



Thyroid oncology in pregnancy

Beata Wojtczak¹, Krzysztof Kaliszewski¹, Michał Binko¹, Monika Sępek¹, Rafał Mulek², Jerzy Rudnicki¹, Marek Bolanowski^{3^}, Marcin Barczyński^{4^}

¹Department of General, Minimally Invasive and Endocrine Surgery, Wrocław Medical University, Wrocław, Poland; ²Department of General and Endoscopic Surgery, EuroMediCare Hospital, Wrocław, Poland; ³Department of Endocrinology, Diabetes and Isotope Therapy, Wrocław Medical University, Wrocław, Poland; ⁴Department of Endocrine Surgery, Third Chair of General Surgery, Jagiellonian University Medical College, Krakow, Poland

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Correspondence to: Beata Wojtczak, MD, PhD. Department of General, Minimally Invasive and Endocrine Surgery, Wrocław Medical University, Borowska Street 213, 50-556 Wrocław, Poland. Email: beata.wojtczak@umed.wroc.pl.

Abstract: Thyroid cancer is the second most commonly diagnosed malignancy during pregnancy (after breast cancer), with 14 cases per 100,000 pregnancies. It is always a challenge for clinicians, requiring special consideration and attention for both the patient and her developing child. The main protocols for diagnosing and treating thyroid cancer in pregnancy are the same as in cases diagnosed in the rest of the population, with some restrictions: administration of radioactive iodine (RAI) as a part of therapy is forbidden. There are many aspects that should be discussed regarding thyroid malignancy during pregnancy, such as the timing of surgery, systemic therapy for thyroid cancer during pregnancy and the effect of pregnancy on thyroid cancer outcomes. The influence of RAI ablative therapy and therapy with levothyroxine (LT4) after thyroid cancer treatment should be considered in relation to possible future pregnancies. The aim of this study was to evaluate the recent literature and guidelines regarding thyroid malignancy in pregnancy, and to provide answers to these questions.

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Introduction

Thyroid disorders in young women of reproductive age are common; more than 11% of them have autoimmune thyroid diseases, 3% have hypothyroidism and 2% have hyperthyroidism (1). The incidence of thyroid cancer—the most common endocrine malignancy—has been rising in the last few decades, and often affects women between 20 and 39 years of age. Thyroid cancer is the second most commonly diagnosed malignancy during pregnancy (after breast cancer), with 14 cases per 100,000 pregnancies. It is always a huge challenge for clinicians, requiring special

consideration and attention for both the patient and her developing child (2). On the one hand, the main protocols for diagnosing and treating thyroid cancer in pregnancy are the same as in cases diagnosed in the rest of the population, with some restrictions [e.g., administration of radioactive iodine (RAI) as a part of therapy is forbidden] (3,4). On the other hand, “*there is always a conflict between maternal optimal therapy and fetal well-being*” according to Oducan’s review of maternal-fetal issues related to malignancies in pregnant women (5). There are many aspects that should be discussed regarding thyroid malignancy during pregnancy, such as

[^]Marek Bolanowski, ORCID: 0000-0002-2360-6596; Marcin Barczyński, ORCID: 0000-0001-6062-1851.

the timing of surgery, systemic therapy for thyroid cancer during pregnancy and the effect of pregnancy on thyroid cancer outcomes. The influence of RAI ablative therapy and therapy with levothyroxine (LT4) after thyroid cancer treatment should be considered in relation to possible future pregnancies.

The aim of this study was to evaluate the recent literature and guidelines regarding thyroid malignancy in pregnancy, and to provide answers to these questions.

Changes in thyroid physiology during pregnancy

During pregnancy, physiological changes in the maternal thyroid hormones are observed: thyroid-stimulating hormone (TSH) levels decrease in the first trimester and then return to normal before delivery. This is due to high levels of β -human chorionic gonadotropin (β -hCG) produced by the placenta, which stimulates production of thyroid hormones by cross-reacting with TSH-receptors, increasing the activity of the maternal thyroid gland (6,7). Both TSH and β -hCG are glycoprotein hormones encoded by the same gene (8). This leads to suppression of maternal TSH secretion through negative feedback mechanisms, and the increased production of thyroid hormones via β -hCG stimulation results in elevated levels of free T4 and free T3. Throughout pregnancy, the range of TSH secretion is lower than the reference levels for non-pregnant women. Due to the transfer of thyroid hormones to the fetus and increased maternal thyroxine-binding globulin (TBG) stimulated by high estrogen levels, maternal thyroid hormone requirements increase up to 50% during gestation (9). In the second and third trimesters of pregnancy, thyroid hormone secretion returns to normal when β -hCG levels decrease.

Knowledge of fetal thyroid development is equally important. At approximately 10 weeks of gestation, small amounts of thyroid hormone are produced by the fetal thyroid gland, with progression at about 35 weeks. It follows that in the first trimester of pregnancy, the fetus is totally dependent on the transfer of thyroid hormones from the mother (10). Precise regulation of thyroid hormone levels during gestation is crucial to achieve optimal outcomes for both the mother and child. Maternal hypothyroidism is one of the most common complications of pregnancy, increasing the risk of miscarriage, preeclampsia, neurologic and congenital impairment or abnormal fetal growth (3,11). While euthyroid pregnant women are able to compensate for all the physiological changes during gestation, it is strongly recommended for overt hypothyroidism to be

treated during pregnancy (3,7).

The relationship between estradiol, β -hCG and the thyroid gland is under investigation by many researchers as a potential risk factor for thyroid malignancy in pregnancy (3,12-14). The meta-analysis in Mannathazhathu *et al.* supports an association due to changes in female hormones during menstrual cycle and pregnancy with the risk of thyroid carcinoma (TC) and explains female preponderance (15).

Epidemiology of thyroid cancer and pregnancy

Thyroid cancer is the most common malignancy among endocrine disorders, accounting for 3.6% of all malignant tumors. During pregnancy, thyroid cancer is the second most common malignancy (after breast cancer), with a rate of 14 per 100,000 live births; papillary thyroid carcinoma (PTC) is the most frequent pathological type. The time of diagnosis has been reported as follows: 3.3/100,000 cases are diagnosed before delivery; 0.3/100,000 are diagnosed at delivery; and 10.8/100,000 within 1 year post-partum (2,3). Further, it is known that there is a high frequency of co-occurrence of differentiated thyroid cancer (DTC) and breast cancer (4). Easy access to modern diagnostic tools, particularly to ultrasound examination, could be one of the reasons why the incidence of thyroid cancer has increased in recent decades all over the world (16,17). Increases observed in some geographical regions in Eastern Europe are associated with radioactive fallout from the Chernobyl nuclear power station accident (18).

The incidence of thyroid cancer generally increases with age, and it is more common in females than in males; the female to male ratio is 3:1 (3). The predominance among females suggests that hormonal factors may be involved. Some studies suggest that biological changes during pregnancy may increase the risk of TC (12-14,19-21); but others show no significant correlation between pregnancy and the risk of thyroid malignancy (22,23). A study by Horn-Ross *et al.* found that for woman under 45 years old, the risk of thyroid cancer increased in the first 5 years following pregnancy, again suggesting that pregnancy could be a potential risk factor for TC. Moreover, in women older than 45 years old, the use of estrogen replacement therapy was associated with a trend toward an increased risk of PTC (21). In contrast, a population-based retrospective study by Mack *et al.* concluded that the risk of thyroid cancer was not altered by the use of estrogens (oral contraceptive pills). Interestingly, they found a correlation between the prevalence of thyroid cancer and lactation: in women

who suppressed lactation post-partum they observed an increased incidence of cancer, while the rate of thyroid cancer decreased among women who had ever breastfed; and a longer duration of lactation was associated with lower incidence of cancer (22). In another big-cohort study, including 117,646 women, the authors showed an association between a late age of menarche, a longer menstrual cycle (more than 30 days) and an increased risk of thyroid cancer (24). One of the biggest meta-analyses, including 21 studies with 406,329 cases, showed a strong association between parity (>3 pregnancies) and the risk of thyroid cancer.

Thyroid nodules during pregnancy

Thyroid cancer is usually diagnosed within a thyroid nodule. The high level of β -hCG and estrogens and the negative iodine balance during pregnancy causes up to 30% growth not only of the thyroid gland, but also in preexisting thyroid nodules. Moreover, all these changes stimulate the formation of new thyroid nodules (25,26). In most cases, the increased nodule volume returns to pre-pregnancy diameter 3 months post-partum (27). According to American College of Obstetricians and Gynecologists, if a nodule is present during the first trimester of pregnancy, up to 20% of women will develop a second nodule during the same pregnancy (26). According to American Thyroid Association (ATA) recommendations, any thyroid nodule recognized during pregnancy should undergo the same evaluation as a nodule detected in any other patient (3). This means that patients should be asked about their personal and family history of TC, about multiple endocrine neoplasia type 2 (MEN2) and familial adenomatous polyposis (FAP). Any history of neck irradiation, compressive symptoms, dysphagia or dysphonia should be taken under consideration in the diagnosis (3,28). In all nodules suspicious for malignancy or in nodules greater than 1 cm in diameter, a fine needle aspiration (FNA) biopsy should be performed. This can be done at any time during pregnancy; there is no risk for either the mother or the fetus (29). Some authors suggest that the FNA could be delayed if the nodule is recognized late in the pregnancy or if treatment is postponed until after delivery, assuming that an ultrasound exam reveals no signs of malignancy (29,30).

TSH measurement should be performed on any thyroid nodule recognized in a pregnant woman. It is important to be careful with TSH interpretation. Subnormal serum TSH in non-pregnant women suggests a functioning nodule, but in pregnancy it could be a physiological change (3).

A serum calcitonin measurement is required only in pregnant women with a history of medullary TC, MEN2 or known *RET* gene mutations. Pentagastrin stimulation test is contraindicated in pregnancy (3,30,31); serum TG measurement is not recommended either (26). Finally, RAI scans and scintigraphy with either technetium-99m or iodine-131 (I-131) are strictly contraindicated during pregnancy, because I-131 crosses the placenta (32).

To sum up, the diagnosis of a thyroid nodule during pregnancy is in most cases based on cancer risk stratification, including clinical examination, history, ultrasonography, serum TSH measurement and FNA.

Treatment of thyroid cancer and timing of surgery

Total thyroidectomy is the treatment of choice in thyroid malignancy (3), but in pregnancy, both maternal and fetal outcomes need to be taken under consideration before making decisions about surgery. According to the ATA and the Endocrine Society, in most cases a thyroidectomy can be delayed until the post-partum period (3,33). In the treatment of PTC and follicular thyroid cancer (FTC), there is no evidence of worse outcomes when surgical treatment is delayed several months (*Figure 1*) (3). If thyroid cancer is diagnosed in the first trimester, it is necessary to monitor the lesion by regular neck ultrasound examinations in each trimester. Usually tumors remain stable, but if significant growth is observed (i.e., more than 50% in volume and more than 20% in diameter) or if lymph node metastases are observed, surgery is recommended.

If the thyroid cancer is recognized in the second or third trimester, the operation should be delayed until after delivery, except in cases where advanced disease is observed. If bulky cervical adenopathy is observed, confirming advanced disease, the thyroid operation should be performed as soon as possible (3,6,32,33). The optimal timing for surgery in pregnant women is the second trimester, when organogenesis is completed, but the rate of complication is always higher in pregnant women than in non-pregnant patients (3,30-33). In an analysis involving 201 pregnant women who underwent thyroid and parathyroid operations, Kuy *et al.* found that they were twice as likely as non-pregnant controls (over 31,000) to experience complications. There are many risk factors for complications in pregnant women (34). An enlarged thyroid gland makes surgery more difficult, and anesthesia is more complicated because of gestational physiological changes. The most dangerous for both the mother and fetus seems to

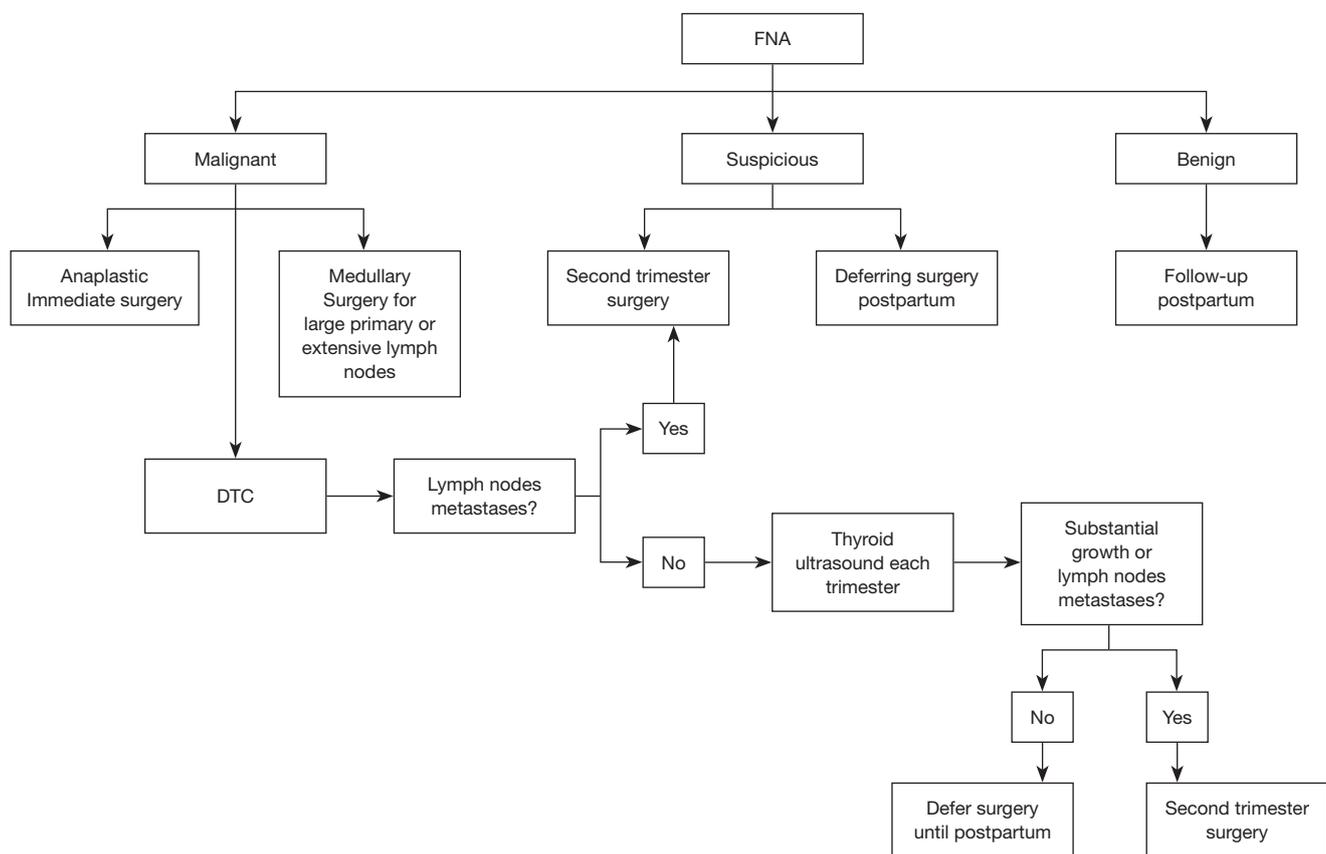


Figure 1 Management of thyroid nodules during pregnancy based on FNA cytology. FNA, fine needle aspiration; DTC, differentiated thyroid cancer.

be the first trimester, with the risk of spontaneous abortion (3,5,33); whenever it is possible, first-trimester surgery should be avoided.

In all cases of thyroid malignancy recognized during pregnancy, suppressive doses of LT₄ are recommended, maintaining optimal TSH levels between 0.1–0.5 mIU/L. Suppressive treatment is not recommended in suspicions of malignancy diagnosed by FNA, because in the literature up to 70% of such tumors are benign (35). Appropriate LT₄ supplementation is necessary following a thyroidectomy to prevent maternal and fetal hypothyroidism. The goal is to maintain maternal TSH <2.5 mIU/L during the first trimester and <3.0 mIU/L during the second and third trimesters. Serum TSH levels should be measured every 4 weeks until the end of the pregnancy.

The ATA and the Endocrine Society have established guidelines for using radioactive I-131 therapy in some cases of DTC. In pregnant women I-131 is always contraindicated due to the risk of exposing the fetus to

radioactivity. Exposure to RAI during gestation causes fetal hypothyroidism, cognitive disorders and mental retardation. If RAI is indicated it should be recommended as soon as possible post-partum, and breast feeding should be stopped at least 6 weeks before ablation therapy (14,36).

Outcomes of thyroid cancer during pregnancy

Usually the treatment of thyroid cancer diagnosed during pregnancy is delayed until after delivery, which raises the question of whether the postponement causes greater morbidity and mortality. According to many studies, it seems that the diagnosis of thyroid cancer during pregnancy and the frequent delay of surgery does not have a significant impact on the prognosis and outcomes (37–39). Moosa *et al.* compared the outcomes of DTC in women diagnosed during pregnancy with those diagnosed outside pregnancy. In their study, 77% of the pregnant women with carcinoma underwent surgery post-partum; 20% had their surgery in

the second trimester. The 20 years of follow-up included recurrences of cancer, distant metastases and cancer deaths; the outcomes for women with TC diagnosed during pregnancy were similar to those for women diagnosed postpartum. Moreover, there were no differences in the results of treatment among pregnant women operated on in the second trimester as opposed to postpartum (37). A study by Herzon *et al.* found similar results: among pregnant women aged 18–46 with recognized TC, the survival rates were similar to those of women with carcinoma diagnosed postpartum (38). These results were confirmed by Yasmeen *et al.*, whose study compared thyroid cancer prognoses and maternal and fetal outcomes among pregnant and non-pregnant groups. They found no significant differences between these groups in terms of thyroid cancer prognoses or in any of the maternal or fetal outcomes measured (39). Finally, neither the timing of the thyroid cancer diagnosis, nor the timing of the initial thyroidectomy influence maternal or fetal outcomes. The decision to delay thyroidectomy in DTC during pregnancy is an acceptable option with no impact on outcomes.

Another important question related to malignancy and pregnancy is whether pregnancy alters the course of DTC. Could women who become pregnant after treatment for DTC be at increased risk of disease progression and recurrence? A retrospective study by Hirsch *et al.* found that among women without any structural or biochemical evidence of DTC at the time of conception, pregnancy did not increase the risk of recurrence during a 4-year postpartum follow-up period. Despite these findings, disease progression might always occur during pregnancy (33). In the retrospective study by Rakhlin *et al.*'s there is a conclusion that none of the patients with an excellent, indeterminate or biochemical incomplete response to therapy prior to pregnancy developed structurally identifiable disease after a full-term delivery. Even if progression was seen in almost a third of the patients with structural disease prior to pregnancy, only a minority of these patients had changes sufficient to warrant additional therapy. The study confirmed that pre-pregnancy response to therapy status is an excellent predictor of pregnancy-associated disease progression in women previously treated for DTC (40–43). Pregnancy outcomes after thyroid cancer was evaluated in Spiegel *et al.*'s study (44). Interestingly neonates of mothers with thyroid cancer were not found to be at increased risk for the adverse neonatal outcomes examined, specifically, congenital malformations, intrauterine growth restriction, fetal death and preterm

labor (44).

To sum up, the history of thyroid cancer does not meaningfully impact the risk of adverse pregnancy outcomes (41–44). Clinicians usually advise avoiding pregnancy for 12 months after RAI treatment to ensure remission (40,45).

The impact of I-131 treatment of DTC on fertility, pregnancy and breastfeeding

There are only a few publications investigating the impact of I-131 therapy for DTC on fertility, pregnancy and breastfeeding. Bal *et al.* evaluated 40 women who conceived 7–12 months after RAI ablation of DTC. According to that study, RAI therapy had no effect on fertility, pregnancy complications such as miscarriage, or the health of the offspring, even in mothers treated with large doses of I-131 and in women who conceived less than 12 months after RAI treatment (46). Despite the slight risk that RAI therapy could impact a future pregnancy, the ATA recommends delaying pregnancy until 6 months to 1 year following I-131 (3,46). It is known that RAI ablation treatment can adversely affect gonads in males and females. There are some studies aiming to determine ovary damage and infertility risk due to RAI, using serum anti-Müllerian hormone (AMH) level, in females who received RAI ablation treatment (47–51). Acibucu *et al.* in his study, compared female patients who have not gone through the menopause and had received RAI ablation treatment for well-DTC in premenopausal period with healthy females as control groups (47). In this study no statistically significant relation between RAI exposure duration and AMH levels was determined. According to these studies, it may be concluded that low AMH levels due to RAI treatment can cause damage to the ovaries of patients; nevertheless, considering the AMH levels and the absence of infertility in the patients, the infertility risk was found to be low (47). Similar results we found in Giust *et al.* and Mittica *et al.* and studies; they conclude that nowadays the age is the only predictor of AMH levels (48,49). While Yaish *et al.* pointed that RAI in DTC has a rapid and profound effect on ovarian reserve, with only a partial recovery potential. In an era of declining human fertility, it is of relevance to recognize the potentially adverse effect of RAI in women of reproductive age (50). Also, Evranos *et al.*'s study confirmed that AMH is considered an important marker of ovarian reserve. But this study shows that ovarian reserve decreased after RAI therapy (51).

The RAI therapy should also be considered to breastfeeding. Because of the transfer of radioiodine to

human breast milk, it is recommended that women avoid breastfeeding for 6 months to 1 year following I-131 treatment (3).

Conclusions

The treatment of thyroid malignancy in pregnancy is a challenge for physicians and requires a multi-disciplinary approach, including the patient's obstetrician, an endocrinologist, an endocrine surgeon, a nuclear medicine specialist and the baby's pediatrician. The treatment of choice for DTC—thyroidectomy followed by RAI ablation—poses a significant risk for both the mother and the fetus, and in most cases it can be delayed until postpartum without any negative impact on either maternal or fetal outcomes. If surgical treatment is necessary during pregnancy due to aggressive thyroid malignancy, the optimal time for surgery is the second trimester. RAI therapy, however, is contraindicated during pregnancy. The outcomes of DTC in pregnancy do not usually differ from the rest of the population with thyroid malignancy.

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