gestation to be captured. The diagnosis of WDTC was identified using CCR variables ''SITE_O2'' C739 and C73.9 and histology codes 8050, 8260, 8330, 8331, 8332, 8335, 8340, 8342, 8343, 8344, and 9690. The CCR database captures all cases of cancer in California and meets all National Program of Cancer Registries (NPCR; a program within the Center for Disease Control and Prevention) and Surveillance, Epidemiology, and End Results (SEER) standards for quality, timeliness, and completeness. Every cancer diagnosis made in California from 1988 onward is required by law to be reported to the CCR. All data were then linked to the Office of Statewide Health Planning and Development (OSHPD) to allow for longitudinal follow-up regarding pregnancy and other subject demographics. Live births were abstracted from the OSHPD database using International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes (650–659).

Histopathologic disease characteristics (tumor size, extrathyroidal extension, and stage at diagnosis [localized disease, regional metastases, distant metastases]), disease status at last follow-up, and disease-specific survival were defined using CCR variables. Tumor status at last follow-up is defined by the CCR database as: ''Free of this tumor; Not free of this tumor; Tumor status unknown.'' These determinations are made by the CCR upon collected data requested from hospitals and other medical facilities on cancer cases in the state. The CCR collates these data, performs thorough quality control measures, and analyzes the data on a statewide basis.

The Wilcoxon rank sum test was used to compare differences of tumor size, extrathyroidal extension, stage at diagnosis, and tumor status between recently pregnant cases and non-pregnant controls. The Kaplan–Meier estimate was used to compare differences in five-year disease-specific survival. After controlling for patient age and race/ethnicity, multivariate logistic regression was performed to determine whether recent pregnancy was a significant predictor of tumor size, extrathyroidal extension, and stage at diagnosis. All data analyses were performed using SAS v9.3 (SAS Institute, Cary, NC). Two-tailed p-values were reported and considered statistically significant if <0.05. Study approval was obtained from the UCLA Institutional Review Board (IRB) and the California State Committee for the Protection of Human Subjects IRB.

Results

The study sample of 1204 women included 301 recently pregnant women matched against 903 non-pregnant controls. Baseline subject demographics were similar between recently pregnant women and non-pregnant controls (Table 1). The mean age $\pm$ standard deviation for the full cohort was 30.9 ± 5.5 years, and 46.5% of subjects were non-Hispanic whites. For the 301 case patients, the median time between pregnancy and thyroid diagnosis was 2.62 years (range 0.37–4.99 years). The median time between thyroid diagnosis and last contact or death was 7.92 years (range 0–14.17 years) for cases and 12.42 years (range 0–15.11 years) for controls.

Histopathologic characteristics of WDTC were similar between the recently pregnant and non-pregnant groups (Table 2). There were no significant differences with respect to tumor size (2.2 ± 1.6 vs. 2.3 ± 3.9 cm; $p = 0.39$), extrathyroidal extension (12.0% vs. 14.1%; $p = 0.46$), or stage at diagnosis (localized disease: 67.4% vs. 62.8%; regional metastases: 30.6% vs. 33.4%; distant metastases: 2.0% vs. 3.8%; $p = 0.17$). There was also no significant difference in the tumor status between the two groups (free of this tumor vs. not free of this tumor; $p = 0.48$). Finally, the five-year disease-specific survival was comparable among cases and controls (99.47% vs. 99.54%). In multivariate analyses, after controlling for patient age and ethnicity, recent pregnancy was not a significant predictor of tumor size ($p = 0.66$), extrathyroidal extension ($p = 0.97$), or stage at diagnosis ($p = 0.23$).

Discussion

In this matched-control study, recent pregnancy did not affect histopathological characteristics of WDTC. Tumor size, extrathyroidal extension, and nodal metastases were similar between women with a history of recent pregnancy and non-pregnant women. Disease status at last follow-up and five-year disease-specific survival were also unaffected by recent pregnancy. In the present study, the cohort was derived from a 13-year time period utilizing comprehensive linked data, yielding a large number of cases with information about both inpatient hospitalizations and outpatient visits. Furthermore, the study reviewed cases of women diagnosed with thyroid cancer within five postpartum years, allowing inclusion of women with thyroid cancers that may have taken more time to progress.

Previous studies have investigated the potential for progression of thyroid cancer during and after pregnancy, highlighting the thyroid-stimulating effects of human chorionic

Table 1. Subject Demographics of Recently Pregnant Cases and Non-Pregnant Controls

Characteristics	*Recently pregnant cases* (n = *301*)	*Non-pregnant controls* (n = *903*)	*Total subjects* (n = *1204*)	*Standardized difference*[a]
Average age at diagnosis (years), mean ± *SD*	30.8 ± 5.4	30.9 ± 5.6	30.9 ± 5.5	–0.0308
Race/ethnicity, *n* (%)				0.0031
Non-Hispanic white	140 (46.5)	420 (46.5)	560 (46.5)	
Non-Hispanic black	10 (3.3)	30 (3.3)	40 (3.3)	
Hispanic	120 (39.9)	360 (39.9)	480 (39.9)	
Asian/Pacific Islander	28 (9.3)	84 (9.3)	112 (9.3)	
Non-Hispanic American Indian	2 (0.4)	6 (0.4)	8 (0.4)	
Socioeconomic status (SES),[b] *n* (%)				0.2089
Lowest SES	62 (20.6)	183 (20.3)	245 (20.4)	
Lower-middle SES	50 (16.6)	195 (21.6)	245 (20.4)	
Middle SES	68 (22.6)	221 (24.5)	289 (24)	
Higher-middle SES	65 (21.6)	192 (21.3)	257 (21.4)	
Highest SES	52 (17.3)	109 (12.1)	161 (13.4)	

[a]Standardized differences of 0.2, 0.5, and 0.8 represent small, medium, and large effect sizes, respectively.
[b]SES quintiles derived from the Yost index of SES level (16).
SD, standard deviation.

gonadotropin (hCG) and increased levels of estrogen during pregnancy as possible mechanisms (10). In a recent meta-analysis, Zhou *et al.* reported that the odds ratio of developing thyroid carcinoma among women with a history of pregnancy was similar to non-pregnant controls. Furthermore, of those with thyroid carcinoma, the risks of having lymphatic metastasis or distant metastasis were also similar (11). However, the incidence of thyroid carcinoma was significantly increased in women with a history of three or more pregnancies, as well as in women within five years of their most recent pregnancy (11). Messuti *et al.* reported a statistically higher rate of persistence or recurrence when WDTC was diagnosed during pregnancy or within the first two postpartum years (7). Similarly, Vannucchi *et al.* noted a high rate of persistent disease (60%) in 10 patients with WDTC during pregnancy compared to non-pregnant controls (4.2–3.1%) (8).

A similar weight of evidence supports the contrary stance that no differences exist in the rate of disease progression, recurrence, or long-term survival of women with WDTC identified either before or during pregnancy. In a retrospective case study of 63 women with a history of papillary thyroid cancer (PTC) and recent pregnancy, Hirsch *et al.* demonstrated that pregnancy was not correlated with thyroid cancer recurrence in PTC patients who were devoid of structural or biochemical evidence of disease at the time of conception (12). In a retrospective review of 235 women who had a term pregnancy after initial treatment for differentiated thyroid cancer (1997–2015), Rakhlin *et al.* reported that the majority of thyroid cancer patients who had an excellent, indeterminate, or biochemical incomplete response to treatment prior to pregnancy did not demonstrate progression or recurrence after delivery (13). In a recent study of 19 patients who were diagnosed with WDTC just before or during early pregnancy,

Table 2. WDTC Characteristics Between Recently Pregnant Cases and Non-Pregnant Controls

Characteristics	*Recently pregnant cases* (n = *301*)	*Non-pregnant controls* (n = *903*)	*Total cases* (n = *1204*)	p-*Values*
Tumor size (cm), mean ± *SD*	2.2 ± 1.6	2.3 ± 3.9	2.3 ± 3.4	0.39
Extrathyroidal extension, *n* (%)				
Present	36 (12.0)	127 (14.1)	163 (13.5)	0.46
Not present	265 (88.0)	774 (85.7)	1039 (86.3)	
Unknown	0 (0)	2 (0.2)	2 (0.2)	
Stage at diagnosis, *n* (%)				
Localized disease	203 (67.4)	557 (62.8)	760 (64.0)	0.17
Regional metastases	92 (30.6)	296 (33.4)	388 (32.7)	
Distant metastases	6 (2.0)	34 (3.8)	40 (3.4)	
Tumor status at last follow-up, *n* (%)				
Free of tumor	258 (85.7)	748 (82.8)	1006 (83.6)	0.48
Not free of tumor	28 (9.3)	105 (11.6)	133 (11.1)	
Unknown	15 (5.0)	50 (5.5)	65 (5.4)	
Five-year disease-specific survival rate, %	99.47%	99.54%		

WDTC, well-differentiated thyroid cancer.

the primary tumor size remained stable in most patients, and no patients developed cervical lymph node or distant metastasis during follow-up (14). Finally, in a retrospective case-control review, Yasmeen *et al.* demonstrated that tumor characteristics, stage at diagnosis, and overall survival were similar between women with pregnancy-associated thyroid cancer and non-pregnant controls (15).

The present results support prior studies that found no significant impact on disease progression or long-term outcomes for recently pregnant women with WDTC. Still, several limitations should be mentioned. First, because this was a retrospective cross-sectional study, potential cases of rapid disease progression necessitating prompt surgical management during pregnancy could not be ascertained. Second, the database was limited to capturing women who carried pregnancies to at least 20 weeks. Therefore, women with advanced disease who may have been more likely to terminate early pregnancies or undergo pregnancy loss before that time would not have been captured in the data set. Finally, because the last cases included women who were diagnosed with thyroid cancer in 2012, the long-term follow-up needed to assess five-year disease-specific survival was limited. Additional studies, including those focusing on the underlying mechanisms supporting an estrogenic cause of growth of thyroid cancer, are needed to determine the potential associations between pregnancy and progression of thyroid cancer.

In summary, recent pregnancy was not associated with high-risk pathological features of WDTC, the status of the tumor at most recent follow-up, or five-year disease-specific survival in this study. These findings support the 2017 ATA guidelines for the diagnosis and management of thyroid disease during pregnancy and the postpartum, which recommend delaying surgery in most pregnant patients with WDTC until after delivery. Decisions on the management of thyroid cancer during planning and the course of pregnancy should be individualized, with engagement between the patient and her multidisciplinary care team.

Author Disclosure Statement

The authors have no conflicts of interest to disclose.

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