Scientific Research Publishing

Case Reports in Clinical Medicine, 2023, 12, 22-29
https://www.scirp.org/journal/crcm
ISSN Online: 2325-7083
ISSN Print: 2325-7075

Papillary Thyroid Carcinoma and Pregnancy: What Impact on Prognosis?

Loubna Saadaoui[1], Fatima Zahra Lahmamssi[1], Hayat Aynaou[1,2,3], Houda Salhi[1,2,3], Nadia Alaoui Ismaili[2,3,4], Hanan El Ouahabi[1,2,3]

[1]Department of Endocrinology, Diabetology and Nutrition, Hassan II University Hospital, Fez, Morocco
[2]Faculty of Medicine and Pharmacy of Fez, Sidi Mohamed Ben Abdullah University, Fez, Morocco
[3]Laboratory of Epidemiology and Research in Health Sciences, Fez, Morocco
[4]Nuclear Medicine Department, Hassan II University Hospital, Fez, Morocco
Email: loubna.saadaoui24@gmail.com

How to cite this paper: Saadaoui, L., Lahmamssi, F.Z., Aynaou, H., Salhi, H., Ismaili, N.A. and El Ouahabi, H. (2023) Papillary Thyroid Carcinoma and Pregnancy: What Impact on Prognosis? *Case Reports in Clinical Medicine*, **12**, 22-29.
https://doi.org/10.4236/crcm.2023.121004

Received: November 19, 2022
Accepted: January 15, 2023
Published: January 18, 2023

Abstract

Introduction: The impact of pregnancy on the prognosis of papillary thyroid carcinoma (PTC) has been debated for several decades; however, no definitive conclusions have been reached. The main objective of this study is to demonstrate the short-term influence of pregnancy on the evolution and prognosis of PTC. **Materials and Methods:** A prospective descriptive and analytical study was conducted in the Endocrinology and Diabetology Department at the Hassan II University Hospital in Fez, including patients followed for papillary thyroid carcinoma presenting with a pregnancy during the year 2019 and 2020. The follow-up of these patients was continued until 1 year postpartum. We studied the clinical, paraclinical and therapeutic factors that could influence the prognosis of the disease. **Results:** We included 26 patients. Our study showed a significant correlation between recurrence and the presence of unfavorable histological signs ($p = 0.02$) as well as the initial Tg level (0.01). However, pregnancy was not an influencing factor ($p = 0.41$). **Conclusion:** Pregnancy does not seem to be a factor aggravating the prognosis of differentiated thyroid cancers.

Keywords

Papillary Thyroid Carcinoma, Well Differentiated, Pregnancy, Recurrence, Prognostic Factors

1. Introduction

Differentiated papillary thyroid carcinoma (PTC) accounts for 80% of thyroid cancers and is most frequently found in women of childbearing age [1]. Its inci-

dence is increasing during the last decades. Pregnancy is a favorable condition for the development of benign or malignant thyroid nodules, probably due to an imbalance in the iodine balance and the secretion of hormones with thyroid-stimulating activity [2] [3]. In particular, the increase in estrogen and HCG levels, which have a certain homology with TSHus, may be responsible for the rapid increase in the size of thyroid tumors during pregnancy [4].

Nevertheless, the impact of pregnancy on the prognosis of PTC remains a matter of debate. Some studies have suggested that pregnancy is a risk factor [5] [6]. Other retrospective series have reported that pregnancy has no significant impact on the prognosis of differentiated cancers [7] [8]. The first study to investigate the impact of pregnancy on the increase in papillary microcarcinoma size was conducted by Shindo *et al.* [9]. This study included nine patients with microPTC (tumor size ≤ 1) and suggested a risk of tumor enlargement during pregnancy. In contrast, a recent study of the same group of patients concluded that only 8% of the 51 patients showed an increase in tumor size of microPTCs, and no new cervical lymph node (LN) metastases were detected [10].

The main objective of the present study was to evaluate the effect of pregnancy on the course and prognosis of PTC in the short term through a prospective study.

2. Materials and Methods

2.1. Patients and Study Design

A prospective descriptive and analytical study was conducted in the Department of Diabetes Endocrinology at the Hassan II University Hospital in Fez. We included after consent, patients diagnosed with a well-differentiated papillary carcinoma of the thyroid and who presented a pregnancy during the year 2019 and 2020. The follow-up of these patients was continued until 1 year post-partum. Patients who had a miscarriage and those who were lost to follow-up were excluded from the study. Epidemiological, clinical, and paraclinical data were collected from the patients' medical records

Our patients were classified according to the **TNM classification of thyroid cancers UICC/AJCC2017,** and according to the risk of relapse, they were divided into 3 groups: low, intermediate and high risk.

All Patients were followed up clinically, biologically by thyroglobulin, anti-Tg antibodies and TSHus, and radiologically by cervical ultrasound.

The prognostic factors studied were: the presence of distant metastases at the time of diagnosis, tumor stage, lymph node involvement, tumor size greater than 4 cm, multifocality, tumor capsule invasion and vascular invasion.

2.2. Definitions

Remission was defined by an undetectable Tg level (<1 ng/ml), negative anti-Tg antibodies and negative cervical imaging.

Persistent disease was defined by the presence of any of the following criteria:

1) Detectable Tg level > 1 ng/ml
2) Presence of a residue on cervical imaging
3) Presence of a focus of radioactive iodine uptake on whole body scan.
4) Persistent anti-Tg antibodies with a consistent upward trend.

2.3. Definition of Risk Groups

Risk of relapse according to the 2015 ATA classification:

Low risk	*Papillary thyroid cancer (with all of the following) No local or distant metastases *All macroscopic tumors has been resected *No tumor invasion of loco-regional tissues or structures *The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) *If 131I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first post treatment whole-body RAI scanNo vascular invasion *Clinical N0 or 5 pathologic N1 micro metastases (< 0.2 cm in largest dimension) Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer *Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (< 4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAF-V600E mutated (if known)
Intermediate risk	*Microscopic invasion of tumor into the perithyroidal soft tissues *RAI-avid metastatic foci in the neck on the first post-treatment whole-body RAI scanAggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion *Clinical N1 or > 5 pathologic N1 with all involved lymph nodes < 3 cm in largest dimensionMultifocal papillary microcarcinoma with ETE and BRAFV600E mutated (if known)
High risk	*Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE), Incomplete tumor resection *Distant metastases *Postoperative serum thyroglobulin suggestive of distant metas-tases Pathologic N1 with any metastatic lymph node 3 cm in largest dimension

Postpartum cancer progression was determined biologically by an increase in Tg levels of 20% or more, and radiologically by a 20% increase in a pre-pregnancy lesion, or the appearance of a new metastatic lesion.

Statistical analysis

The variables collected were analyzed descriptively: mean, standard deviation, for quantitative parameters and frequency, 95% confidence interval (CI) for qualitative

parameters. Relationships between two variables were analyzed by chi-square test.

The relationship between clinical features and thyroid cancer progression was analyzed by the Pearson test. The factors identified as significant by univariate analysis were analyzed by linear regression.

$P < 0.05$ was considered statistically significant.

All statistical analysis was performed using SPSS version 21 software.

3. Results

3.1. Epidemiological, Anthropometric and Clinical Characteristics of Patients

We collected 26 patients. The mean age was 33.2 years ± 6.2. Most cases were sporadic, and a history of thyroid cancer was identified in only 3 patients (11.5%). The most frequent reason for initial consultation was a thyroid nodule in 86.3%. The diagnosis of PTC was made by cytopunction in 28% and by anatomopathological study of the thyroidectomy operation in the rest. All our patients underwent total thyroidectomy, lymph node dissection was performed in 13.8%, and supplementation with iratherapy was indicated in 67.8% before pregnancy. Contraception was indicated in all patients. The mean time between treatment and pregnancy was 2.3 years ± 1.4. All patients were undergoing thyroxine suppression therapy. The TSHus target was <0.1 in 44.3%, between 0.1 - 0.5 in 24.8% and between 0.5 - 2 in 30.9%, of cases.

According to the 2017 UICC/AJCC TNM, our patients were classified according to tumor stage into stage I in 75%, and stage II in 25% (Table 1). Concerning the risk of recurrence, the patients were divided into 3 risk groups: low risk (30.9%), intermediate risk (24.8%), and high risk (44.3%) (Figure 1). 66.3% of the patients were declared cured before conception, 12.8% had persistent disease, and 20.9% had a pregnancy before the efficacy assessment. The mean thyroglobulin level of our patients was 4.03 ng/ml ± 3.28.

3.2. Study of Prognostic Factors

The postpartum evaluation did not show any recurrence in patients declared cured before conception. In the 2 patients with persistent disease, cervical ultrasound did not show any increase in the size of the thyroid residue. Recurrence was noted in only 17.8% of cases.

We studied the clinical, paraclinical and therapeutic factors that could influence the prognosis of the disease. Our study showed a significant correlation between recurrence and the presence of unfavorable histological signs ($p = 0.02$), and the initial thyroglobulin level ($p = 0.01$). However, pregnancy was not an influencing factor ($p = 0.41$) (Table 2).

4. Discussion

The impact of pregnancy on the prognosis of PTC is variable among studies. The effect of estrogen and HCG on both benign and malignant thyroid pathology has

Table 1. The staging of patients according to the 2017 UICC/AJCC TNM classification of thyroid cancers.

Stade tumoral	TNM	n = 16	
Stade I	T1aN0M0	4/26	15.4%
	T1bN0M0	2/26	7.7%
	T2N0M0	7/26	26.9%
	T3N0M0	8/26	30.8%
Stade II	T4N1M1	3/26	11.5%
	T3N1M1	2/26	7.7%

Table 2. Multivariate study of factors influencing prognosis.

The variables	Standardized coefficients	95.0% confidence interval		P value. 5%
Age	−0.146	−0.03	0.04	0.1
Tumor size > 4 cm	0.203	0.10	0.26	0.2
A tumor residue	0.755	0.18	0.39	0.06
The tumor stage	0.186	0.02	0.122	0.09
Unfavorable histological signs	0.160	0.16	0.39	0.02
The rate of Tg	0.304	0.21	0.37	0.01
The TSHus level	0.128	−0.11	0.04	0.09
Pregnancy	0.213	0.02	0.03	0.41

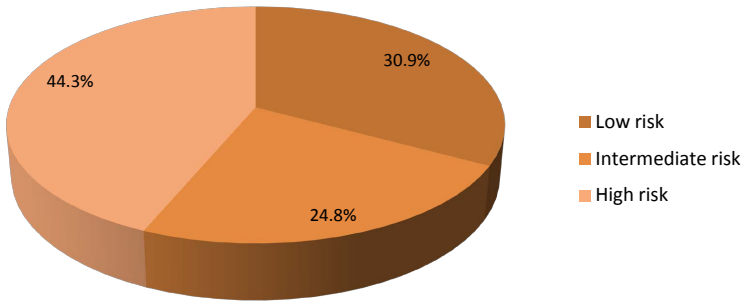

Figure 1. Distribution of patients by risk groups.

long been suggested [4] [11]. A recent study has shown that estrogen can alter the proliferation of thyroid cancer cells and potentially enhance the action of certain carcinogens [12]. The actions of estrogens are probably mediated by nuclear and membrane estrogen receptors (ER), in particular ER-alpha [13]. According to the results of a study, these receptors were present in papillary differentiated thyroid carcinoma in pregnant women (DTC), and absent in nulliparous women, explaining the more aggressive behavior of DTC in association with pregnancy [14]. Nevertheless, our study did not demonstrate this association (p = 0.41). Our results were in agreement with those of several series: for example, Leboeuf *et al.*, who explored the impact of pregnancy in 36 patients

followed for DTC for an average of 04 months after delivery, concluded that pregnancy is not a risk factor for DTC recurrence in women in remission [15]. Another study conducted by Budak *et al.* comparing the relapse rate between 2 groups of pregnant and non-pregnant women, concluded that there was no significant difference between the 2 groups [16]. In addition, Yasuhiro *et al.* in a series including 50 pregnant patients concluded that pregnancy and delivery was associated with an increase in size of papillary thyroid microcarcinomas (PMCs) in only 8% of the 51 pregnancies/delivery cases. None of the patients developed nodal metastasis during pregnancy [17].

Our study showed in bivariate analysis that the risk of recurrence was correlated with tumor stage ($p = 0.01$), the presence of unfavorable histological signs ($p = 0.02$), and the initial thyroglobulin level ($p = 0.01$). On the other hand, in multivariate analysis, the association was significant for the presence of unfavorable histological signs ($p = 0.02$), and for the initial thyroglobulin level ($p = 0.01$). These same prognostic factors have been identified by several studies [17] [18] [19] [20] [21]. Age is controversial prognostic factors [19] [22], Nevertheless, our study did not show a significant association. Other factors have been reported in the literature, namely tumor size > 4 cm, extrathyroidal extension, presence of lymph node invasion, multifocality, adjuvant treatment with radioiodine [23] [24].

Concerning hormone suppressive therapy, several lines of evidence indicate that suppressive l-T4 treatment decreases the risk of progression in patients with persistent disease, and reduces the rates of recurrence in high-risk cancer patients. However, in other subgroups of thyroid cancer patients, the use of L-T4 therapy is not associated with any significant improvement in recurrence or survival rates [25], in our series this association was not demonstrated ($p = 0.09$).

However, it is very important to note that careful monitoring of these patients should be recommended even if there is no effect of pregnancy on the prognosis of the disease.

5. Conclusions

The identification of poor prognostic factors at the time of initial management is essential in order to identify high-risk patients and to adapt the therapeutic strategy.

Our study shows that the risk of recurrence of PTC is correlated with the presence of unfavorable histological signs and the initial thyroglobulin level. However, pregnancy does not seem to be a risk factor.

The Limitations of the Study

Our study has some limitations, including the small sample size and the short duration of patient follow-up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Ahn, H.S., Kim, H.J. and Welch, H.G. (2014) Korea's Thyroid-Cancer "Epidemic"—Screening and Overdiagnosis. *The New England Journal of Medicine*, **371**, 1765-1767. https://doi.org/10.1056/NEJMp1409841

[2] Alves, G.V., Santin, A.P. and Furlanetto, T.W. (2011) Prognosis of Thyroid Cancer Related to Pregnancy: A Systematic Review. *Journal of Thyroid Research*, **2011**, Article ID: 691719. https://doi.org/10.4061/2011/691719

[3] Kung, A.W.C., Chau, M.T., Lao, T.T., Tam, S.C.F. and Low, L.C.K. (2002) The Effect of Pregnancy on Thyroid Nodule Formation. *The Journal of Clinical Endocrinology & Metabolism*, **87**, 1010-1014. https://doi.org/10.1210/jcem.87.3.8285

[4] Yoshimura, M. and Hershman, J.M. (1995) Thyrotropic Action of Human Chorionic Gonadotropin. *Thyroid*, **5**, 425-434. https://doi.org/10.1089/thy.1995.5.425

[5] Truong, T., Orsi, L., Dubourdieu, D., Rougier, Y., Hémon, D. and Guénel, P. (2005) Role of Goiter and of Menstrual and Reproductive Factors in Thyroid Cancer: A Population-Based Case-Control Study in New Caledonia (South Pacific), a Very High Incidence Area. *American Journal of Epidemiology*, **161**, 1056-1065. https://doi.org/10.1093/aje/kwi136

[6] Wartofsky, L. and Nostrand, D.V. (2007) Thyroid Cancer: A Comprehensive Guide to Clinical Management. Springer Science & Business Media, Berlin. https://doi.org/10.1007/978-1-59259-995-0

[7] Zamperini, P., Gibelli, B., Gilardi, D., Tradati, N. and Chiesa, F. (2009) Pregnancy and Thyroid Cancer: Ultrasound Study of Foetal Thyroid. *ACTA Otorhinolaryngologica Italica*, **29**, 339-344.

[8] Moosa, M. and Mazzaferri, E.L. (1997) Outcome of Differentiated Thyroid Cancer Diagnosed in Pregnant Women. *The Journal of Clinical Endocrinology & Metabolism*, **82**, 2862-2866. https://doi.org/10.1210/jcem.82.9.4247

[9] Shindo, H., *et al.* (2014) Papillary Thyroid Microcarcinoma Might Progress during Pregnancy. *Thyroid*, **24**, 840-844. https://doi.org/10.1089/thy.2013.0527

[10] Ito, Y., *et al.* (2016) Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Re-Evaluated in the Entire Patient Series at Kuma Hospital. *Thyroid*, **26**, 156-160. https://doi.org/10.1089/thy.2015.0393

[11] James, C., Ting, J., Blight, C., Anthony, J. and Justin, S. (2012) Papillary Thyroid Carcinoma in Pregnancy: A Variant of the Disease? *Annals of Surgical Oncology*, **19**, 4210-4216. https://doi.org/10.1245/s10434-012-2556-3

[12] Przybylik-Mazurek, E., Hubalewska-Dydejczyk, A., Fedorowicz, A. and Pach, D. (2012) Factors Connected with the Female Sex Seem to Play an Important Role in Differentiated Thyroid Cancer. *Gynecological Endocrinology*, **28**, 150-155. https://doi.org/10.3109/09513590.2011.563909

[13] Zane, M., *et al.* (2014) Estrogens and Stem Cells in Thyroid Cancer. *Frontiers in Endocrinology*, **5**, Article No. 124. https://doi.org/10.3389/fendo.2014.00124

[14] Vannucchi, G., *et al.* (2010) Clinical and Molecular Features of Differentiated Thyroid Cancer Diagnosed during Pregnancy. *European Journal of Endocrinology*, **162**, 145-151. https://doi.org/10.1530/EJE-09-0761

[15] Leboeuf, R., Emerick, L.E., Martorella, A.J. and Tuttle, R.M. (2007) Impact of Pregnancy on Serum Thyroglobulin and Detection of Recurrent Disease Shortly after Delivery in Thyroid Cancer Survivors. *Thyroid*, **17**, 543-547. https://doi.org/10.1089/thy.2007.0020

[16] Budak, A., Gulhan, I., Aldemir, O.S., Ileri, A., Tekin, E. and Ozeren, M. (2013) Lack

of Influence of Pregnancy on the Prognosis of Survivors of Thyroid Cancer. *Asian Pacific Journal of Cancer Prevention*, **14**, 6941-6943. https://doi.org/10.7314/APJCP.2013.14.11.6941

[17] Akslen, L.A. and LiVolsi, V.A. (2000) Prognostic Significance of Histologic Grading Compared with Subclassification of Papillary Thyroid Carcinoma. *Cancer*, **88**, 1902-1908. https://doi.org/10.1002/(SICI)1097-0142(20000415)88:8<1902::AID-CNCR20>3.0.CO;2-Y

[18] Ito, Y. and Miyauchi, A. (2012) Prognostic Factors of Papillary and Follicular Carcinomas in Japan Based on Data of Kuma Hospital. *Journal of Thyroid Research*, **2012**, Article ID: 973497. https://doi.org/10.1155/2012/973497

[19] Mazzaferri, E.L. and Jhiang, S.M. (1994) Long-Term Impact of Initial Surgical and Medical Therapy on Papillary and Follicular Thyroid Cancer. *The American Journal of Medicine*, **97**, 418-428. https://doi.org/10.1016/0002-9343(94)90321-2

[20] Sipos, J.A. and Mazzaferri, E.L. (2010) Thyroid Cancer Epidemiology and Prognostic Variables. *Clinical Oncology*, **22**, 395-404. https://doi.org/10.1016/j.clon.2010.05.004

[21] Lo, C.-Y., Chan, W.-F., Lam, K.-Y. and Wan, K.-Y. (2005) Follicular Thyroid Carcinoma: The Role of Histology and Staging Systems in Predicting Survival. *Annals of Surgery*, **242**, 708-715. https://doi.org/10.1097/01.sla.0000186421.30982.d2

[22] Jukkola, A., Bloigu, R., Ebeling, T., Salmela, P. and Blanco, G. (2004) Prognostic Factors in Differentiated Thyroid Carcinomas and Their Implications for Current Staging Classifications. *Endocrine-Related Cancer*, **11**, 571-579. https://doi.org/10.1677/erc.1.00826

[23] Schlumberger, M.J. (1998) Papillary and Follicular Thyroid Carcinoma. *The New England Journal of Medicine*, **338**, 297-306. https://doi.org/10.1056/NEJM199801293380506

[24] Rouxel, A., *et al.* (2004) Prognostic Factors Associated with the Survival of Patients Developing Loco-Regional Recurrences of Differentiated Thyroid Carcinomas. *The Journal of Clinical Endocrinology & Metabolism*, **89**, 5362-5368. https://doi.org/10.1210/jc.2003-032004

[25] Biondi, B., Filetti, S. and Schlumberger, M. (2005) Thyroid-Hormone Therapy and Thyroid Cancer: A Reassessment. *Nature Clinical Practice Endocrinology & Metabolism*, **1**, 32-40. https://doi.org/10.1038/ncpendmet0020