

THYROID NODULES AND THYROID CANCER PRIOR TO, DURING, AND FOLLOWING PREGNANCY

Christopher W. Rowe, Department of Endocrinology, John Hunter Hospital, Newcastle Australia. School of Medicine and Public Health, University of Newcastle, Australia. christopher.w.rowe@newcastle.edu.au **Kristien Boelaert**, Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom.

Received April 24, 2022

ABSTRACT

Thyroid cancer is the second most common malignancy to co-occur in pregnancy. Further, the rising prevalence of treated thyroid cancer in women of child-bearing age means that survivors of thyroid cancer are frequently presenting for obstetric care, occasionally in the setting of persisting structural disease. To ensure that optimal health outcomes are achieved for mother and child, it is essential that prepregnancy issues are comprehensively addressed, and that management decisions during pregnancy remain both patient and child focused, best achieved through a woman-centered multidisciplinary team. As new data emerge regarding the impact of radioactive iodine on fertility, careful balancing of risk and benefits of this treatment is required.

INTRODUCTION

Thyroid nodules are common in women of childbearing age. Thyroid nodules may be detected due to symptoms of local compression (either due to larger size, or pressure on the trachea or esophagus), but are more commonly detected incidentally on imaging performed for other reasons. As well as determining if compressive symptoms are present, all thyroid nodules must be risk-stratified for the presence of malignancy. A third factor is to determine whether the nodule is functional (i.e., autonomously producing thyroid hormone), however this cannot be reliably assessed during pregnancy as it is dependent on radionucleotide imaging which is contra-indicated during pregnancy.

In general, the investigation or treatment of any new or co-existent medical conditions in pregnancy should be weighed against the separate risks and benefits to both the mother and fetus. Although most thyroid nodules will not grow during pregnancy, and therefore permit management decisions to be deferred to after birth (thus prioritizing fetal wellbeing), a small proportion of cases will require emergent management within pregnancy to prioritize maternal wellbeing (1).

Thyroid carcinomas generally develop from follicular epithelial cells (termed differentiated thyroid cancer, DTC) and present morphologically as papillary (PTC) or follicular (FTC) subtypes. Anaplastic thyroid cancer (ATC) is a rare, highly aggressive de-differentiated variant of DTC. Rarely, parafollicular, neuro-endocrine derived C-cells can give rise to medullary thyroid cancers (MTC). Thyroid lymphoma and metastases from other solid organ cancers are rare. In general, DTC has an greater than 98% 10 year survival in women of child-bearing age (2).

EPIDEMIOLOGY OF THYROID NODULES AND THYROID CANCER

Thyroid Nodules

There is a clear female preponderance for the development of thyroid nodules that is demonstrated in studies from varied ethic groups, and in populations that are iodine-replete and iodine deficient (3-5). Thyroid nodules are also more prevalent with increasing age (6). This may partly be explained by exposure to female reproductive hormones, as studies have demonstrated associations with increasing thyroid nodularity and multiparity, older age at menopause, and the presence of uterine fibroids (6-9). In a single study, use of oral contraceptive hormones was associated with reduced thyroid volume, but not a change in thyroid nodularity (10).

Carcinoma of the Thyroid Gland

The increased prevalence of thyroid nodules in females is matched by an increased prevalence of thyroid cancer amongst women. SEER data from the United States cancer registry reports thyroid cancer incidence at 21 cases per 100,000 females, compared to 7.1 per 100,000 males (11). When stratified by age, it is evident that this gender-based divergence is seen as early as puberty (Figure 1). The peak incidence of thyroid cancer amongst females occurs in midlife (age 35-59), and occurs earlier than the peak incidence in males (age 65-75), which corresponds with exposure to female reproductive hormones. ATC and MTC have equal incidence between genders.



Figure 1. Incidence of thyroid cancer by age- and gender- in the United States. Data source: SEER 18 (2010-2014). <u>https://seer.cancer.gov/faststats</u>

Although epidemiological data would suggest a strong link between exposure to female reproductive hormones and development of thyroid cancer, firm evidence linking reproductive factors to thyroid cancer risk is less clear. Some studies have shown a small (or transient) increase risk of DTC following pregnancy compared to nulliparous women (12). Age of menarche, menopause, and menstrual cycle patterns present conflicting data (12), however in general, longer exposure to reproductive hormones appears associated with increased thyroid cancer risk (13-15). Conversely, extended periods of breastfeeding (resulting in prolonged reductions in cirulating estradiol), have been associated with with decreased incidence of thyroid cancer (14, 16, 17).

Incidence of Thyroid Carcinoma in Pregnancy

Multiple studies confirm that carcinoma of the thyroid gland is the second most frequent pregnancyassociated cancer, behind carcinoma of the breast. Registry studies suggest that thyroid cancer is present in between 14-27 per 100,000 mothers giving birth (18, 19). In most cases, this represents newly diagnosed thyroid cancer during pregnancy, which is usually organ-confined. However, a combination of increasing diagnosis of thyroid cancer amongst young women and excellent prognosis has resulted in an increasing cohort of survivors of thyroid cancer requiring obstetric care (20). This is demonstrated by data from Taiwan, showing thyroid cancer prevalence amongst women (175 cases per 100,000 women) is 9fold higher than the incidence (18 cases per 100,000 women) (21). Occasionally, pregnancy occurs in a woman with known or suspected metastatic disease. A recent study from the USA reports that a historical diagnosis of thyroid cancer was the most common cancer present in women presenting for obstetric care (22).

IMPACT OF A PREGNANCY ON NUMBER AND SIZE OF THYROID NODULES

Impact of Pregnancy Hormones on Thyroid Follicular Epithelium

Pregnancy represents a stimulatory environment for thyroid follicular cells.

The pregnancy hormone human chorionic gonadotrophin (HCG) is a heterodimeric glycoprotein. Although the beta subunit is unique, the alpha subunit is common to follicle stimulating hormone, luteinizing hormone, and thyroid stimulating hormone (TSH). As a result, this structural homology causes crossstimulation of the TSH receptor by HCG, leading to physiological TSH-independent stimulation of the TSH-receptor, predominantly in the first trimester when HCG levels are highest. As well as contributing to gestational hyperthyroidism, in this way HCG mediated TSH-receptor signaling acts to stimulate growth of the thyroid follicular epithelium (23). Sustained activation of the signaling cascade mediated by the TSH-receptor has been associated with an increased risk of thyroid cancer in large observational studies. However, it is not known whether more limited periods of increased TSHreceptor signaling, such as would occur during pregnancy, materially contributes to thyroid cancer risk (24).

lodine (not a pregnancy hormone) is a trace element required for normal maternal thyroid function and fetal thyroid development and function. Pregnancy increases maternal demands for iodine and a daily intake of approximately 250-300mcg is recommended (25). Iodine excess and iodine deficiency states are both associated with an increased prevalence of thyroid nodules (3, 26).

Changes in Number and Size of Thyroid Nodules During Pregnancy

As previously outlined, the hormonal environment of pregnancy is associated with the development of new thyroid nodules, and with potential growth of existing thyroid nodules. Using ultrasound screening, thyroid nodules are demonstrated in 3-21% of pregnant women (26-28), although most nodules are small (<1cm) and not detectable clinically (26). Prospective studies of pregnant women show an increase in thyroid nodule number and size during pregnancy. In a study of 221 women in China using repeated sonographic evaluation, an increase in nodule volume during pregnancy was shown in 15% of women in whom nodules were already present at baseline evaluation. New thyroid nodules were detected in 13% of the cohort. Post-partum, the number of women with thyroid nodules had increased from 15% to 24% (26). All nodules had a benign sonographic appearance. Similarly, a study of 726 pregnant women in Belgium identified a 3% incidence of thyroid nodules at baseline (determined by two-step screening with palpation followed by ultrasound). Of those with nodules, 60% showed an increase in size of at least 50%. Further, 20% (4/20) of women with regular sonographic surveillance developed new nodules during pregnancy (27).

PRESENTATION OF A NEW THYROID NODULE IN THE PREGNANT PATIENT

A thyroid nodule usually comes to attention in pregnancy following the identification of a palpable abnormality. Screening for thyroid nodules in asymptomatic individuals without risk factors, both in the pregnant and non-pregnant population, is not recommended (29).

Thyroid nodules should be assessed using a triple assessment, including clinical assessment, sonographic risk stratification, and biopsy (in selected cases). Scintigraphy, which is part of the standard workup for functional nodules in the non-pregnant population, is contra-indicated in pregnancy due to the risk of ionizing radiation to the fetus.

Important historical factors that increase the chance of a nodule being malignant include the presence of:

- A familial cancer syndrome, including multiple endocrine neoplasia 2 (MEN2), familial PTC, Cowden's syndrome, familial adenomatosis polyposis, and Carney Complex.
- Neck irradiation in childhood, e.g., treatment for cancers of the head and neck
- Exposure to ionizing radiation in early life (age <18 years)

On clinical examination, a palpable lump should be characterized. The presence of a large, very firm or rapidly growing nodule should raise concern for malignancy. Neck lymph nodes should be evaluated. Symptoms and signs of compression of local adjacent structures should be sought.

Many thyroid nodules are functional, however the determination of the functional status of a thyroid nodule in pregnancy is limited. Firstly, although TSH should be checked, a low TSH may reflect gestational hyperthyroidism and should be interpreted with reference to the current gestational age. Most functional nodules progress slowly, therefore a prepregnancy TSH level which is at, or below, the lower limit of the reference range may provide a helpful clue. Secondly, radioactive isotopes used for thyroid scintigraphy readily cross the placenta, and the radiation exposure to the fetus does not justify the use of this modality in pregnancy. Therefore, conclusive determination of whether a thyroid nodule is functional (and thus of very low malignant potential), or nonfunctional, during pregnancy is usually not possible.

Serum biomarkers for thyroid cancer are not currently in routine use. Although serum calcitonin is highly sensitive for the diagnosis of MTC (30), it is not validated for use in pregnancy, especially as calcitonin levels rise over the course of a normal pregnancy. Further, its use in assessment of thyroid nodules in non-pregnant women is not universally established. Carcino-embryonic antigen, also a marker of MTC, can rise during pregnancy, and should be interpreted with caution (31).

Neck ultrasound is the definitive tool for assessment of thyroid nodules, and is safe in pregnancy. A highfrequency linear transducer is optimal to provide detailed characterization of the sonographic features, including size, echogenicity, shape, margins, the presence of calcification, and the presence of abnormal lymph nodes in the central and lateral neck. All nodules should be risk stratified according to a validated scoring system, such as from the American Thyroid Association (32) or the American College of Radiology (33). If fine-needle aspiration biopsy (FNAB) is required, this can be safely performed in all trimesters of pregnancy, with indications identical to that of the non-pregnant population (32).

Nodules with higher risk features, such as larger size, growth in pregnancy, suspicion of extra-thyroidal extension, presence of large-volume nodal metastases, or suspicion for MTC or ATC should be considered for biopsy and surgery during pregnancy. However, for smaller nodules without any high-risk features, consideration should be given to deferring biopsy (and any planned intervention) until the post-partum period, as several studies have confirmed that there is no survival benefit for surgery during pregnancy for low risk DTC (34).

IMPACT OF PREGNANCY ON A NEW DIAGNOSIS OF THYROID CANCER

Impact of Pregnancy on Outcome of Thyroid Cancer

A diagnosis of thyroid cancer during pregnancy has the same excellent long term survival outcomes as seen in other settings. Large retrospective studies in the US population between 1962-1999 (35-37) show similar mortality data irrespective of the diagnosis setting (inside or outside pregnancy) or the timing of surgery (during pregnancy or post-partum). Although these studies have the benefit of long follow up periods, they are inherently retrospective. Further, the ability of these studies to assess impact of pregnancy on thyroid cancer recurrence is limited, not only due to their retrospective nature, but also due to lack of availability of highly sensitive thyroglobulin assays and high resolution neck ultrasound in historic series (34).

In contrast, recent studies suggest that thyroid cancer diagnosed in pregnancy may have a higher risk of recurrence. A retrospective study from Italy showed higher rates of persistent or recurrent thyroid cancer in women diagnosed either during pregnancy or within 12 months after birth (60% persistent or recurrent disease), compared to women diagnosed with thyroid cancer more than 12 months after a pregnancy (4% persistent or recurrent disease) or women who were never pregnant (13% persistent or recurrent disease) (38). However, it is important to note that most of the pregnant women with thyroid cancer underwent surgery in the second trimester (73%), and it is possible that a more limited surgical approach in this setting may have confounded these results.

Similarly, a second retrospective Italian study found a higher rate of persistent or recurrent disease in women with thyroid cancer diagnosed within two years of a pregnancy (11%), compared to women diagnosed more than two years after a pregnancy (1%) or those who were never pregnant (5%) (39).

A pathology study from Australia found that DTC diagnosed within 12 months of pregnancy were more likely to be larger, and have nodal metastases than matched controls (40).

Overall, these data should reassure clinicians and patients that the impact of pregnancy on a newly diagnosed thyroid cancer is low, with excellent overall survival outcomes. Epidemiological and clinical data would suggest that the stimulatory milieu of pregnancy may contribute to a slightly higher overall risk of recurrence, which should be taken into consideration when planning follow up strategies.

Timing of Thyroidectomy

Expert consensus affirms that thyroidectomy can safely be performed in the second trimester, but is often more appropriately deferred to the post-partum period (34). Clinical markers of aggressive pathology, such as large primary size, rapid growth, or bulky lateral neck nodal disease, would support a strategy of earlier surgery. At present, these clinical markers of aggressiveness are detected by specialized thyroid and neck ultrasound, which should occur at first assessment, and subsequently around 20 weeks (to allow for planning of thyroidectomy in the second trimester, if indicated). Suspicion of non-DTC pathology, such as MTC and ATC, should warrant strong consideration of early surgery.

The optimal timing of surgery in the peri-partum period is uncertain. Whist many women undergo safe surgery and anesthesia in the second trimester, small risks for mother and fetus remain. However, deferring surgery to the post-partum period potentially disrupts dyadic attachment between mother and child, and may interrupt breast-feeding. As evidence is lacking, patient-centered decision making, with inputs from a multi-disciplinary team, is appropriate.

Small case series support a strategy of deferred surgery for low-risk lesions. For example, 19 women with PTC diagnosed around the time of conception were followed sonographically in pregnancy (41). Nearly 70% were microcarcinomas, and 3 cases had sonographic N1 disease. During pregnancy, 3 tumors had a detectable increase in maximal diameter, while 5 increased in volume. In 2 out of 3 with N1 disease, lymph nodes increased in size although no new nodal disease was detected, and the extent of surgery was not changed. Post-partum, 16 cases proceeded to surgery around 12 months following diagnosis.

Maternal Supportive Management During Pregnancy

Thyroid stimulating hormone (TSH) is a trophic factor for follicular thyroid cells and is associated with progression of thyroid cancer (23). However, there is no evidence to support the practice of pharmacological suppression of TSH to minimize growth of a primary tumor in pregnancy, and exogenous maternal hyperthyroidism is associated with fetal risk. Maintaining maternal serum TSH within the lower half of the pregnancy-specific reference range is a reasonable therapeutic goal, and levothyroxine should be initiated, if required, to achieve this target.

Dietary iodine should not be restricted, as it is essential for fetal thyroid development. Maternal physiological demands for iodine increase in pregnancy, and maternal iodine deficiency is associated with development of goiter in the mother.

A recent cohort study found that pregnancies complicated by a diagnosis of thyroid cancer prior to or during pregnancy had a higher incidence of venous thromboembolism (odds radio 2.4) and blood transfusions (odds ratio 2.1), however there was no impact on neonatal outcomes (42). Similarly, the rate of post-partum hemorrhage in women with a history of thyroid cancer was higher than controls (odds ratio 1.23) in a large retrospective observational study, however no other adverse maternal, neonatal, or child outcomes (followed to 80 months post-partum) were found (43).

Measurement of Serum Thyroglobulin

During pregnancy, maternal serum thyroglobulin levels are higher than pre-pregnancy. This may be an effect of stimulation of maternal thyrocytes by estrogen and HCG. Therefore, maternal thyroglobulin levels during pregnancy must be interpreted with caution. Maternal serum thyroglobulin levels return to baseline values within 1-6 months of pregnancy (44-46). In general, thyroglobulin status should be assessed no earlier than 6 weeks post-partum.

Considerations in the Planning of Radioiodine Therapy

Radioactive iodine therapy following total thyroidectomy, either for remnant ablation, or as adjuvant therapy, is recommended for a subset of DTC with higher risk of recurrence (32). The administration of radioiodine following pregnancy poses unique challenges, both medically and socially. Firstly, radiation safety precautions necessitate that close contact between the mother and her infant (as well as other young children) must be avoided for around 7 days following a radioactive iodine dose (precise recommendations are determined at the time of therapy) (47). Radioactive iodine is contra-indicated in pregnancy, and if administered, the risks to the fetus must be carefully assessed, based on administered dose and gestational age (48). Secondly, breast tissue expresses the sodium-iodide symporter, which is upregulated during lactation to concentrate iodine in

breast milk (48, 49). Consequently, to minimize exposure of breast tissue to ionizing radiation, lactation should cease a minimum of 8 weeks before radioactive iodine and should not be recommenced so as to avoid potential breast-milk associated radioactive iodine exposure.

In light of this, the timing of radioactive iodine (if required) should be considered, balancing the potential risk of DTC progression without treatment, the benefits of a period of breastfeeding, and family unit dynamics. The literature is conflicting as to whether radioiodine administered early (within 3 months) or late (within 12 months), has any impact on prognosis. For example, a large retrospective database study including more than 9,000 patients diagnosed with high-risk PTC (primary tumor >4cm, N1 disease, positive surgical margins) found that timing of radioactive iodine within the first 12 months did not impact mortality (the median survival in this cohort was 75 months), after adjustment for confounders (50). In contrast, a small retrospective study of patients with lower risk DTC (235 cases classified as either ATA Low- or ATA-Intermediaterisk) found that deferring radioactive iodine longer than 3 months post-operatively was associated with higher rates of biochemical incomplete or structural incomplete responses compared to earlier radioactive iodine ablation(19% vs 4%) (51).

PRE-CONCEPTION CARE OF WOMEN WITH A HISTORY OF THYROID CANCER

Pregnancy following diagnosis and treatment for thyroid cancer is common, and presents specialized management issues. Nonetheless, excellent obstetric outcomes are expected (52). Pre-conception counselling is recommended for all women with a past history of thyroid cancer.

Checklist: Management issues prior to pregnancy in survivors of thyroid cancer.

- 1. Assessment of thyroid cancer status:
- Remission? Assessment of disease status: structural and biochemical
- Potential impact of pregnancy on disease progression
- 2. Impact of prior radioiodine therapy on timing of conception and future fertility
- Ensure > 6 months between radioactive iodine and conception
- 3. Thyroid hormone replacement
- Pre-pregnancy optimization of levothyroxine replacement
- Pre-emptive adjustment to levothyroxine dosing following conception
- Potential for unmasking thyroid hormone insufficiency in women with sufficient prepregnancy thyroid hormones from a residual hemithyroid

• Use of pregnancy supplements that may interfere with levothyroxine absorption

Establishment of Thyroid Cancer Status

To provide a framework for discussing the potential impact of thyroid cancer on pregnancy, an assessment of disease status is valuable, such as recommended by the ATA in its 2015 guidance (Table 1) (32). Evidently, counselling and management discussions will differ depending on what treatment has previously been received (total thyroidectomy vs hemithyroidectomy), the presence of any functional thyroid hormone production (if prior hemithyroidectomy only), the timing of any radioactive iodine administration, and the presence of any residual cancer. MicroPTC under active surveillance is a distinct management issue which is discussed separately.

Table 1. 2015 American Thyroid Association Risk Stratification for DTC	
2015 ATA Response-	Description
to-Therapy	
classification	
Excellent response	No clinical, biochemical or structural evidence of persistent or
	recurrent thyroid cancer.
Biochemical-	Elevated serum thyroglobulin, or rising anti-thyroglobulin
incomplete response	antibodies, in the absence of structural disease identifiable on
	imaging.
Structural-incomplete	Persistent or recurrent thyroid cancer visible on imaging, either
response	in neck or distant metastases
Indeterminate	Non-specific biochemical or structural findings that are not able
response	to be classified as benign or malignant (includes stable/declining anti-thyroglobulin antibody levels without evidence of structural disease)

2015 American Thyroid Association Risk Stratification for DTC, tabulated from Haugen et al. (2016). Refer to ATA Guideline (32) for full discussion of each class and qualifying criteria (Table 13).

In women with a history of MTC, the tumor markers calcitonin and CEA are sensitive to detect residual or recurrent disease, and allow for post-operative risk stratification (53). There are no studies examining whether pregnancy impacts the prognosis of MTC.

Discussing Impact of Pregnancy on Risk of Recurrence

There is a growing body of evidence reporting the long-term oncological outcomes in the setting of pregnancy following treatment for thyroid cancer. Key studies are reviewed below.

Leboeuf et al. (46) reported outcomes of 36 women between 1997 and 2006, with pregnancy a median 4 years following treatment for DTC. Three women had structural disease present prior to pregnancy, and of these, one showed growth in a cervical lymph node. A further two women developed recurrence following pregnancy that was not present on pre-operative physical examination. Of the full cohort, 22% had a sustained >20% rise in serum thyroglobulin postpartum.

Rosario et al. (54) describe the outcome of 64 pregnancies, occurring a median of 2.4 years after treatment for DTC. In this cohort, no patient had evidence of structural disease either prior to or following pregnancy. Of the subset 49 women with undetectable thyroglobulin prior to pregnancy, this remained undetectable in the post-partum period. Of the 8 patients with low level thyroglobulin prior to pregnancy, no significant post-partum change was observed.

Hirsch et al. (55) studied the outcome of 63 women, where pregnancy occurred a median of 5 years after treatment for PTC. Of the subset of 6 women with known structural disease prior to conception, 80% were found to have progressed within 12 months of birth (2 with biochemical progression, 3 with structural progression). Of the subset of 5 women with detectable pre-pregnancy thyroglobulin, no significant change was observed post-partum. Of the remaining 39 women with undetectable pre-pregnancy thyroglobulin, no progression was observed. Finally, Rakhlin et al. reported the outcome of pregnancy in 235 women following treatment for DTC (56), retrospectively grouped into ATA Response to Therapy criteria (Table 1). In the 197 women without structural disease prior to pregnancy, no new structural disease was detected following post-partum evaluation. However, 8% had a significant rise in thyroglobulin.

Overall, these data are reassuring that women with an ATA Excellent response to therapy have a very low risk of DTC progression occurring during pregnancy, and a low risk of DTC progression following pregnancy. As such, additional monitoring of thyroid cancer status during pregnancy for these women is not required (34).

However, women with biochemical or structural evidence of disease may have a progression of their thyroid cancer status as a result of pregnancy. Based on the above studies, the degree of disease progression appears minor, only affects a subset of women, and does not appear to have an impact on the outcome of the pregnancy.

Reducing the Impacts of Prior Thyroid Cancer Treatment on Pregnancy.

LEVOTHYROXINE REPLACEMENT

It is essential that all women who are planning pregnancy receive written instructions for the management of thyroid hormone replacement prior to, and immediately following conception. Requirements for thyroid hormone rise early in gestation, in part as a result of an increase in thyroid-binding globulin. Adequate levels of thyroid hormones are required for healthy fetal development and pregnancy progression.

Women previously treated with hemithyroidectomy may unmask relative thyroid hormone deficiency

following conception, and may require early initiation of levothyroxine therapy in the first trimester.

Women who have been treated with total thyroidectomy will always require an increase in thyroid hormone replacement at conception, of a magnitude between 15-40% of the total weekly dose. A common practice is to advise women to "double the dose" of levothyroxine that they take on two days of the week as soon as pregnancy is confirmed, with further adjustment based on regular thyroid function tests throughout pregnancy (34, 57). Women who adhered to this advice were more likely to have TSH at the pregnancy target than those that deferred thyroxine adjustment until the first specialist consultation (58).

Importantly, pregnancy multivitamins, iron supplements, or calcium supplements may interfere with the absorption of thyroxine, and women should be specifically instructed to take such supplements at a different time of day to minimize interference (59).

Women should be reassured that levothyroxine is both safe and essential for a healthy pregnancy, as inadvertent discontinuation in early pregnancy has been reported (60). In most cases, the TSH target prior to pregnancy (usually targeting the lower half of the normal range) will remain appropriate in pregnancy. Pharmacological suppression of TSH with supraphysiological doses of levothyroxine could be continued in the setting of persistent structural disease, however care should be taken to avoid overt hyperthyroidism, which increases pregnancy risk. In settings where a TSH-suppression strategy has been pursued outside of pregnancy, but in the absence of known structural disease, a careful balancing of risk and benefit should be considered, as although mild hyperthyroidism in pregnancy has not been shown to lead to maternal or fetal complications, greater degrees of hyperthyroidism are associated with adverse pregnancy outcomes (34, 61, 62).

IMPLICATIONS OF PREVIOUS RADIOIODINE

Women should defer conception for at least 6 months after radioactive iodine administration. This period includes the expected time for radioactive iodine to fully decay (approximately 10 weeks), thus avoiding exposing the fetus to gamma-particle emission). A recent large population-based cohort study found that pregnancy occurring within 5 months of radioactive iodine had a higher rate of congenital malformations (odds ratio 1.74, 95%CI, 1.01-2.97; P = .04), which was not seen if conception occurred after 6 months (63). Deferring pregnancy for at least 6 months has the additional benefit of permitting assessment of the response to radioactive iodine therapy, and to determine that no additional treatment with radioactive iodine would be recommended in the following 15 months (conception, pregnancy and the post-partum (64). Stabilization of levothyroxine period) replacement can also take a period of months.

In the 12 months following radioactive iodine, 8-16% of women experience amenorrhea, and 12-31% have menstrual irregularities (65). Several studies (including a meta-analysis) have confirmed a small but significant fall in AMH levels following radioactive iodine, and a slightly earlier age of menopause than women who did not receive radioactive iodine (49.5 vs 51 years) (65, 66).

Most studies have not shown that radioactive iodine has an impact on future fertility (65, 67, 68). However, in a retrospective database study comparing survivors of thyroid cancer, women in the age 35-39 subgroup who received radioactive iodine had a lower birth rate (11 vs 16 births per 1000 woman-years) than women who did not receive radioactive iodine. However, as the time from diagnosis of thyroid cancer to first live birth was also prolonged in this study, it is not clear whether this finding is due to physician recommendation to delay pregnancy, or the biological

effects of radioactive iodine (68). In addition, a recent population case-control study found a higher rate of infertility diagnosis amongst survivors of thyroid cancer (69), however this analysis did not take into account any disease-specific factors such as type of treatment received.

In women with a history of thyroid cancer requiring assisted reproductive techniques, pregnancy outcomes were not different compared to controls, although the number of retrieved oocytes was lower (70). A history of radioactive iodine treatment was not associated with differing rates of clinical pregnancy or live birth rates in this group (71).

A large longitudinal study followed 2,673 pregnancies and did not show an increase in maternal or fetal adverse events in women previously administered radioactive iodine (72). A population-based cohort study of women with thyroid cancer in Korea, 59,483 women who comparing underwent thyroidectomy alone, with 51,976 women who had thyroidectomy followed by radioactive iodine found no difference in pregnancy or obstetric outcomes in the 9.7% of the cohort where pregnancy occurred (63). A further systematic review (67), and meta-analysis (73), pooling additional studies reported similar findings, providing sufficient time had elapsed following radioactive iodine administration.

In men, radioactive iodine may transiently impact testicular function, with a short-term rise in FSH, and decrease in normal sperm morphology seen in prospective studies (74). It is suggested that men avoid fathering children for 4 months following radioactive iodine (75, 76). In men who desire fertility, and who are expected to require high cumulative activities of radioactive iodine, sperm banking should be considered.

Surveillance and Monitoring During Pregnancy

Based on available data, women with no structural or biochemical evidence of thyroid cancer do not require DTC-specific monitoring during pregnancy. At present, there is no evidence to guide whether additional postpartum surveillance should be instituted beyond that woman's current surveillance strategy, however consideration of neck ultrasound and serum thyroglobulin at least 6 months post-partum is reasonable.

For women with 'ATA Biochemical Incomplete' or 'ATA Indeterminate' classification, surveillance during pregnancy could include periodic neck ultrasound, and determination of thyroglobulin and Tg-Ab levels. Clear evidence of progression of thyroid cancer could prompt an increase in the level of TSH suppression, or rarely prompt expedited delivery. Management in the context of a multidisciplinary team is advised.

CONTINUED ACTIVE SURVELLANCE OF PAPILLARY THRYOID MICROCARCINOMA DURING PREGNANCY

Non-operative management of microPTC (<10mm in maximal dimension) is increasing, with emerging data on implications for active surveillance during pregnancy. Shindo et al report 9 women with microPTC followed during pregnancy, findina demonstrable growth in 44% (compared to microPTC growth of 11% in non-pregnant controls) (77). Ito et al reported outcomes of 50 pregnancies with microPTC, finding growth of >1mm in 8%, reduced size in 2%. The remaining 90% of cases showed no growth in pregnancy, and there were no nodal metastases detected (78). Oh et al described 13 microPTC in pregnancy, with a single lesion demonstrating growth (41). The available evidence supports the continuation of active surveillance during pregnancy, monitored with periodic neck ultrasound. However, women contemplating pregnancy who are under active surveillance should be advised that a small number of microPTC will grow during pregnancy, and this may

result in anxiety for the patient and clinicians. Further studies are awaited in this population (32).

Germline RET Mutations

Women with clinically diagnosed MEN2, or who carry a germline mutation in the REarranged during Transfection (RET) proto-oncogene, should be under the care of a specialized clinical team, and should be offered detailed pre-natal genetic counselling. Individual RET mutations can be characterized for their risk of early-onset MTC, allowing personalized management decisions. The highest risk mutations should prompt consideration of total thyroidectomy in early childhood (53). The presence of hyperparathyroidism and pheochromocytoma should be biochemically excluded prior to pregnancy in any woman with MEN2.

MANAGEMENT OF KNOWN RESIDUAL STRUCTURAL DISEASE IN PREGNANCY

Case series of pregnancy in women with co-existent thyroid cancer metastases have been reported. The largest study retrospectively studied a cohort of 124 women from China, aged 16-35 years, with lung metastases from thyroid cancer, stratified by whether pregnancy occurred (n=35) and followed for a median 68-82 months after completing treatment with radioactive iodine (79). This study found that pregnancy after thyroid cancer had no measurable difference in 5 year or 10-year progression free survival or overall survival. 10-year overall survival in the pregnancy group was 86%, compared to 82% in the non-pregnant group. Although the groups appeared to have similar characteristics, it remains possible that women who chose pregnancy had a lower severity of disease than those who avoided pregnancy.

Another study retrospectively described outcomes for 38 women at a large cancer center in the USA (56). Included in the cohort were 10 women with pulmonary metastases at the time of diagnosis (and of whom 7 had persistent structural disease prior to pregnancy). During pregnancy, 29% of women had progression of structural disease (11/38, with 5/38 increasing size of known abnormal nodes, 3/38 with newly abnormal lymph nodes, and 1/38 with progression of distant metastases). In total, 3/38 (~8%) were considered "clinically significant" by the study team (required further treatment within 12 months of birth).

These data are reassuring that the clinical impact of pregnancy in the setting of persistent structural disease appears low, despite in vitro studies and smaller case series confirming that pregnancy represents a potentially stimulatory setting for thyroid cancer cells.

In general, TSH suppression should be maintained where benefit is felt to outweigh risk to the pregnancy. Serial neck ultrasound during pregnancy will monitor the status of neck disease, however imaging the chest is usually avoided to minimize ionizing radiation to the chest. Where progression of lung metastases is to be monitored, serial lung function testing may be informative.

Currently approved small molecule tyrosine kinase inhibitors have been shown to have embryotoxicity, fetotoxicity, and teratogenicity in rats and rabbits (80, 81), and pregnancy should be avoided in women on this treatment. A case report of a pregnancy in a women treated with vandetanib up until 6 weeks gestation described no fetal adverse outcomes (82).

REFERENCES

- Oduncu FS, Kimmig R, Hepp H, Emmerich B. Cancer in pregnancy: maternal-fetal conflict. Journal of cancer research and clinical oncology. 2003;129(3):133-46.
- Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? Thyroid. 2017;27(6):751-6.
- Song J, Zou SR, Guo CY, Zang JJ, Zhu ZN, Mi M, et al. Prevalence of Thyroid Nodules and Its Relationship with lodine Status in Shanghai: a Population-based Study. Biomedical and environmental sciences : BES. 2016;29(6):398-407.
- Moifo B, Moulion Tapouh JR, Dongmo Fomekong S, Djomou F, Manka'a Wankie E. Ultrasonographic prevalence and characteristics of non-palpable thyroid incidentalomas in a hospital-based population in a sub-Saharan country. BMC medical imaging. 2017;17(1):21.
- Knudsen N, Laurberg P, Perrild H, Bulow I, Ovesen L, Jorgensen T. Risk factors for goiter and thyroid nodules. Thyroid. 2002;12(10):879-88.
- Reiners C, Wegscheider K, Schicha H, Theissen P, Vaupel R, Wrbitzky R, et al. Prevalence of thyroid disorders in the working population of Germany: ultrasonography screening in 96,278 unselected employees. Thyroid. 2004;14(11):926-32.
- Wang K, Yang Y, Wu Y, Chen J, Zhang D, Liu C. The association of menstrual and reproductive factors with thyroid nodules in Chinese women older than 40 years of age. Endocrine. 2015;48(2):603-14.
- Spinos N, Terzis G, Crysanthopoulou A, Adonakis G, Markou KB, Vervita V, et al. Increased frequency of thyroid nodules and breast fibroadenomas in women with uterine fibroids. Thyroid. 2007;17(12):1257-9.
- 9. Kim MH, Park YR, Lim DJ, Yoon KH, Kang MI, Cha BY, et al. The relationship between thyroid nodules and uterine fibroids. Endocrine journal. 2010;57(7):615-21.
- Knudsen N, Bulow I, Laurberg P, Perrild H, Ovesen L, Jorgensen T. Low goitre prevalence among users of oral contraceptives in a population sample of 3712 women. Clin Endocrinol (Oxf). 2002;57(1):71-6.
- 11. Thyroid Cancer Bethesda, Maryland: National Cancer Institute; 2016 [Available from: http://seer.cancer.gov/statfacts/html/thyro.html.

- Moleti M, Sturniolo G, Di Mauro M, Russo M, Vermiglio F. Female Reproductive Factors and Differentiated Thyroid Cancer. Frontiers in endocrinology. 2017;8:111.
- He JL, Zhang C, Hu MJ, Wu HB, Lu XL, Hao JH, et al. Reproductive and menstrual factors for papillary thyroid cancer risk: A case-control study in Chinese women. Cancer Epidemiol. 2021;73:101964.
- Kim H, Kim KY, Baek JH, Jung J. Are Pregnancy, Parity, Menstruation and Breastfeeding Risk Factors for Thyroid Cancer? Results from the Korea National Health and Nutrition Examination Survey, 2010 to 2015. Clin Endocrinol (Oxf). 2018.
- Schubart JR, Eliassen AH, Schilling A, Goldenberg D. Reproductive Factors and Risk of Thyroid Cancer in Women: An Analysis in the Nurses' Health Study II. Womens Health Issues. 2021;31(5):494-502.
- Yi X, Zhu J, Zhu X, Liu GJ, Wu L. Breastfeeding and thyroid cancer risk in women: A dose-response meta-analysis of epidemiological studies. Clinical nutrition (Edinburgh, Scotland). 2016;35(5):1039-46.
- 17. Wang M, Gong WW, He QF, Hu RY, Yu M. Menstrual, reproductive and hormonal factors and thyroid cancer: a hospital-based case-control study in China. BMC Womens Health. 2021;21(1):13.
- Smith LH, Danielsen B, Allen ME, Cress R. Cancer associated with obstetric delivery: results of linkage with the California cancer registry. American Journal of Obstetrics & Gynecology. 2003;189(4):1128-35.
- Cottreau CM, Dashevsky I, Andrade SE, Li DK, Nekhlyudov L, Raebel MA, et al. Pregnancy-Associated Cancer: A U.S. Population-Based Study. J Womens Health (Larchmt). 2019;28(2):250-7.
- Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in Thyroid Cancer Incidence and Mortality in the United States, 1974-2013. Jama. 2017;317(13):1338-48.
- Liu F-C, Lin H-T, Lin S-F, Kuo C-F, Chung T-T, Yu H-P. Nationwide cohort study on the epidemiology and survival outcomes of thyroid cancer. Oncotarget. 2017;8(45):78429-51.
- Wu PMMD, Jordan KPP, Chew-Graham CAMMD, Mohamed MOM, Barac AMDP, Lundberg GPMD, et al. In-Hospital Complications in Pregnant Women With Current or Historical Cancer Diagnoses. Mayo Clinic Proceedings. 2021;96(11):2779-92.

- 23. Rowe CW, Paul J, Geyde C, Tolosa J, Bendinelli C, McGrath S, et al. Targeting the TSH receptor in thyroid cancer. Endocrine Related Cancer. 2017.
- Nieto HR, Boelaert K. Thyroid stimulating hormone in thyroid cancer: does it matter? Endocrine-related cancer. 2016.
- Delange F. Iodine requirements during pregnancy, lactation and the neonatal period and indicators of optimal iodine nutrition. Public health nutrition. 2007;10(12a):1571-80; discussion 81-3.
- Kung AW, Chau MT, Lao TT, Tam SC, Low LC. The effect of pregnancy on thyroid nodule formation. J Clin Endocrinol Metab. 2002;87(3):1010-4.
- Glinoer D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, et al. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. J Clin Endocrinol Metab. 1991;73(2):421-7.
- Struve CW, Haupt S, Ohlen S. Influence of frequency of previous pregnancies on the prevalence of thyroid nodules in women without clinical evidence of thyroid disease. Thyroid. 1993;3(1):7-9.
- 29. US Preventative Services Task Force. Screening for thyroid cancer: US Preventive Services Task Force Recommendation Statement. Jama. 2017;317(18):1882-7.
- Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. Journal of Clinical Endocrinology and Metabolism. 2007;92(2):450-5.
- Ercan S, Kaymaz O, Yucel N, Orcun A. Serum concentrations of CA 125, CA 15-3, CA 19-9 and CEA in normal pregnancy: a longitudinal study. Archives of gynecology and obstetrics. 2012;285(3):579-84.
- 32. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.
- Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, et al. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): White Paper of the ACR TI-RADS Committee. Journal of the American College of Radiology : JACR. 2017;14(5):587-95.
- Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid. 2017;27(3):315-89.

- Moosa M, Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metab. 1997;82(9):2862-6.
- Yasmeen S, Cress R, Romano PS, Xing G, Berger-Chen S, Danielsen B, et al. Thyroid cancer in pregnancy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2005;91(1):15-20.
- Herzon FS, Morris DM, Segal MN, Rauch G, Parnell T. Coexistent thyroid cancer and pregnancy. Archives of otolaryngology--head & neck surgery. 1994;120(11):1191-3.
- Vannucchi G, Perrino M, Rossi S, Colombo C, Vicentini L, Dazzi D, et al. Clinical and molecular features of differentiated thyroid cancer diagnosed during pregnancy. Eur J Endocrinol. 2010;162(1):145-51.
- Messuti I, Corvisieri S, Bardesono F, Rapa I, Giorcelli J, Pellerito R, et al. Impact of pregnancy on prognosis of differentiated thyroid cancer: clinical and molecular features. Eur J Endocrinol. 2014;170(5):659-66.
- 40. Lee JC, Zhao JT, Clifton-Bligh RJ, Gill AJ, Gundara JS, Ip J, et al. Papillary thyroid carcinoma in pregnancy: a variant of the disease? Ann Surg Oncol. 2012;19(13):4210-6.
- Oh H-S, Kim WG, Park S, Kim M, Kwon H, Jeon MJ, et al. Serial Neck Ultrasonographic Evaluation of Changes in Papillary Thyroid Carcinoma During Pregnancy. Thyroid. 2017;27(6):773-7.
- 42. Spiegel E, Spence AR, Czuzoj-Shulman N, Abenhaim HA. Pregnancy outcomes after thyroid cancer. J Perinat Med. 2019;47(7):710-6.
- Cho GJ, Kim SY, Lee HC, Lee KM, Han SW, Oh MJ, et al. Risk of Adverse Obstetric Outcomes and the Abnormal Growth of Offspring in Women with a History of Thyroid Cancer. Thyroid. 2019;29(6):879-85.
- Nakamura S, Sakata S, Komaki T, Kojima N, Kamikubo K, Miyazaki S, et al. Serum thyroglobulin concentration in normal pregnancy. Endocrinologia japonica. 1984;31(6):675-9.
- 45. Rasmussen NG, Hornnes PJ, Hegedüs L, Feldt-Rasmussen U. Serum thyroglobulin during the menstrual cycle, during pregnancy, and post partum. Acta Endocrinologica. 1989;121(2):168-73.
- Leboeuf R, Emerick LE, Martorella AJ, Tuttle RM. Impact of pregnancy on serum thyroglobulin and detection of recurrent disease shortly after delivery in thyroid cancer survivors. Thyroid. 2007;17(6):543-7.
- 47. Sisson JC, Freitas J, McDougall IR, Dauer LT, Hurley JR, Brierley JD, et al. Radiation safety in the treatment of patients with thyroid diseases by radioiodine 1311 : practice recommendations of the American Thyroid Association. Thyroid. 2011;21(4):335-46.

- 48. lijima S. Effects of fetal involvement of inadvertent radioactive iodine therapy for the treatment of thyroid diseases during an unsuspected pregnancy. Eur J Obstet Gynecol Reprod Biol. 2021;259:53-9.
- 49. Azizi F, Smyth P. Breastfeeding and maternal and infant iodine nutrition. Clinical endocrinology. 2009;70(5):803-9.
- Suman P, Wang CH, Abadin SS, Block R, Raghavan V, Moo-Young TA, et al. Timing of radioactive iodine therapy does not impact overall survival in high-risk papillary thyroid carcinoma. Endocr Pract. 2016;22(7):822-31.
- 51. Li H, Zhang YQ, Wang C, Zhang X, Li X, Lin YS. Delayed Initial Radioiodine Therapy Related to Incomplete Response in Low- to Intermediate-Risk Differentiated Thyroid Cancer. Clin Endocrinol (Oxf). 2018.
- 52. Liu D, Wei Y, Zhao Y, Li R, Yan J, Qiao J. Obstetric outcomes in thyroid cancer survivors: A retrospective cohort study. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2021;155(1):119-24.
- Wells SA, Jr., Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid. 2015;25(6):567-610.
- 54. Rosario PW, Barroso AL, Purisch S. The effect of subsequent pregnancy on patients with thyroid carcinoma apparently free of the disease. Thyroid. 2007;17(11):1175-6.
- Hirsch D, Levy S, Tsvetov G, Weinstein R, Lifshitz A, Singer J, et al. Impact of pregnancy on outcome and prognosis of survivors of papillary thyroid cancer. Thyroid. 2010;20(10):1179-85.
- Rakhlin L, Fish S, Tuttle RM. Response to Therapy Status Is an Excellent Predictor of Pregnancy-Associated Structural Disease Progression in Patients Previously Treated for Differentiated Thyroid Cancer. Thyroid. 2017;27(3):396-401.
- Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. The New England journal of medicine. 2004;351(3):241-9.
- Minakata M, Ito M, Kishi T, Hada M, Masaki Y, Nakamura T, et al. The magnitude of increased Levothyroxine dose during pregnancy in patients on thyroid-stimulating hormone (TSH) suppression treatment after total thyroidectomy for papillary carcinoma. Endocrine journal. 2021.
- Zamfirescu I, Carlson HE. Absorption of Levothyroxine When Coadministered with Various Calcium Formulations. Thyroid. 2011;21(5):483-6.

- Rowe C, Murray K, Woods A, Gupta S, Smith R, Wynne K. Metastatic Thyroid Cancer in Pregnancy: Risk and Uncertainty. Endocrinolgy Diabetes & Metabolism Case Reports. 2016.
- Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. Obstetrics and gynecology. 2006;107(2 Pt 1):337-41.
- Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and preeclampsia in pregnancies complicated by hyperthyroidism. Obstetrics and gynecology. 1994;84(6):946-9.
- Kim HO, Lee K, Lee SM, Seo GH. Association Between Pregnancy Outcomes and Radioactive Iodine Treatment After Thyroidectomy Among Women With Thyroid Cancer. JAMA Intern Med. 2020;180(1):54-61.
- 64. International Atomic Energy Agency. Radiation protection of pregnant women in nuclear medicine: International Atomic Energy Agency; [Available from: <u>https://www.iaea.org/resources/rpop/health-</u> professionals/nuclear-medicine/pregnant-women.
- Piek MW, Postma EL, van Leeuwaarde R, de Boer JP, Bos AME, Lok C, et al. The Effect of Radioactive Iodine Therapy on Ovarian Function and Fertility in Female Thyroid Cancer Patients: A Systematic Review and Meta-Analysis. Thyroid. 2021;31(4):658-68.
- 66. Yaish I, Azem F, Gutfeld O, Silman Z, Serebro M, Sharon O, et al. A Single Radioactive Iodine Treatment Has a Deleterious Effect on Ovarian Reserve in Women with Thyroid Cancer: Results of a Prospective Pilot Study. Thyroid. 2018;28(4):522-7.
- 67. Sawka AM, Lakra DC, Lea J, Alshehri B, Tsang RW, Brierley JD, et al. A systematic review examining the effects of therapeutic radioactive iodine on ovarian function and future pregnancy in female thyroid cancer survivors. Clin Endocrinol (Oxf). 2008;69(3):479-90.
- Wu JX, Young S, Ro K, Li N, Leung AM, Chiu HK, et al. Reproductive outcomes and nononcologic complications after radioactive iodine ablation for well-differentiated thyroid cancer. Thyroid. 2015;25(1):133-8.
- 69. Velez MP, Richardson H, Baxter NN, McClintock C, Greenblatt E, Barr R, et al. Risk of infertility in female adolescents and young adults with cancer: a populationbased cohort study. Hum Reprod. 2021;36(7):1981-8.
- Huang N, Zeng L, Yan J, Chi H, Qiao J. Analysis of in vitro fertilization/intracytoplasmic sperm injection outcomes in infertile women with a history of thyroid cancer: a retrospective study. Reproductive Biology and Endocrinology. 2021;19(1):82.
- 71. Huang N, Zeng L, Yan J, Chi H, Qiao J. Impact of thyroid cancer treatment on assisted reproductive technology

outcomes in women with infertility. J Assist Reprod Genet. 2021;38(8):2121-8.

- Garsi JP, Schlumberger M, Rubino C, Ricard M, Labbe M, Ceccarelli C, et al. Therapeutic administration of 1311 for differentiated thyroid cancer: radiation dose to ovaries and outcome of pregnancies. J Nucl Med. 2008;49(5):845-52.
- Zhang L, Huang Y, Zheng Y, Cai L, Wen J, Chen G. The effect of I-131 therapy on pregnancy outcomes after thyroidectomy in patients with differentiated thyroid carcinoma: a meta-analysis. Endocrine. 2021;73(2):301-7.
- Bourcigaux N, Rubino C, Berthaud I, Toubert ME, Donadille B, Leenhardt L, et al. Impact on testicular function of a single ablative activity of 3.7 GBq radioactive iodine for differentiated thyroid carcinoma. Hum Reprod. 2018;33(8):1408-16.
- Pacini F, Gasperi M, Fugazzola L, Ceccarelli C, Lippi F, Centoni R, et al. Testicular function in patients with differentiated thyroid carcinoma treated with radioiodine. J Nucl Med. 1994;35(9):1418-22.
- Poppe K, Bisschop P, Fugazzola L, Minziori G, Unuane D, Weghofer A. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. Eur Thyroid J. 2021;9(6):281-95.

- 77. Shindo H, Amino N, Ito Y, Kihara M, Kobayashi K, Miya A, et al. Papillary thyroid microcarcinoma might progress during pregnancy. Thyroid. 2014;24(5):840-4.
- Ito Y, Miyauchi A, Kudo T, Ota H, Yoshioka K, Oda H, et al. Effects of Pregnancy on Papillary Microcarcinomas of the Thyroid Re-Evaluated in the Entire Patient Series at Kuma Hospital. Thyroid. 2015;26(1):156-60.
- 79. Xi C, Zhang Q, Song H-J, Shen C-T, Zhang G-Q, Sun J-W, et al. Pregnancy Does not Affect the Prognoses of Differentiated Thyroid Cancer Patients With Lung Metastases. The Journal of Clinical Endocrinology & Metabolism. 2021;106(8):e3185-e97.
- 80. U.S Food & Drug Administration. Lenvima Prescribing Information: FDA; 2015 [Available from: <u>https://www.accessdata.fda.gov/drugsatfda_docs/label/20</u> <u>16/208692s000lbl.pdf</u>.
- 81. U.S Food & Drug Administration. Nexavar Prescribing Information: FDA; 2013 [Available from: <u>https://www.accessdata.fda.gov/drugsatfda_docs/label/20</u> <u>13/021923s016lbl.pdf</u>.
- Thomas N, Glod J, Derse-Anthony C, Baple EL, Obsborne N, Sturley R, et al. Pregnancy on vandetanib in metastatic medullary thyroid carcinoma associated with multiple endocrine neoplasia type 2B. Clin Endocrinol (Oxf). 2018.