Post-hemithyroidectomy Pregnancy Thyroid Function Surveillance - Frequency, Adherence and Guideline Impact

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Abstract

Purpose: Post-hemithyroidectomy women are at increased risk for gestational subclinical hypothyroidism. Therefore, the American Thyroid Association (ATA) recommends increased thyroid function surveillance for this subgroup of pregnant women. The Purpose of this study was to evaluate the frequency of thyroid function surveillance during pregnancy in post-hemithyroidectomy women, and to evaluate the adherence to the 2017 ATA guidelines and its possible impact since being published, on thyroid function surveillance rates.

Materials and Methods: A retrospective study including all pregnancies conceived by post-hemithyroidectomy women operated at Kaplan Medical Center between the years 1997-2020. The study cohort was subdivided by pregnancy date prior to 2018 and 2018 and onwards to evaluate the impact of the 2017 ATA guidelines. Adherence to the guidelines was defined as at least one TSH test in each trimester.

Results: After exclusions, a total of 120 pregnancies conceived by 66 women who underwent hemithyroidectomy surgeries were included in this study. Overall, serum TSH examinations were performed during the first, second and third pregnancy trimesters in 86.6%, 40% and 16.6% of pregnancies (P<0.005), respectively. The examination rate since 2018 was 88%, 40% and 8% for first, second and third trimester, respectively (P<0.005). No significant differences were found in serum TSH examination rates between pregnancies prior to and following the beginning of 2018 (P=.533).

Conclusions: Adherence to the latest ATA guidelines is low and its publication in 2017 did not increase the thyroid function surveillance rate in post-hemithyroidectomy women. Better patient education regarding the risks of gestational hypothyroidism following hemithyroidectomy and improved communications between treating surgeons, obstetricians, and endocrinologists may improve these rates.

Introduction

Hypothyroidism occurs in approximately 20% of patients following hemithyroidectomy and in about 15% of women during pregnancy.[4, 28] The rising number of thyroidectomies in the past decades is characterized by female predominance and earlier diagnosis which together with a trend towards advanced maternal age, results in considerable numbers of post-hemithyroidectomy women of childbearing age.[13, 15, 19, 23] These women are at an increased risk for gestational hypothyroidism, known to be associated with adverse maternal and fetal outcomes.[12, 21] A recent study demonstrated that about a third of post-hemithyroidectomy women had serum TSH levels higher than the trimester-specific recommended range throughout pregnancy.[14]

In 2017, the American Thyroid Association (ATA) revised their guidelines from 2011 for gestational hypothyroidism screening in high-risk groups, which also includes post-hemithyroidectomy women. The 2011 guidelines recommended a single TSH test in the first trimester. This was revised to repeated TSH examinations every four weeks until mid-gestation and at least once around 30 weeks gestation[3, 24], a
change that acknowledges the increased thyroid hormone demand through mid-pregnancy.[2] However, currently, there are no studies that have evaluated the thyroid function surveillance rate in post-hemithyroidectomy pregnant women.

The aim of this study was to evaluate the frequency of thyroid function surveillance during pregnancy in post-hemithyroidectomy women, and to evaluate for the first time, the adherence to the 2017 ATA guidelines and the impact of its publication on thyroid function surveillance rates.

Materials And Methods

Study Population

This study was performed in line with the principles of the Declaration of Helsinki. After obtaining institutional review board approval (July 2020, KMC-0069-19), we extracted the records from the institute's electronic medical records (EMR) (Chameleon, Elad Software Ltd., Israel) of all female patients who underwent hemithyroidectomies, registered as either hemi- or partial thyroidectomy surgery (ICD9 06.2, 06.3) at Kaplan Medical Center, Clalit Health Services, (Rehovot, Israel) from February 1997 to February 2020. Included in this study, were female patients who were pregnant at least once following thyroid surgery. Patients were excluded if they were younger than 18 years at the time of surgery or conception, had any known thyroid disease (including Hashimoto thyroiditis, Graves’ disease, clinical or subclinical hypo- or hyperthyroidism) prior to pregnancy, underwent total or sub-total thyroidectomy, had an abortion prior to the gestational age of 10 weeks or if insufficient data was found. The study cohort was subdivided by pregnancy date to prior to 2018 and 2018 and onwards to evaluate the impact of the 2017 ATA guidelines for the diagnosis and management of thyroid disease.

Study Outcomes

The primary outcome of this study was the frequency of thyroid function measurements during pregnancy and adherence with the 2017 ATA guidelines for the management of thyroid disease during pregnancy recommendations for TSH monitoring in post-hemithyroidectomy women. [3] In this study, this was measured by the proportion of pregnancies in which serum TSH was examined at least once every trimester for each pregnancy included. Although this is an incomplete overlap with the ATA’s recommendations, it was used to increase measurement uniformity and to reduce sampling error.

The secondary outcome was the impact of the 2017 ATA guidelines on the proportion of pregnancies in which serum TSH was examined at least once in each trimester. Since the guidelines were published in August 2017, we compared pregnancies prior to and following 2017. The study group was defined as 2018 and onwards pregnant women, who were compared to a control group which included patients who became pregnant between 1997–2017. A trimester in which no TSH examination was taken was considered as non-adherence.

Data Collection
All medical records were reviewed using two separate EMRs, our institute's (Chameleon, Elad Solutions Ltd, Tel-Aviv, Israel) and an integrated hospital-community online medical records system (Ofek Database System, Clalit Health Services, Israel), which allows online access to imaging, pathology reports, lab reports, admissions, and surgical procedures done in the community and in other institutions.

Data was collected for each pregnancy separately. Patient characteristics included age, smoking history (defined as at least 5 pack-years described by the patient, or a smoker status documented in the EMRs), and status of diabetes mellitus (documented according to the patients’ problem list or if a medication for this condition was documented in their drug list).

Peri-operative data included indication for surgery (malignancy/suspected malignancy, symptomatic thyroid disease (pressure symptoms), patient's will (mostly for cosmetic purposes) and specimen pathology results.

Follow-up data included the timing and value of serum TSH (mU/L) examinations during pregnancy. TSH levels were evaluated according to the ATA 2011 recommended upper range (TSH > 2.5 mIU/L for the first trimester, TSH > 3.0 mIU/L for the second and third trimester) and the ATA 2017 recommended upper range (TSH > 4.0 mIU/L). Also included were serum examinations for free T4 (FT4, pmol/L), thyroid peroxidase antibody (TPOAb, status) and thyroglobulin antibody (TgAb, status). TPOAb, TgAb and FT4 levels were seldomly measured and therefore, we only included examination rates in the analysis. The total number of endocrinology clinic visits during pregnancy was documented (endocrinology clinic visits were considered only if they related directly to the thyroid state). Pregnancy and birth related information included gravidity and parity state, pregnancy date and gestational age at delivery or abortion. The pregnancy date was defined as the first day of the last menstruation.

**Statistical analysis**

Statistical analysis was performed using SPSS software (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, USA). Categorical variables were described using frequencies and percentages. Variables that were normally distributed were described using mean and standard deviation (SD) and abnormally distributed variables were described using median and interquartile ranges. The association between non-categorical (continuous) variables, categorical variables and nonparametric variables was calculated using Student's t-tests, chi-squared tests and Mann-Whitney tests, respectively. TSH examination rates were estimated using the Kaplan-Meier method, and examination rates were compared by using a log-rank test.

Variables with p-values under 0.05 were included in the multivariate analysis. A two-tailed p-value < 0.05 was considered significant.

**Results**

The study flowchart is presented in Fig. 1. During the 23-year study period, 1067 patients underwent either hemi or partial thyroidectomy surgery in our institution. Of this cohort, 66 patients had no known thyroid
disease prior to pregnancy and conceived 120 pregnancies with sufficient data to qualify for this study.

Patient characteristics are presented in Table 1. The mean (standard deviation [SD]) age at surgery was 26.5 [± 7.2] years. The most common indication for surgery was suspicion of malignancy (80.8%). The mean age at pregnancy was 31.8 [± 5.6] years.

<table>
<thead>
<tr>
<th>Total, N = 120</th>
<th>Pregnancy before 2018, N = 95</th>
<th>Pregnancy 2018 and onwards, N = 25</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, year, mean (SD)</td>
<td>26.5 (7.2)</td>
<td>25.2 (6.5)</td>
<td>27.4 (6.5)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>23 (19.1%)</td>
<td>19 (20%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (2.5%)</td>
<td>3 (3.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Indication for hemithyroidectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>97 (80.8%)</td>
<td>78 (82.1%)</td>
<td>19 (76%)</td>
</tr>
<tr>
<td>Pressure symptoms</td>
<td>19 (15.8%)</td>
<td>15 (15.7%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Cosmetic</td>
<td>4 (3.3%)</td>
<td>2 (2.1%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Pathology (malignant)</td>
<td>10 (8.3%)</td>
<td>9 (9.4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Time between surgery to pregnancy, year, median (CI)</td>
<td>5.6 (4.4-7)</td>
<td>5.1 (5.1-7)</td>
<td>7.2 (5.1–9.4)</td>
</tr>
<tr>
<td>Age at pregnancy, year, mean (SD)</td>
<td>31.8 (5.6)</td>
<td>31.3 (5)</td>
<td>34.9 (4.2)</td>
</tr>
<tr>
<td>Gravidity, mean (SD)</td>
<td>3.7 (2.2)</td>
<td>3.6 (2.2)</td>
<td>4.1 (2.2)</td>
</tr>
<tr>
<td>Abortions</td>
<td>14 (11.6%)</td>
<td>10 (10.5%)</td>
<td>4 (16%)</td>
</tr>
</tbody>
</table>

N-number of pregnancies; Data are represented as n (%) unless otherwise indicated.

Pregnancy follow-up data is presented in Table 2. Mean number of serum TSH examinations during pregnancy was 1.91 [± 1.3] and time between pregnancy and first TSH examination was longer in pregnancies since 2018. However, this did not reach significance. Figure 2 presents the distribution of the total number of serum TSH examinations during pregnancy, where most patients (45%) were examined only once during pregnancy.
Table 2
Comparison of Pregnancy Follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Pregnancy before 2018, N = 95</th>
<th>Pregnancy 2018 and onwards, N = 25</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of TSH examinations during pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.91 (1.3)</td>
<td>1.98 (1.3)</td>
<td>1.68 (1.1)</td>
</tr>
<tr>
<td>Median</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mode</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Time between Pregnancy and first TSH examination, days, median (CI)</td>
<td>60.5 (57–68)</td>
<td>57.5 (55.3–67.3)</td>
<td>63.5 (53.4–80.6)</td>
</tr>
<tr>
<td>Tg or TPO antibody examination</td>
<td>9 (7.5%)</td>
<td>8 (8.4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>FT4 examination</td>
<td>6 (5%)</td>
<td>5 (5.2%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Endocrinology clinics visits</td>
<td>6 (5%)</td>
<td>5 (5.2%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Thyroid replacement therapy initiated during pregnancy</td>
<td>7 (5.8%)</td>
<td>6 (6.3%)</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

N-number of pregnancies; Data are represented as n (%) unless otherwise indicated.

CI = confidence interval; SD = standard deviation; Tg = Thyroglobulin; TPO = Thyroperoxidase; TSH = Thyroid stimulating hormone; FT4 = Free T4.

Rates of hypothyroidism according to different serum TSH cutoffs are presented in Table 3. Pregnancies prior to 2018 had higher rates of hypothyroidism in the first trimester according to the high limit serum TSH reference range of 2.5 mU/L. No other significant differences were seen between pregnancies prior to 2018 and those from 2018 onwards.
### Table 3
Comparison of pregnancy serum TSH.

<table>
<thead>
<tr>
<th>Total</th>
<th>Pregnancy before 2018</th>
<th>Pregnancy 2018 and onwards</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 104</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH &gt; 2.5</td>
<td>31 (29.8%)</td>
<td>29 (35.4%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>TSH &gt; 4</td>
<td>5 (4.8%)</td>
<td>4 (4.9%)</td>
<td>0.94</td>
</tr>
<tr>
<td>Second trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH &gt; 3</td>
<td>7 (14.5%)</td>
<td>5 (13.1%)</td>
<td>0.52</td>
</tr>
<tr>
<td>TSH &gt; 4</td>
<td>2 (4.1%)</td>
<td>2 (5.2%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Third trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH &gt; 3</td>
<td>10 (50%)</td>
<td>9 (50%)</td>
<td>1</td>
</tr>
<tr>
<td>TSH &gt; 4</td>
<td>3 (15%)</td>
<td>2 (11.1%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

N-number of pregnancies; Data are represented as n (%) unless otherwise indicated. TSH value units are in (mU/L)

* indicates significant values.

TSH = Thyroid stimulating hormone.

In this cohort, serum TSH examinations were performed during the first, second and third trimester of pregnancy in 86.6%, 40% and 16.6% of pregnancies (P < 0.005), respectively. Figure 3 compares the proportions of serum TSH examinations performed during each trimester between pregnancies prior to 2018 and those from 2018 onwards. Pregnancies prior to 2018 had a higher proportion of examinations performed in the third trimester of pregnancy (18.9% vs. 8%). However, this did not reach significance (P = .533).

In a sub-analysis comparing solely first pregnancies following surgery, proportions of serum TSH examinations performed during each trimester in pregnancies prior to 2018 and those from 2018 onwards did not reach significance (P = .203).

### Discussion

This study examines the quality of thyroid function surveillance during pregnancy in post-hemithyroidectomy women with regard to the ATA guidelines and whether these guidelines have led to a change in follow-up frequency. Previous ATA and other endocrine society guidelines recommended that women with prior thyroid surgery should be examined for serum TSH once early in their pregnancy.\[1, 24\] Our study has shown that thyroid function surveillance during pregnancy is suboptimal. TSH measurement rates in the first, second and third trimesters of pregnancy were 86.6%, 40% and 16.6%, respectively. To the best of our knowledge, this is the first study to examine the screening rate for gestational hypothyroidism in post-hemithyroidectomy women. The revised ATA guidelines, published in
2017, recommend that post-hemithyroidectomy women should be monitored with serum TSH measurements approximately every four weeks until mid-gestation and at least once near 30 weeks of gestation.[3] Within our limited cohort, only 8% of pregnancies were adherent with this recommendation and the publication of the guidelines did not result in an increase of the tests taken.

The basis for thyroid function surveillance in pregnancy has several reasons.

First, a woman’s thyroid physiology undergoes certain changes during pregnancy that contribute to an increase in serum TSH, including the doubling of thyroxine-binding globulin concentration, a 30–40% increase in plasma volume, and rising levels of estradiol.[2, 5, 10]

Second, the prevalence of gestational hypothyroidism is not negligible. In the largest national survey from the United States, gestational hypothyroidism was seen in 15.5% of women, of which 2.4% had overt hypothyroidism.[4] Using the same TSH limit reference ranges (2.5 mU/L in the first trimester, and 3 mU/L in the second and third trimester), we found gestational hypothyroidism in 29.8%, 14.5% and 50% of our cohort in the first, second and third trimesters, respectively. Our higher rates of gestational hypothyroidism may be explained by the fact that our cohort consisted of post-hemithyroidectomy women. Another study observed post-hemithyroidectomy women, and found hypothyroidism in 39%, 36% and 31% during the first, second and third trimester of pregnancy, respectively.[14] Our lower rates of hypothyroidism in the first and second trimesters could be due to the fact that we excluded women with known previous thyroid diseases.

Both overt and subclinical gestational hypothyroidism have been associated with numerous maternal and fetal complications.[7, 17, 20, 26, 30, 31] Although the impact of subclinical hypothyroidism on pregnancy and labor is debated [6, 8, 9, 18, 22], the simplicity of thyroid function measurement (serum TSH) and the inexpensive treatment (levothyroxine) has resulted in a recommendation for routine examinations during pregnancy from the ATA.

A limited number of studies examined thyroid function surveillance during pregnancy in the general population. In a large national survey from the United States, only 23% of pregnant women were tested for gestational hypothyroidism.[4] Clinical practice surveys show variable results from 42–81% of responders, mostly endocrinologists and obstetricians, supporting routine serum TSH examination during pregnancy.[25, 27, 29] We found no studies examining the surveillance rates in post-hemithyroidectomy patients. In our study, most pregnancies were examined for serum TSH at least once (86.6%) during the first trimester, which may be the result of a local tendency towards screening in pregnancy.[16] The American College of Obstetricians and Gynecology guidelines do not recommend ongoing serum TSH testing throughout pregnancy for subclinical hypothyroidism and state that “it is unlikely to progress to overt hypothyroidism during pregnancy in otherwise healthy women”.[11] This notion could provide an explanation for the discrepancy between our high first trimester screening rates (86.6%) and our low second and third trimester surveillance rates (40% and 16.6%). The latest ATA guidelines were the first to recommend thyroid function surveillance throughout pregnancy in post-hemithyroidectomy women.
However, our study shows that surveillance rates were not improved following the publication of the guidelines and were far from being accomplished de facto.

While the ATA guidelines’ main readers are clinicians from the thyroid field, obstetricians would usually be the ones to perform the gestational screening and surveillance. Thus, an explanation for the low surveillance rates in later stages of pregnancy may be that obstetricians are typically not exposed to these recommendations or prioritize guidelines by obstetrics and gynecology societies. This notion is supported in our study by the fact endocrinologists were consulted in only 5% of this cohort’s pregnancies and that the median time between surgery to pregnancy was 5.6 years, when patients are rarely in postoperative surveillance. Thus, we can conclude that most of the pregnancies in our cohort were followed solely by the treating obstetrician.

Possible means to improve follow-up rates would be in educating surgeons and patients, as well as better multidisciplinary statements. Regarding education, surgeons must acknowledge the growing rates of childbearing patients undergoing partial thyroidectomies, and rates of hypothyroidism following hemithyroidectomy, which has been shown in recent decades to be higher than previously assumed.[28] This information should also be given to the patient when consenting for surgery, advising her that in case of future pregnancies, either a repeated TSH measurement or an endocrine visit is warranted. From a guideline point of view, mutual endocrine-obstetrics guidelines and mutual discussions may improve the quality of surveillance.

This study suffers from the limitations of a retrospective design that exposes its conclusions to information bias. We attempted to reduce this bias by a double verification overview of the patients’ records. The Ofek Database System provides a unique comprehensive patient follow-up using online access lab reports, admissions, and clinic visits in the community and in other institutions. However, patients may have theoretically changed their insurance and we could not subtract their records.

The cohort was relatively small, and the groups of comparison were largely uneven both in size and in follow-up period. In addition, a major limitation of this study is that a substantial part of included pregnancies were multiple pregnancies conceived by a smaller number of patients. We attempted to overcome this bias by a performing a sub-analysis that included solely the first pregnancies following surgery. Also, a considerable part of pregnancies (~10%) ended in an abortion, so full-length pregnancy surveillance could not be completed. These should be considered when interpreting the results.

We found differences between group characteristics in our cohort. Pregnancies from 2018 and onwards had a longer procedure to pregnancy time interval. However, previous studies did not find this parameter to be associated with differences in serum TSH levels.[14]

Last, we failed to demonstrate the proportions of overt hypothyroidism and autoimmune thyroid disease since very few patients were examined for serum FT4 and autoantibodies.

**Conclusion**
The results of this study demonstrate low adherence to the latest ATA recommendations for thyroid function surveillance throughout pregnancy in post-hemithyroidectomy women. The publication of the guidelines had no impact on the extent of thyroid function surveillance in this population. This calls for better patient education regarding the risks of gestational hypothyroidism in young to middle-aged women following hemithyroidectomy and calls for improved communication between treating surgeons, obstetricians, and endocrinologists that may be achieved by interdisciplinary guidelines.

**Declarations**

**Statements & Declarations**

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. Also, the authors have no relevant financial or non-financial interests to disclose.

**References**


30. The authors declare, that no funds, grants, or other support were received during the preparation of this manuscript. Also, the authors have no relevant financial or non-financial interests to disclose
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Figures
Figure 1

A flowchart showing the study cohort selection.

Figure 2

Comparison of the distribution of total number of TSH examinations in pregnancies prior to 2018, and 2018 and onwards. P value = .36. TSH = thyroid stimulating hormone.
Figure 3

Comparison of Kaplan-Meier TSH examination rate curves in pregnancies prior to 2018 and 2018 and onwards. Serum TSH examinations during first, second and third trimesters were performed in 86.3%, 40% and 18.9% of pregnancies prior to 2018; and 88%, 40% and 8% of pregnancies since 2018; respectively. Log-rank P value = .533. TSH = thyroid stimulating hormone.