Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy

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Abstract

Objective: Pregnancy represents a favorable condition for the development of thyroid nodules, likely due to the secretion of hormones with stimulatory activity. In particular, differentiated thyroid cancer (DTC) represents the second most frequent tumor among those diagnosed during pregnancy. However, few and discordant data are available about the impact of pregnancy on tumor outcome.

Methods: A total of 123 women with DTC were divided into three groups according to the timing of tumor diagnosis (group 1, at least 1 year after the delivery; group 2, during pregnancy or in the first year after delivery; and group 3, before pregnancy or nulliparity) and evaluated according to the international guidelines. Furthermore, immunohistochemical studies of estrogen receptor α (ERα) were performed in 38 papillary thyroid cancer tissues from the three groups.

Results: Thyroid cancer diagnosed during pregnancy was associated with a poorer prognosis compared to tumors developed in nongravidic periods (P<0.0001). Accordingly, at the stepwise logistic regression analysis, the diagnosis of DTC during pregnancy or in the first year post partum was the most significant indicator of persistent disease (P=0.001). Interestingly, ERα expression significantly differed among tumors of the three groups, being detected in 31% of group 1, in 87.5% of group 2, and in 0% of group 3 (P=0.01).

Conclusions: Present data indicate that pregnancy has a negative impact on the outcome of thyroid cancer. The presence of ERα in the majority of tumors diagnosed during pregnancy indicates that the poorer outcome of these cases could be related to the estrogen-mediated growth stimulus.

Introduction

About 10% of thyroid cancers occurring during the reproductive years are diagnosed during pregnancy or in the first year after delivery (SEER Cancer Statistics Review, National Cancer Institute Surveillance, Epidemiology, and End Results: 1975–2005. Available from http://seer.cancer.gov). Differentiated thyroid cancer (DTC) represents the second most frequent tumor among those diagnosed during pregnancy, with a prevalence of 14 per 100 000 births (1). Indeed, pregnancy represents a favorable condition for the onset and growth of either benign or malignant thyroid nodules (2, 3), likely due to the negative iodine balance, to several growth factors, and to the secretion of hormones with thyroid stimulatory activity (4, 5). In particular, the high serum levels of chorionic gonadotropin, which has close homology with TSH, may lead to a rapid increase in thyroid tumor size during pregnancy and may stimulate the growth of benign and malignant thyroid lesions (6). In addition, the high estrogen levels can contribute to the growth of thyroid nodules during pregnancy. Indeed, the long-lasting use of several estrogen-containing preparations has been found to be associated with an increased risk of thyroid cancer (7). Consistently, several in vitro studies demonstrated that estrogens significantly increase the expression of estrogen receptor α (ERα) in thyroid cancer cell lines and activate diverse intracellular signaling pathways and proliferation (8–10). In addition, studies in neoplastic, hyperplastic, and normal thyroid tissues suggested that estrogen might promote follicular growth in the thyroid under the control of TSH (11). Indeed, there is increasing evidence to suggest that tumorigenesis in certain organs and tissues, including thyroid, is influenced by endocrine function and hormones, particularly estrogen, via the induction of ERα expression and activation of intracellular signaling.
pathways. Indeed, ERs have been found to be expressed in thyroid cancer tissues (12–14), but also expressed in gastric, bladder, and lung carcinomas (15–17).

Few data are available about the features and the prognosis of DTC diagnosed during pregnancy. Indeed, besides some discordant case reports, only two large series have been published to date on this topic, both reporting the lack of a significant impact of pregnancy on outcome (18, 19). However, it should be noticed that, in one of these studies, the evaluation of the outcome was based only on imaging techniques without the biochemical determination of the neoplastic marker thyroglobulin (18), while in the other (19) only the overall survival rate was considered.

Thus, the aim of the present study was to evaluate the clinical and molecular features and the outcome of DTC diagnosed during pregnancy according to the recent international guidelines for persistence/relapse assessment (20, 21). To this purpose, 123 women with DTC were enrolled and divided into three groups according to the timing of tumor diagnosis and to the pregnant period. In addition, to evaluate the possible impact of estrogens on tumor outcome, immunohistochemical studies for ER on several tumor tissues from the different groups were done.

Material and methods

Patients

Among patients followed up for DTC at the Endocrine Surgery Unit from 1995 to 2006, 123 women with an age of <45 years at diagnosis were retrospectively studied. None of these patients had a history of familial thyroid cancer or of neck external irradiation. All patients underwent total thyroidectomy associated, only in those with a preoperative diagnosis of malignancy, with pretracheal and paratracheal lymphadenectomy (levels VI–VII). Patients with clinical and/or cytological suspicion of metastases were also submitted to mono- or bilateral laterocervical lymph node dissection. In order to evaluate the impact of pregnancy on DTC outcome, patients were divided into three groups according to the time of tumor diagnosis. Group 1 included women (n=47, mean age 36.1±5.3, mean follow-up 68.2 months) with DTC diagnosis at least 1 year after delivery. Group 2 was composed of 14 women (mean age 32.2±6.4, mean follow-up 60.1 months) diagnosed with DTC during pregnancy and submitted to thyroidection during the second trimester (n=11) or in the first year after delivery (n=4). It is worth noting that the patient #1 of group 2 was considered twice (#1a and #1b) since she developed two thyroid cancers: a follicular carcinoma during the first pregnancy, treated by lobectomy and followed elsewhere (a confirmation of the histological diagnosis has been obtained), and a 18 mm papillary tumor in the controlateral lobe 8 years later during the second pregnancy when the patient came to our attention. Group 3 included patients who were nulliparous, or diagnosed and treated for DTC before pregnancy (n=61, mean age 34.1±6.2, mean follow-up 64.7±43.5 months).

Tumors were classified according to the thyroid malignancy World Health Organization classification (22) and staged according to the 6th edition of TNM staging (American Joint Committee on Cancer, AJCC). Criteria used to identify remission or persistent/recurrent disease were based on the European and American guidelines for the management of DTC (20, 21). In brief, in patients with papillary thyroid cancer (PTC) submitted to total thyroidectomy and radiiodine ablation, remission was defined by the presence of undetectable (<0.2 μg/l) basal and stimulated Tg levels at the recombinant human TSH (rhTSH, Thyrogen–Genzyme) test performed 10–12 months after initial treatments with negative antithyroglobulin autoantibodies and neck ultrasound, while persistent/recurrent disease was identified by the finding of at least one of the following: i) basal Tg levels >2 μg/l on consecutive determinations; ii) Tg response to rhTSH higher than 2 μg/l or higher than 1 μg/l in two rhTSH tests performed within a 10–12-month interval; iii) presence of neck or body masses with a cytology and/or Tg washout levels positive for metastasis of thyroid cancer; iv) presence of radiiodine uptake outside the thyroid bed; and v) persistence of anti-Tg antibodies for more than 4 years with a trend to increase or show a sudden rise of autoantibodies, according to the concept that an increased antibody production or the appearance of antibodies depends on the increase of autoantigen in the body (growth of persistent or relapsing tissue: 23, 24).

Patients were maintained on TSH-suppressive L-thyroxine treatment unless disease remission was documented and were then shifted to lower doses, aimed to reach TSH levels between 0.5 and 1.0 mU/l.

Molecular characterization

The DNA extracted from the neoplastic tissue of 11 cases of group 2 was submitted to BRAF analysis by PCR amplification using specific intronic primers, as previously described (25). After purification, PCR products were directly sequenced with ABI PRISM Big-Dye terminators and run on an ABI PRISM 310 Genetic Analyzer (PE Applied Biosystems, Foster City, CA, USA). One sequence read from each direction across the entire coding region and including intron–exon boundaries was obtained for each sample.

Immunohistochemical analysis of ERα in tumor tissues

Immunohistochemical studies of ERα were performed in 38 paraffin-embedded PTC tissues (16 of group 1, 8 of group 2, and 14 of group 3). Formalin-fixed,
paraffin-embedded tissue sections (4 μm) were dewaxed in xylene and rehydrated in graded ethanol solutions. Antigen retrieval was obtained by incubating tissue sections at 100 °C for 30 min in 0.05 M EDTA, pH 8.0. Endogenous peroxidase block was performed by immersion of the slides in 3% hydrogen peroxide. Sections were incubated for 30 min with the primary MAB ERα, clone 1D5, diluted 1:100 supported by Dako (Carpinteria, CA, USA), then with Post Primary Block (Novocastra, Newcastle upon Tyne, UK) for 30 min, and finally with NovoLinkTM Polymer for an additional 30 min. Peroxidase activity was developed with diaminobenzidin (DAB) working solution, and the sections were counterstained with hematoxylin, and examined after dehydration and mounting. ERα immunohistochemistry was classified as negative, weakly positive when a focal positivity was found, and positive when a plurifocal positivity was recorded (Fig. 1).

**Statistical analysis**

The following clinical, histopathological, and therapeutic variables were analyzed and compared in the three groups: age at diagnosis, months of follow-up, pTNM, histotype, radioiodine ablation, ERα expression, outcome. Relationships between discrete variables were evaluated by means of one-way ANOVA or χ² test, as appropriate. A stepwise logistic regression analysis was done by entering the following variables into the model: extrathyroidal extension, lymph-nodal metastases, radioiodine treatment, pregnant or nonpregnant status, histotype, tumor size ≤2 or >2 cm. In this analysis, at any step in the procedure, the most important variable, in statistical terms, is the one that would result in the largest likelihood ratio statistic, considering outcome as output. Backward stepwise regression, where the analysis begins with a full or saturated model and variables are eliminated from the model in an iterative process, and forward stepwise regression were used. Finally, univariate analyses between covariates related to treatment, such as the time of thyroidectomy (during pregnancy or in the 12 months after delivery) and the period between thyroidectomy and radioiodine ablation (≤2 or >2 months), and risk of recurrence were performed using χ² test. Statistical significance was defined as P<0.05. All statistical analyses were performed using SPSS 8.0 statistical package for Windows (SPSS, Inc., Chicago, IL, USA).

**Results**

In Table 1, clinical, biochemical, and histopathological features are reported. All patients had an age of <45 years at diagnosis, without significant differences between the three groups. No significant differences were noted either in the duration of the follow-up period or in the tumor size or extrathyroidal invasion (T parameter of TNM score). Patients of group 2 had a higher lymph-nodal metastatic involvement at diagnosis (N parameter), though this data did not reach the statistical significance. A significantly higher rate of follicular cancers (20%) was recorded in group 2 patients. According to the stage and following guideline indications, radioiodine ablation was performed in 80.8, 100, and 86.9% of patients belonging to the groups 1, 2, and 3 respectively (P=0.17), and the total administered mean dose of radioiodine did not differ among the three groups.

ERα expression results were significantly different among the three groups, being detected in 5/16 (31%) of group 1, in 7/8 (87.5%) of group 2, and in 0/14 of group 3 tumors (P=0.01). The ERα positivity was plurifocal in about 35–40% of cases of both groups 1 and 2.
Table 1 Clinical, biochemical, and histopathological features of all patients. The immunohistochemical data on the estrogen receptor \( \alpha \) (ER\( \alpha \)) at the tumor tissue level are also reported. Statistics by one-way ANOVA and \( \chi^2 \) analyses, as appropriate.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 ( n=47 ) (%)</th>
<th>Group 2 ( n=15 ) a</th>
<th>Group 3 ( n=61 ) (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (mean ( \pm ) s.d.)</td>
<td>36.1 ( \pm ) 5.3</td>
<td>32.3 ( \pm ) 6.4</td>
<td>34.1 ( \pm ) 6.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Months of follow-up (mean ( \pm ) s.d.)</td>
<td>68.2 ( \pm ) 63.9</td>
<td>60.1 ( \pm ) 52.1</td>
<td>64.7 ( \pm ) 43.5</td>
<td>0.92</td>
</tr>
<tr>
<td>pTNM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>18/47 (38.3)</td>
<td>5/15 (33.3)</td>
<td>20/61 (32.8)</td>
<td>0.97</td>
</tr>
<tr>
<td>T2</td>
<td>9/47 (19.1)</td>
<td>2/15 (13.3)</td>
<td>12/61 (19.7)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>19/47 (40.4)</td>
<td>7/15 (46.6)</td>
<td>27/61 (44.3)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>1/47 (2.1)</td>
<td>0/15 (0)</td>
<td>2/61 (3.3)</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>15/47 (31.9)</td>
<td>3/15 (20)</td>
<td>18/61 (29.5)</td>
<td>0.44</td>
</tr>
<tr>
<td>N1</td>
<td>12/47 (25.5)</td>
<td>2/15 (13.3)</td>
<td>18/61 (29.5)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>20/47 (42.5)</td>
<td>10/15 (66.6)</td>
<td>25/61 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Papillary histotype b</td>
<td>46/47 (97.9)</td>
<td>12/15 (80)</td>
<td>60/61 (98.3)</td>
<td>(&lt;0.0001^*)</td>
</tr>
<tr>
<td>Radioiodine ablation</td>
<td>38/47 (80.8)</td>
<td>15/15 (100)</td>
<td>53/61 (86.9)</td>
<td>0.17</td>
</tr>
<tr>
<td>( ^{131} )I MBq (mean ( \pm ) S.D.)</td>
<td>3826 ( \pm ) 2053</td>
<td>5602 ( \pm ) 5975</td>
<td>4912 ( \pm ) 3873</td>
<td>0.31</td>
</tr>
<tr>
<td>ER( \alpha ) tumor expression</td>
<td>5/16 (31)</td>
<td>7/8 (87.5)</td>
<td>0/14</td>
<td>(&lt;0.0001^\dagger)</td>
</tr>
<tr>
<td>Persistence</td>
<td>2/47 (4.2)</td>
<td>9/15 (60)</td>
<td>8/61 (13.1)</td>
<td>(&lt;0.0001^\dagger)</td>
</tr>
</tbody>
</table>

* Group 1 versus group 2, \( P=0.01 \); group 1 versus group 3, \( P=0.85 \); group 2 versus group 2, \( P=0.004 \); \( ^\dagger \) group 1 versus group 2, \( P=0.009 \); group 1 versus group 3, \( P=0.11 \); group 2 versus group 2, \( P<0.0001 \); group 1 versus group 2, \( P<0.0001 \); group 1 versus group 3, \( P=0.02 \); group 2 versus group 2, \( P<0.0001 \). Significant \( P \) values are shown in bold.

b One patient of this group has been considered twice due to the diagnosis of two thyroid tumors during pregnancies occurred in different years.

Overall, the disease was persistent/recurrent in 19/123 (15.4%) patients. Interestingly, when considering the three groups of patients, a significant better outcome was observed in those belonging to groups 1 and 3 compared to patients of group 2 \( (P<0.0001) \).

Accordingly, at the stepwise logistic regression analyses, where the selection or deletion of variables from a model is based on a statistical algorithm that checks for the ‘importance’ of variables (in the present study, the impact on outcome), the diagnosis of DTC during pregnancy or in the first year post partum was the most significant indicator of persistent disease (Table 2; \( P=0.001 \)).

In Table 2, the clinical, biochemical, histological, and molecular features of patients belonging to group 2 are reported. Three cases were found to harbor a somatic \( BRF^V600E \) mutation. The histotype was papillary in 12 cases and follicular in three cases, and an extrathyroidal invasion was found in 53.3% of cases. The surgical intervention was performed in ten patients during the second trimester of pregnancy, and in the remaining four women at 2, 4, 5, or 11 months after delivery. Moreover, total thyroidectomy was associated in 11/15 cases with central neck lymph node dissection. All group 2 patients underwent \( ^{131} \)I ablation 1–10 months (mean 3.6 months) after delivery. Ten patients wished to nurse and were allowed to do so for a mean period of 3 months (range 1–4 months). The disease was defined as persistent in 9/13 patients, and the reasons for this diagnosis were the following: i) lung metastases in one patient (this is the only case with distant metastases among all patients enrolled in the present study); ii) neck lymph nodes with a cytology and/or Tg washout levels positive for metastasis in two cases; iii) serum Tg levels \( >10 \mu g/l \) during TSH-suppressive treatment in four patients; and iv) progressively increasing very high anti-Tg levels in two patients.

Finally, in order to exclude that the worst outcome observed in group 2 patients could be influenced by a delayed treatment due to pregnancy, a univariate analysis considering as variables the time of thyroidectomy (during pregnancy or in the 12 months after delivery) and the period between thyroidectomy and radioiodine ablation (\( \leq 2 \) months or \( >2 \) months) was done. None of the two variables were found to be significantly associated with persistent/recurrent disease (\( P=0.47 \) and \( P=0.14 \) respectively; data not shown).

**Discussion**

Pregnancy represents a favorable condition for the onset and growth of either benign or malignant thyroid nodules, possibly due to the action of several growth factors, including chorionic gonadotropin and estrogens...
(2, 3, 6). The existence of a correlation between thyroid cancer and pregnancy is further confirmed by the present data reporting a patient who developed a follicular thyroid cancer during the first pregnancy and a PTC in the contralateral lobe 8 years later during the second pregnancy.

Moreover, the data obtained strongly suggest that pregnancy has a negative impact on the outcome of thyroid cancer. Indeed, thyroid cancer diagnosed during pregnancy (group 2) was found to be significantly associated with persistence or relapse of the disease compared to that diagnosed more than 1 year after delivery (group 1) or before pregnancy (group 3). Consistently, pregnancy was found to be the most significant predictor of persistent/relapsing disease at the stepwise logistic regression analyses.

It is worth noting that the three groups were not significantly different, as far as age and length of follow-up were concerned. Moreover, the worst outcome of group 2 patients cannot be referred to the high prevalence of the follicular histotype since two out of three cases are in remission. The prognostic role of BRAF mutations on the outcome of PTC is still controversial (25, 26). However, the possible influence of this genetic alteration on the poorer outcome of the patients of group 2 can be excluded since the three cases harboring BRAF<sup>V600E</sup> mutation are cured. No significant differences were found between the three groups concerning surgical and radiometabolic treatment. In addition, among patients of group 2, no significant differences in outcome were found either between women treated during pregnancy or in the 12 months after delivery, or between patients ablated during the first 2 months after thyroidectomy or after a longer period.

Despite the pregnant period, a pretracheal and paratracheal lymphadenectomy (levels VI–VII) was performed in 11 patients of group 2, and all were subsequently submitted to radiiodine ablation. Besides the lack of significant differences between the three groups in tumor size and capsular invasion, group 2 had a higher, though not statistically significant, lymph-nodal involvement at diagnosis (66.6% vs 42.5 of group 1 and 66.6% vs 40.9 of group 3). This finding that could be, at least partially, correlated with the poorer outcome has two possible explanations: i) the percentage of patients of group 2 submitted to the prophylactic central neck dissection (VI and VII levels) is higher with respect to patients of groups 1 and 3, for many of whom the diagnosis was incidental after a total thyroidectomy done for diseases other than cancer. Thus, consistent with the findings of the literature reporting that cervical lymph node metastases in DTC are present at diagnosis in 30–90% of cases (21, 27, 28), the percentage of N1 grade was higher and that of Nx was lower in patients of group 2 with respect to groups 1 and 3; ii) the effects of estrogens in the growth of the tumor are at the basis of this finding.

Nevertheless, present data are in disagreement with those obtained in large series reporting a similar outcome between pregnant and nonpregnant women affected with DTC (18). The discrepancy could be due to the criteria used for outcome assessment, since in those studies the disease persistence was based only on the finding of positive whole body scans, while in the present study highly sensitive Tg/AbTg basal and rhTSH-stimulated determinations were used, in accordance with the recent European and American guidelines (20, 21). The lack of impact of pregnancy on the survival rate, regardless of the persistence/recurrence of disease,
has been reported also in another large series (19), and indeed, it can be shared that pregnancy would not alter the disease-related survival rates. However, particularly for a tumor such as DTC, with a likelihood of death very low, a prompt complete remission has a great significance for both the patient and treating physician.

In order to identify a possible factor leading to the poorer outcome of patients who developed DTC during pregnancy, immunohistochemical studies were performed on the tumor tissues from patients of the three groups, and significant differences in ER expression were demonstrated \((P=0.01)\). In particular, ER expression was found in most patients (87.5%) who developed DTC during pregnancy, in about 30% of patients with tumor diagnosis at least 1 year after delivery, and in none of the patients who developed DTC before pregnancy or who were nulliparous. ER expression has also been demonstrated in other tumors. In particular, in gastric adenocarcinoma, a ER expression has been found to be present only in the tumor, and not in the surrounding normal tissue, and to be correlated with the depth of invasion (15), whereas in bladder transitional cell carcinoma, neoplastic tissues were found to express approximately threefold more ER than normal tissue (16). Moreover, in lung cancer, ER expression has been found to be significantly more frequent in the neoplastic tissue of women with respect to men (85 vs 15%) (17). The finding of highly expressed levels of ER in tumors reinforces the data obtained in cellular systems, suggesting that tumorigenesis in certain organs and tissues, including thyroid, is influenced by hormones, particularly estrogens. Indeed, estradiol \((E_2)\) has been demonstrated to significantly increase the expression of ER in thyroid cancer cell lines and to promote their proliferation (8–10). Several studies in different cellular systems, including breast cancer cells, pheochromocytoma cells, hippocampal neurons, male germ cells (reviewed in (9)), and thyroid cancer cells (8, 9), have demonstrated that \(E_2\) can rapidly activate a diverse array of intracellular signaling cascades via nongenomic mechanisms, mainly due to the interaction between \(E_2\) and ER (9, 29). Among the activated pathways, it should be highlighted that the RAS/RAF/MAPK/ERK pathway has been shown to have a predominant role in estrogen-dependent growth stimulation, being strongly phosphorylated, and thus activated, in response to \(E_2\) in thyroid cancer cell lines (8). On the other hand, the RAS/RAF/MAPK/ERK pathway has been shown to phosphorylate the ER, leading to its activation and to its proliferation (10, 31). Although definitive conclusions await additional studies, it is possible to speculate that also \(E_2\) in vivo exposure to high levels of \(E_2\) during pregnancy could favor the expression of ER in tumor tissues, providing them with a high proliferation potential by further enhancing ERK activity and thus explaining the present finding of a more aggressive phenotype of tumors diagnosed during the gravidic period.

In conclusion, thyroid cancer diagnosed during pregnancy has been found to be associated with a poorer prognosis compared to tumors developed in a non-pregnancy period. Although the series of patients is limited, the outcome has been evaluated according to recent guidelines, in order to accurately identify remission or persistence/recurrence. In addition, the presence of ER in the majority of tumors diagnosed during pregnancy allows speculation that ER may play a critical role in thyroid cancer growth during pregnancy and that the poorer outcome of these cases could be related to the estrogen-mediated growth stimulus. Present results, consistent with previous in vitro evidence showing that estrogens contribute to proliferation and growth of thyroid cancer cells, via MAPK cytoplasmic signaling, indicate the need to perform, in pregnant women with goiter, an accurate follow-up including neck ultrasonography and fine needle aspiration. It is worth noting that the present evidence is not strong enough to unconditionally indicate the need either to terminate pregnancy or to undergo surgical intervention during pregnancy, after the diagnosis of DTC. Nevertheless, the results obtained suggest performing a total thyroidectomy, possibly associated with prophylactic central neck dissection, during the second trimester, when a thyroid cancer is diagnosed in early pregnancy. Radioiodine treatment is always recommended, regardless of the tumor staging, and should be performed as soon as possible after delivery.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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