Effect of Pregnancy and Menopause on Micropapillary Thyroid Carcinomas During Active Surveillance

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Abstract

Background: The effect of estrogen and beta-human chorionic gonadotropin on micropapillary thyroid carcinoma (mPTC) is not defined. Pregnancy and menopause could represent critical moments during active surveillance (AS) for women with mPTC.

Objective: To evaluate the effect of either pregnancy or menopause on growth of mPTCs on AS.

Patients and Methods: Women with mPTC on AS who became pregnant or underwent menopause during AS were evaluated in this retrospective observational study. The primary outcome was disease progression according to the AS protocol. The secondary outcome was the shrinkage of mPTCs. We compared the menopause group of patients with 2 unmatched control groups: (1) the pre-menopause group of patients on AS who had not experienced menopause yet and (2) the post-menopause group of patients who started AS while already in menopause.

Results: Five patients who became pregnant and 9 who underwent menopause during AS were enrolled. No patient from either group had a disease progression, and all pregnant patients showed stable disease after pregnancy. Four patients of the menopause group (44%) experienced mPTC shrinkage. The percentage of patients with mPTC shrinkage was significantly higher in the menopause group than in the 2 control groups.

Conclusions: mPTC AS appears to be safe and feasible in patients who become pregnant or undergo menopause during surveillance. Our data suggest a possible association between menopause and mPTC shrinkage during AS.

Key Words: micropapillary thyroid carcinoma, active surveillance, pregnancy, menopause, estrogens, beta-human-chorionic-gonadotropin

Abbreviations: AS, active surveillance; hCG, human chorionic gonadotropin; IQR, interquartile range; LT4, levothyroxine; mPTC, micropapillary thyroid carcinoma; nUS, neck ultrasound; PTC, papillary thyroid carcinoma.

The incidence of papillary thyroid carcinoma (PTC) has noticeably increased over the past few decades, while the mortality from PTC has remained stable [1]. It has been reasonably assumed that a greater number of subclinical thyroid-differentiated cancer with diameters ≤ 10 mm, defined as low-risk micropapillary thyroid carcinoma (mPTC), which have no clinical relevance for patients' survival, have been detected because of the increasing use of diagnostic detection techniques as neck ultrasound (nUS) and fine-needle aspirations cytology [2].

These considerations resulted in the beginning of the first observational clinical trial for mPTC in 1993 at Kuma Hospital, Japan, which showed that active surveillance (AS) for mPTCs is feasible and that surgical treatment for this type of cancer could be delayed until evidence of tumoral growth [3]. Consistent with this Japanese study, other international studies found that AS is a safe and valid alternative to immediate surgery for mPTCs, without a consequent increase of mortality [4-6].

In our Endocrinology Department at the University Hospital of Pisa, an AS program has been ongoing since November 2014 for patients with a thyroid nodule ≤1.3 cm, as measured with nUS, and cytological diagnosis or suspicion of PTC, without any ultrasound evidence of neck lymph node metastasis and/or extrathyroidal extension. The results collected until November 2018 were published, and they were consistent with the conclusions of previous studies [7].

The new 2022 World Health Organization classification recommends not classifying mPTCs differently with respect to PTCs that exceed 1 cm in size [8]. To ensure a parallelism with respect to the previous original work, in this paper the term "mPTC" is used to define low-risk papillary thyroid carcinoma ≤13 mm in size, as measured with nUS, with or without known BRAF mutations and no extrathyroidal extension, vascular invasion, or lymph node or distant metastasis.

Thyroid carcinoma is 3 times more frequent in women than in men, and its incidence in women is higher between puberty and menopause [1]. These epidemiological data suggest a role

of reproductive hormones, such as estrogen, in carcinoma pathogenesis. The presence of estrogen receptors in neoplastic thyroid tissues has been demonstrated by immunohistochemistry and binding assays [9, 10]. Both isoform estrogen receptor alpha and estrogen receptor beta have been found on thyroid tissues. In particular, the binding of estrogen to estrogen receptor alpha has a proliferative and antiapoptotic role, while estrogen receptor beta promotes suppressive and proapoptotic actions [11].

Human chorionic gonadotropin (hCG) is produced during pregnancy. Its alpha subunit is identical to that of TSH, but there is also an important homology between the three-dimensional structure of hCG β-subunit and TSH β-subunit. Consequently, it has been validated that hCG has a thyroid-stimulating activity during pregnancy [12, 13].

These considerations raised the concern that pregnancy, which is characterized by a physiologically increased level of estrogen and hCG, could play a role in thyroid carcinoma growth [14]. Conversely, menopause and its physiological reduction of estrogen levels could influence the growth of mPTCs. So far, it has been observed as an arrest in the growth of benign thyroid nodules in most women after menopause [15].

The aim of this study was to evaluate the growth of mPTC in females who were pregnant or underwent menopause during the AS and to define the feasibility of AS in these groups of patients.

Patients and Methods

Patients

This retrospective study involved women who were on AS at the Unit of Endocrinology at the University Hospital of Pisa for a mPTC and who became pregnant or underwent menopause during the AS period.

According to the AS protocol [7], each patient was monitored with nUS and blood tests every 6 months for the first 2 years of AS, then every 12 months. For both groups of patients, the progression of the mPTC was defined according to the protocol such as an increase of ≥3 mm in each diameter, confirmed in 2 subsequent controls, and/or as a diagnosis of metastatic lymph nodes by ultrasonography exam and fine-needle aspiration cytology.

To define the shrinkage of mPTCs, a reduction ≥3 mm in at least 1 diameter was considered a positive reduction. These patients did not undergo additional medical checks compared to other patients on AS for mPTC.

All patients signed an informed consent to participate this study, which was approved on November 20, 2014, by the local ethical committee (Comitato Etico di Area Vasta Nord-Ovest; protocol number: 334/2014). Moreover, the study was performed according to the Declaration of Helsinki.

Pregnancy group

The exclusion criteria were hormonal pregnancy induction and pregnancies that ended in miscarriage. Patients whose mPTC was not measured before pregnancy and/or after delivery were also excluded.

Menopause and control groups

We retrospectively considered the onset of menopause 12 months after patients' last periods. The exclusion criteria were perimenopause and the use of hormone replacement therapy after menopause.

We compared the menopause group of patients with 2 other unmatched control groups: (1) the pre-menopause group, consisting of patients with a mPTC who began AS before the onset of menopause and who had not experienced menopause yet at the time of the study, and (2) the post-menopause group, consisting of patients who had a diagnosis of mPTC while already in menopause and then began AS.

Methods

Neck Ultrasound

nUS was performed using a real-time instrument (Esaote SPA, My Lab 50 machine with a 7.5-12 MHz linear transducer). During the follow-up, nodules and suspicious lymph nodes in neck stations were inspected. nUS was performed by the same 2 independent US-trained endocrinologists (E.M. and M.C.C.). Accurate descriptions of echogenicity, microcalcifications, integrity of halo, lengths of all diameters, location of the nodule in the thyroid lobe, and volume of the nodule calculated using the ellipsoid formula (ie, antero-posterior diameter × latero-lateral diameter × longitudinal diameter × π/6) were recorded in a computerized database.

Biochemical Assays

Blood tests were done to evaluate thyroid function. TSH was evaluated by a chemiluminescent assay (Immulite 2000; Siemens Healthcare, Gwynedd, UK); serum thyroglobulin was measured using a high-sensitive chemiluminescent assay (Beckman Coulter; Fullerton, CA, USA). Serum thyroglobulin antibody and thyroid peroxidase antibody were measured by immunofluorometric assay using the 2-step immune-enzymometric assay AIA-PACK Tg-Ab system and the TOSOH AIA System Analyzers (Tosoh Biosciences, catalog no. 0020291, RRID: AB_2920885).

Statistical Analysis

Statistical analyses were performed using SPSS (version 21; IBM Corp., Armonk, NY, USA). All statistical tests were two-sided, with the level of significance set at $P < .05$. Continuous variables were expressed as median with interquartile range (IQR). Categorical variables were expressed as frequency and percentages. One-way ANOVA was used to assess overall differences among the 3 groups (menopause, control, and pregnancy groups) after evaluating the homogeneity of variances using Levene's test. Post hoc analyses using Dunnett's test were conducted to assess pairwise differences with respect to the menopause group adjusting for multiple tests. The chi-squared test or the Fisher exact test were used to evaluate differences between groups for categorical variables as appropriate.

Results

Pregnancy Group

Five patients who had a pregnancy during AS were included in this study. Their median age was 30 years (21-34 years, IQR 25.0-33.0) at the time of diagnosis; the median duration of their follow-up period was 70 months (34-86 months, IQR 39.5-82.0). The median dimension of the maximum diameter at the time of diagnosis was 8 mm (4-11 mm, IQR 6.0-11.0),

Table 1. Clinical features of patients of the pregnancy and menopause groups

	Pregnancy group (n = 5)	Menopause group (n = 9)
Age at diagnosis (years)		
Median	30.0	50.0
Range	21-34	44-53
IQR	25.0-33.0	44.5-51.5
AS period (months)		
Median	70.0	49.0
Range	34-86	17-87
IQR	39.5-82.0	41.0-76.0
mPTC maximum diameter at diagnosis (mm)		
Median	8.0	10.0
Range	4-11	7-13
IQR	6.0-11.0	8.5-11.0
mPTC volume at diagnosis (mm^3)		
Median	174.7	249.6
Range	18.7-463.3	87.4-449.3
IQR	28.1-403.3	185.6-386.9

Abbreviations: AS, active surveillance; IQR, interquartile range; mPTC, micropapillary thyroid carcinoma.

with a volume of 174.7 mm^3 (18.7-463.3 mm^3, IQR 28.1-403.3). Just 1 patient had chronic autoimmune thyroiditis with hypothyroidism, and she was consequently on levothyroxine (LT4) therapy. Each patient had 1 single pregnancy during the AS. The clinical characteristics of these patients are summarized in Table 1.

The changes in the dimensions of mPTC of the 5 patients during the AS period are described in Fig. 1. No patient experienced a progression of mPTC when compared to the mPTC diameters before and after pregnancy. One woman had an increase of ≥3 mm in only 2 diameters, and this trend was already present before pregnancy; however, this increase was not sufficient to declare the progression of disease according to the study protocol criteria [7]. To date, all patients are still in AS after the pregnancy.

During AS and specifically before and after pregnancy, TSH levels remained stable and within normal reference range limits for pregnancy. Therapy with LT4 was slightly increased for the patient with hypothyroidism during pregnancy (+25 mcg/day).

Menopause and Control Groups

Nine patients who spontaneously underwent menopause during the AS were described in this study. As described in Table 1, the median age of the patients was 50.0 years (44-53 years, IQR 44.5-51.5) at the tumoral diagnosis, and the patient's median age at the onset of menopause was 51 years; the duration of their follow-up period was 49 months (17-87 months, IQR 41.0-76.0). The median dimension of the maximum diameter at diagnosis was 10.0 mm (7-13 mm, IQR 8.5-11.0), with a median volume of 249.6 mm^3 (87.4-449.3 mm^3, IQR 185.6-386.9). Also in this group,
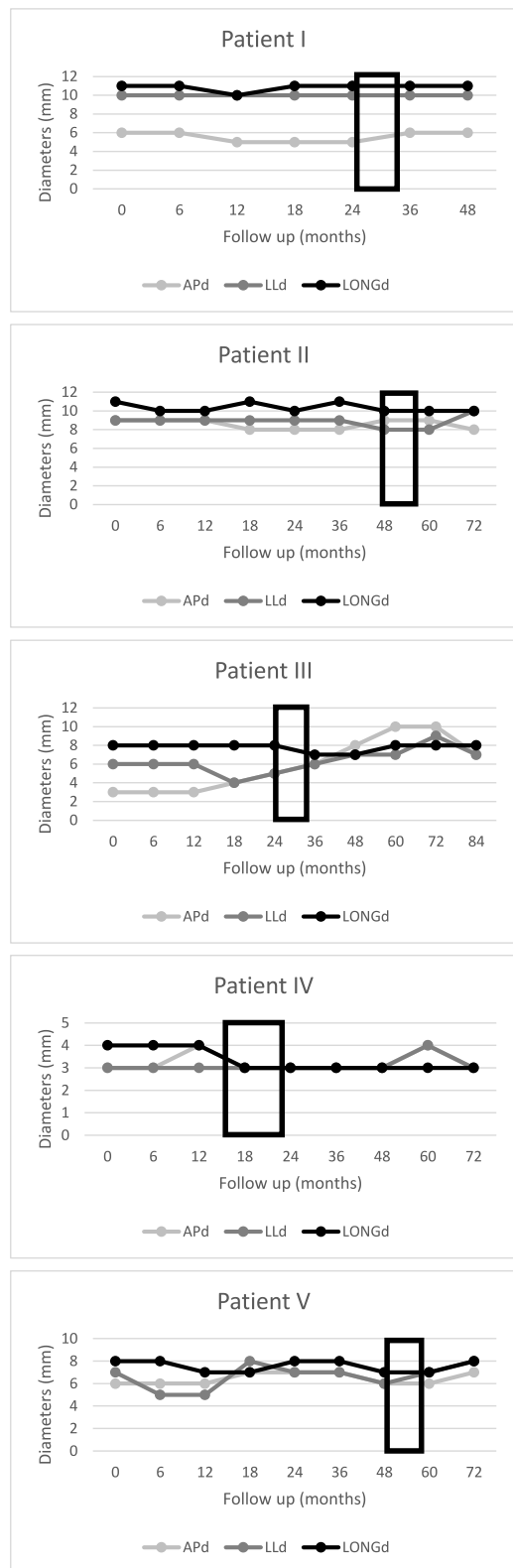

Figure 1. Change of mPTC diameters in 5 patients who were pregnant during AS. The black rectangle represents the period of the patient's pregnancy. No patient had a progression of mPTC when compared to the mPTC diameters before and after pregnancy. Patient III had an increase of ≥3 mm in 2 diameters, but this increase was not sufficient to declare the progression of disease, and this trend was already evident before pregnancy.

Abbreviations: APd, antero-posterior diameter; AS, active surveillance; LLd, latero-lateral diameter; LONGd, longitudinal diameter; mPTC, micropapillary thyroid carcinoma.

Figure 2. Change of mPTC diameters in 4 patients who underwent menopause during AS and who showed a shrinkage of the mPTC after the onset of menopause. The vertical gray line represents the patient's last control before the onset of menopause. All 4 women showed a reduction (≥3 mm) in at least 2 diameters, and patients 1 and 2 showed the same reduction in all the diameters.

Abbreviations: APd, antero-posterior diameter; AS, active surveillance; LLd, latero-lateral diameter; LONGd, longitudinal diameter; mPTC, micropapillary thyroid carcinoma.
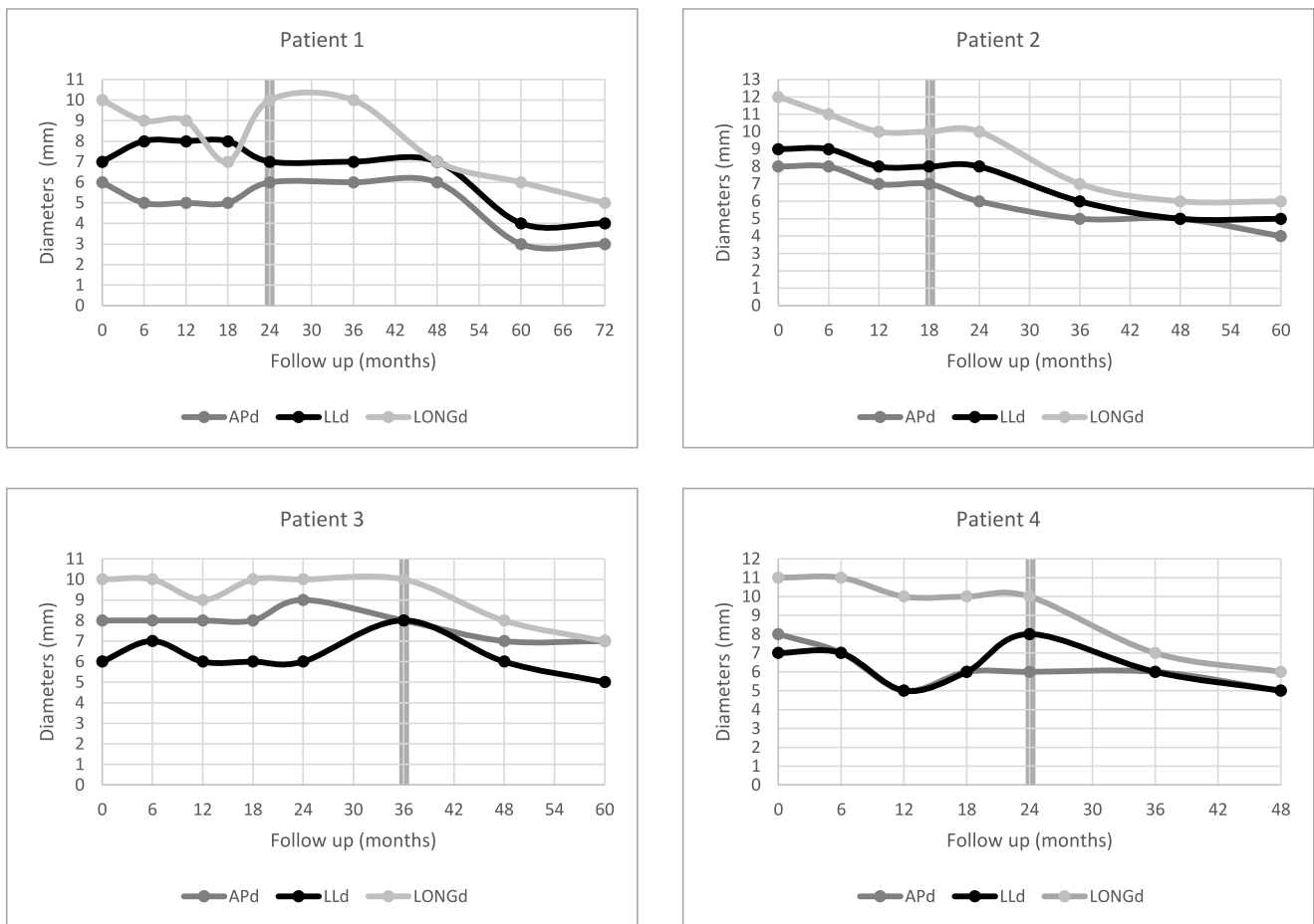
just 1 patient was on LT4 therapy for chronic autoimmune thyroiditis with hypothyroidism.

No patient showed an increase in mPTC diameters after menopause. Four patients (4/9, 44%) had a significative shrinkage of mPTC (a reduction ≥3 mm in at least 1 diameter). In particular, 2 patients showed a reduction ≥3 mm in 2 diameters, and the other 2 (2/9, 22%) showed the same level of reduction in all 3 diameters (Fig. 2). This trend was not evident before menopause. We then compared the group of patients who underwent menopause during the AS with 2 control groups: the pre-menopause group and the post-menopause group.

The pre-menopause group consisted of 39 women with a mean age of 35.0 years (18-51 years, IQR 27.0-43.0) at the tumoral diagnosis; they had a median follow-up of 37.0 months (6-79 months, IQR 23.0-52.0). The median dimension of the maximum diameter at the diagnosis was 8.0 mm (4-13 mm, IQR 6.0-9.0), and the mean volume of mPTC at the diagnosis was 166.4 mm^3 (18.7-728 mm^3, IQR 91.0-233.0).

For the post-menopause group, we considered 38 women with a median age at the tumoral diagnosis of 58.5 years (49-89 years, IQR 53.8-64.0) and a median period on AS of 25.5 months (6-75 months, IQR 16.3-51.3). The median dimension of the maximum diameter at the diagnosis was 9.0 mm (5-13 mm, IQR 7.0-11.0), with a median volume of

233.5 mm^3 (46.8-1142.4 mm^3, IQR 129.5-406.8). As expected, the mean age was significantly different between all groups (global $P < .001$). Moreover, despite unselected, on average the menopause group had a longer follow-up than the other 2 groups (both adj. $P < .05$), and patients from the pre-menopause group had a significantly smaller mPTC by average diameter at the time of diagnosis compared to the menopause group (mean difference: −2 mm, adj. $P = .03$) (Table 2).

From the pre-menopause group, 7.69% (3/39) of patients had a shrinkage of mPTC during AS, specifically in 2 diameters, while 92.31% (36/39) remained strictly stable, meaning no significant change in any dimension. From the post-menopause group, 7.89% (3/38) of patients had a shrinkage of mPTC during AS—specifically, 1 patient (1/3) in 2 diameters and 2 patients (2/3) in a single diameter—while 92.11% (35/38) remained strictly stable. As shown in Fig. 3, the percentage of patients with a mPTC shrinkage was significantly different between the menopause group and either of the 2 control groups (Fisher's exact test: both $P = .02$), while this was not observed between the 2 control groups ($P = .88$).

Of the remaining 5 patients in the menopause group who were classified as unchanged according to the predefined criteria, just 1 woman had a volume increase >50% of the nodule, which was not considered as a progression parameter in

our center [16]. Furthermore, the growth of the nodule's volume was already evident before menopause.

TSH level remained stable and in the normal range during AS for all patients in the menopause group as well. The single patient who was under treatment with LT4 for hypothyroidism was taking the same drug dosage during the entire AS period, even after menopause. All 9 patients are still on AS.

Table 2. Comparison of clinical features between patients in menopause, pre-menopause, and post-menopause groups

	Menopause group (n = 9)	Pre-menopause group (n = 39)	Post-menopause group (n = 38)
Age at diagnosis (years)			
Median	50.0	35.0[a]	58.5[b]
IQR	44.5-51.5	27.0-43.0	53.8-64.0
AS period (months)			
Median	49.0	37.0[c]	25.5[b]
IQR	41.0-76.0	23.0-52.0	16.3-51.3
mPTC maximum diameter at diagnosis (mm)			
Median	10.0	8.0[c]	9.0
IQR	8.5-11.0	6.0-9.0	7.0-11.0
mPTC volume at diagnosis (mm^3)			
Median	249.6	166.4	233.5
IQR	185.6-386.9	91.0-233.0	129.5-406.8

Abbreviations: AS, active surveillance; IQR, interquartile range; mPTC, micropapillary thyroid carcinoma.
[a]$P < .0001$ for the comparison with the menopause group.
[b]$P < .01$ for the comparison with the menopause group.
[c]$P < .05$ for the comparison with the menopause group.

Discussion

The thyroid-stimulating activity during pregnancy and the presence of estrogen receptors on thyroid cells had led to consideration of pregnancy as a possible growth and progression stimulus for differentiated thyroid carcinoma. However, there are no prospective studies that clearly prove it. In a 2011 systematic review on the prognosis of thyroid cancer related to pregnancy, the authors concluded that the impact on long-term survival was unaltered [17]. On the other hand, in the presence of biochemical or structural incomplete response after treatments, disease progression may occur during pregnancy, yet not necessarily because of pregnancy [18].

The American Thyroid Association guidelines for the diagnosis and management of thyroid disease during pregnancy and post-partum suggest that papillary thyroid carcinoma diagnosed during pregnancy can be monitored sonographically: if PTC shows significant progression in early pregnancy, a surgical approach could be considered only during the second trimester, whereas, if PTC remains stable, surgery can be delayed after delivery and, sometimes, after lactation [19]. Furthermore, the same guidelines suggest that women with mPTC on AS who become pregnant should be monitored with serial sonographic evaluations more frequently than in the normal follow-up. This statement is based mainly on the study by Shindo et al, which concludes that mPTC may progress during pregnancy [20]. However, these results have not been subsequently confirmed by the same Japanese group from Kuma Hospital [21].

In our cohort of female patients with mPTC who became pregnant during AS, we did not encounter any case of mPTC progression when confronting the tumor diameters before and after pregnancy, as all nodules remained stable. It is not possible to conclude that mPTCs did not change in dimensions *during* pregnancy, because in our study pregnant women were not subjected to additional controls during pregnancy compared to other patients. However, if it happened, it is possible to conclude that the diameters went back to the size that they had been before pregnancy. On the basis of our results, it appears that there is no need to increase the frequency of the
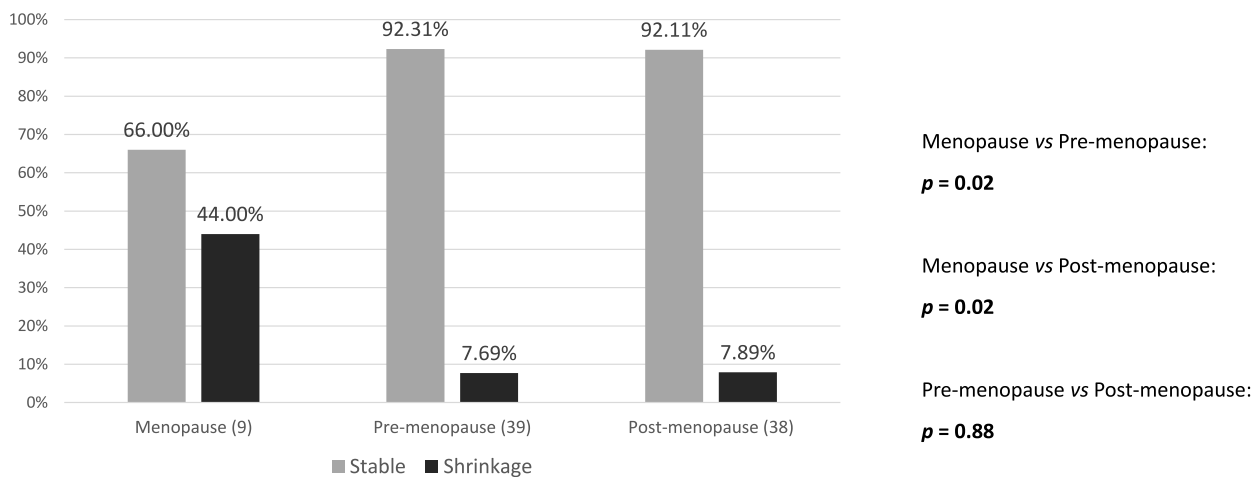

Menopause *vs* Pre-menopause:

***p* = 0.02**

Menopause *vs* Post-menopause:

***p* = 0.02**

Pre-menopause *vs* Post-menopause:

***p* = 0.88**

Figure 3. Percentage of patients who showed a stable disease or a reduction in mPTC dimensions of each group and comparison of the percentage of patients with a reduction in sizes of mPTC between the 3 groups. As shown on the right side of the figure, the percentage of patients with a mPTC shrinkage was significantly different between the menopause group and either of the 2 control groups (Fisher's exact test), while this was not observed between the 2 control groups.
Abbreviations: mPTC, micropapillary thyroid carcinoma.

ultrasound controls during pregnancy. Moreover, from our data it is possible to say that pregnancy does not prevent women from continuing AS, and these results are consistent with those reported by Ito et al [21]. Obviously, the personal choice of patients remains an undeniable indication on whether to continue or interrupt the AS in the face of a clear lesion stability.

There were no published data on the impact of menopause on mPTC growth during AS. Rubio et al concluded in 2017 that increased estrogen receptor alpha expression may be involved in PTC aggressiveness after menopause [22]. We reported the data of 9 patients who developed menopause during AS for mPTC. None of them had progression of mPTC after the beginning of menopause, while 44% of them had a significative shrinkage of at least 1 diameter of mPTC after developing menopause, and this trend was not evident before. We observed a significantly higher number of cases with a diameter reduction in women who underwent menopause during AS with respect to those enrolled and followed before or after menopause. We acknowledge the 3 groups were significantly different in age, but this difference was expected, as we considered women in completely different periods of life. Furthermore, also the follow-up period was significantly different among the 3 groups, as the maximum diameter of mPTC at time of diagnosis was found among the menopause and the pre-menopause groups. Since we have no information about the estrogen profile of our samples, we cannot exclude that the different age and/or mPTC size played a role in determining these differences; however, in our opinion, a role of the estrogen reduction occurring during menopause can be hypothesized.

As already discussed, estrogens could exert a growth stimulus for thyroid nodules and, therefore, also for mPTCs, amplifying the prevailing stimulatory effect of genetic and environmental factors. This hypothesis is supported by the different incidence of differentiated thyroid cancer between the 2 sexes in the fertile period of life, a difference that decreases when considering women in the post-menopausal period of life. The drop in estrogen levels that characterizes the *onset* of menopause could guarantee a lowering in the growth stimulus of mPTCs, and this could explain why a higher occurrence of tumoral size reduction has been observed at that moment of women's lives. Indeed, this effect might happen only at the onset of menopause, explaining why the reduction in mPTC size does not continue during the post-menopausal period. Thus, it is possible to hypothesize that, even if other factors could be involved in the mPTC reduction during AS, menopause per se, with the related reduction of estrogens, might play a key role. The mPTC size reduction is not an indication to abandon AS, but, again, the patient's choice is fundamental to the decision to continue or interrupt it.

Our study also has noticeable limitations, such as its retrospective nature, which implies a potential selection bias, and the small number of patients observed. Moreover, in the menopause group of women, the lack of data concerning estrogen levels before and after menopause is an important limitation to establish if this condition is implicated in the shrinkage of mPTC dimensions.

In conclusion, AS appears to be a safe and feasible management for patients with a mPTC who decide to have a pregnancy or who enter menopause. Based on our experience, there is no need to stress pregnant patients by adding controls to the normal ones. For these patients, the clinical progression

and their personal choice should still be considered as the only indication to interrupt AS. Moreover, the significant association between menopause and mPTC shrinkage during AS that we observed needs to be confirmed by studies on larger samples that include estrogen value measurements and ideally estrogen action at the estrogen receptor alpha and beta subtypes.

Funding

Disclosures

R.E. is a consultant for EISAI, Lilly, Ipsen and Bayer, and A.M. is a consultant for Lilly, but this manuscript was not influenced by this activity. The other authors have nothing to disclose.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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