

## SPECIAL ARTICLE

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# Management of thyroid cancer during pregnancy

## Manejo del cáncer de tiroides durante el embarazo

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### ABSTRACT

Pregnancy is a favorable condition for the formation and growth of thyroid cancer, since the iodine balance can be negative in addition to increasing the production of hormones with thyroid stimulating activity. Most of the cancers found during pregnancy are differentiated thyroid cancers with an excellent prognosis. Those cases diagnosed during the first trimester can be removed by surgery. Thyroidectomy can be safely performed in the second trimester of pregnancy or delayed to the postpartum period, depending on gestational age. The patient should receive levothyroxine at a dose sufficient to keep serum thyroid-stimulating hormone levels low. Serum thyroglobulin is a valuable noninvasive method for evaluating the effects of this treatment. The purpose of this review is to establish the management of thyroid cancer during pregnancy.

**Key words:** Thyroid cancer; Pregnancy complications, neoplastic.

### RESUMEN

El embarazo es una condición favorable para la formación y crecimiento del cáncer de tiroides, ya que el equilibrio de yodo puede ser negativo además de aumentar la producción de hormonas con actividad estimuladora de la tiroides. La mayoría de los cánceres encontrados durante el embarazo son cánceres de tiroides diferenciados con un pronóstico excelente. Aquellos casos diagnosticados durante el primer trimestre pueden ser extirpados por cirugía. La tiroidectomía puede realizarse de manera segura en el segundo trimestre del embarazo o retrasarse al periodo posparto, dependiendo de la edad gestacional. La paciente debe recibir levotiroxina en una dosis suficiente para mantener baja las concentraciones séricas de hormona tiroestimulante. La tiroglobulina sérica es un valioso método no invasivo para evaluar los efectos de este tratamiento. El objetivo de la revisión es establecer el manejo de cáncer de tiroides durante el embarazo.

**Palabras clave.** Cáncer de tiroides, Embarazo, complicaciones neoplásicas.

### INTRODUCTION

The number of new cases of thyroid cancer, according to the National Cancer Institute, is 13.9 per 100,000 people per year, and its 5-year survival rate is 98.1%<sup>(1)</sup>. In recent decades, the incidence of thyroid cancer, mainly those smaller than 2 centimeters in diameter, has increased. This trend does not apply to other types of thyroid cancer (follicular, medullary, or anaplastic)<sup>(2)</sup>. The increase in frequency can be explained by the better diagnostic tools available at present. However, risk factors for thyroid cancer include exposure to ionizing radiation and iodine deficiency. The negative effect of ionization is greater the younger the age of the exposed patients. After Chernobyl events in 1986, incidence of benign and malignant thyroid tumors increased 80 times in children born in vicinity of the power plant<sup>(3)</sup>.

Thyroid cancer like other thyroid diseases is 3 times more common in women than in men. It can occur in women of any age, but the risk is at its highest at a younger age compared to men and with a clear prevalence during reproductive age (more than a third of diagnosed cases), which would indicate a possible effect of sex hormones on pathogenesis<sup>(4,5)</sup>. Cohort studies show that late menarche and prolonged menstrual cycles of more than 30 days increase the risk of papillary can-



cer<sup>(6-8)</sup>. On the other hand, 1% - 2% of patients with thyroid cancer have germline mutations of RET gene<sup>(9)</sup>. People with type 2 multiple endocrine neoplasia have a risk greater than 95% of developing thyroid cancer.

The aim of this review is to establish the management of cervical cancer during pregnancy.

## METHODOLOGY OF THE INFORMATION SEARCH

Between July and January 2019, electronic databases of biomedical scientific literature (UP-TO-DATE, OVIDSP, ScienceDirect, SciELO and PUBMED) were examined to investigate eligible articles in the last 30 years (1989 - 2019), with the search terms: "Thyroid cancer", "Pregnancy", "Malignant thyroid neoplasms", "Diagnosis" and "treatment". Articles in English and Spanish of studies carried out in humans were included, subsequently carrying out an analysis of the different aspects of diagnosis, treatment and management of neoplastic lesions of the thyroid gland in pregnant women.

## DIAGNOSIS

During pregnancy, thyroid gland increases 30% of its volume. The thyroid stimulating hormone (TSH) levels first decrease and then return to normal. These changes lead to an increase in circulating concentration of human chorionic gonadotropin (hCG) and estrogens. hCG stimulates TSH receptors and thus increases the activity of the thyroid gland. The effect of estrogens on the thyroid gland is twofold: indirect, by increasing the concentration of thyroxine-binding globulin, and direct, through estrogen receptors (ERs) found in thyroid cells<sup>(10)</sup>. These intracellular nuclear receptors (alpha and beta) are present in both healthy and neoplastic cells. Estradiol, by binding to ER alpha, increases cell proliferation, while beta receptors inhibit this effect and induce apoptosis<sup>(11,12)</sup>. Research suggests a relationship between the expression of the estrogen receptor and the onset of the disease<sup>(13-15)</sup>.

Pregnancy-related thyroid cancer is diagnosed during pregnancy or within a year after delivery<sup>(16)</sup>. Pregnancy does not adversely affect overall survival<sup>(17,18)</sup>. Data on relapses and mortality associated with disease progression during

pregnancy are not conclusive<sup>(19,20)</sup>. Pregnancy causes an increase in size of the micropapillary carcinoma foci<sup>(20)</sup>.

Thyroid nodular lesions are quite common during pregnancy: they appear de novo or existing lesions increase in size<sup>(21)</sup>. In areas with mild to moderate iodine deficiency, the incidence of thyroid nodules during pregnancy ranges from 3% to 21%<sup>(22-24)</sup>. In pregnant women, thyroid nodules have similar diagnostic criteria to non-pregnant patients, with the exception of images with radioactive agents. It is necessary to determine the serum concentrations of TSH, free thyroxine and evaluate the structure of the gland by ultrasound. Indications for fine needle biopsy do not differ from those in the general population<sup>(25,26)</sup>. Retrospective studies report that 12% - 43% of neoplastic lesions are based on existing benign lesions<sup>(27-30)</sup>.

Another question is the possible impact of pregnancy on the course of the disease, its prognosis and the risk of recurrence in patients previously treated for thyroid cancer. Risk of recurrence is low in women without residual tumor sites and low thyroglobulin concentrations<sup>(31,32)</sup>. Pregnancy does not change the course of differentiated thyroid cancer<sup>(33)</sup>. Women diagnosed with thyroid carcinoma during pregnancy should be closely followed to detect persistent or recurrent disease and monitor for possible complications<sup>(31-34)</sup>. Patients with elevated thyroglobulin or persistent disease should be evaluated by ultrasound at least once each trimester and their thyroglobulin concentrations should be determined<sup>(35)</sup>.

If irregular and hypoechoic margins, increased internal vascularization, presence of lymphadenopathy and / or microcalcifications are observed during the physical examination and ultrasound, it is necessary to perform a fine needle biopsy and subsequent cytological examination, using the Bethesda classification as the gold standard. The procedure must be repeated in case of an inconclusive result<sup>(36,37)</sup>. Due to the free absorption of radioactive elements by the fetal thyroid gland and the possible induction of thyroid cancer in the offspring, the use of radiolabeled iodine ( $I^{131}$ ) is contraindicated in pregnant women. Alternatives are Technetium 99 or Iodine 123<sup>(38)</sup>.



## TREATMENT

Thyroid cancer is not an indication for termination of pregnancy<sup>(15)</sup>. Subtotal or total thyroidectomy is the primary treatment for these cases. Before the diagnosis of follicular cancer, it is necessary to consider surgery during pregnancy. In cases of differentiated tumor, it is advisable to postpone surgery until after delivery. If treatment is postponed, ultrasound checks are required every trimester. If tumor size does not change, treatment should be established to keep TSH values between 0.1 - 1.5 mIU / L<sup>(26,35)</sup>.

In cases of rapid tumor growth in early pregnancy, presence of lymph node metastases, signs of histological malignancy or symptoms of compression, surgery may be performed in second trimester of pregnancy, as it is safe for both mother and fetus.<sup>(27,35)</sup> Surgery during pregnancy is associated with a higher risk of postoperative complications<sup>(39)</sup>. In retrospective studies in pregnant women undergoing thyroidectomy, surgical (11% compared to 4%) and endocrine (16% compared to 8%) complications were greater in pregnant women compared to non-pregnant women<sup>(40)</sup>. Endocrine complications include: maternal hypoparathyroidism, hypocalcemia, and recurrent laryngeal nerve damage. Surgical complications depend on the experience of the surgeon. Due to the increased risk of preterm delivery and alterations in fetal well-being during the procedure, diagnosis during the second trimester should lead to a delay in surgery until the postpartum period<sup>(36,41,42)</sup>.

In most patients, complementary therapy after surgery is treatment with I<sup>131</sup><sup>(43)</sup>, which reduces the risk of recurrence and distant metastasis. This can only be done after delivery and breastfeeding<sup>(15)</sup>. Exposure of the fetus to I<sup>131</sup> causes hypothyroidism, cognitive impairment, and mental retardation<sup>(42)</sup>. If postpartum treatment is necessary, breastfeeding should be completed 6 to 8 weeks prior to treatment<sup>(44)</sup>. This recommendation is due to the increased activity of iodine in glandular tissue subjected to the effects of estrogen, leading to accumulation of radiolabeled iodine in the breast. Dopamine agonists are helpful in lowering prolactin levels and shortening the time to start treatment<sup>(45)</sup>. There is no evidence that this treatment affects fertility<sup>(46)</sup>. It is desirable to maintain an interval of 6 to 12 months after completing the treatment to

conceive, which allows achieving remission and maintaining adequate replacement therapy<sup>(34,46)</sup>.

Levothyroxine can be administered for a variety of indications: treatment when surgery is postponed, replacement after thyroidectomy, or treatment for persistent disease. The suppressive dose maintains TSH concentration at 0.1 - 1 mIU / L. It should be indicated as soon as possible after confirmation of pregnancy diagnosis, then every month until mid-pregnancy and at least once between 26 and 32 weeks<sup>(35)</sup>. After surgery, levothyroxine replacement during pregnancy is necessary due to the risk of fetal hypothyroidism. Doses should be modified due to the 20-30% increase in the needs of the growing fetus. The switch should be made when TSH concentrations exceed 0.5 mIU / L, which can occur early in pregnancy<sup>(46)</sup>. The simultaneous supplementation of iron and / or calcium affects the absorption of levothyroxine<sup>(36,47)</sup>.

Suppression doses in persistent or residual neoplastic disease should ensure that TSH concentrations are kept below 0.1 mIU / L. Most studies establish that the target value in pregnant women should be less than 0.5 mIU / L. For high-risk patients, doses that achieve TSH suppression are recommended, as is done outside of pregnancy<sup>(48)</sup>. Radioactive iodine-resistant thyroid cancer can be treated with tyrosine kinase inhibitors. However, these drugs are contraindicated in pregnancy, as they are classified in category D according to the US Food and Drug Administration<sup>(47,49)</sup>.

## CONCLUSIONS

Thyroid cancer is often found in young women. The association between pregnancy and thyroid cancer is not uncommon, since 10% of thyroid cancer cases that occur during reproductive age are diagnosed during pregnancy or in puerperium. Most of the cancers found during pregnancy are differentiated thyroid cancers with an excellent prognosis and disease-free survival in pregnant women does not differ compared to nonpregnant women of similar age and stage. The main objectives of the management of pregnant women with thyroid cancer are: to achieve an adequate balance of thyroid hormones necessary for the normal maturation of the fetal central nervous system and to maintain optimal hormonal concentrations that prevent the re-



currence or spread of the disease. Those cases diagnosed early in pregnancy can be treated with surgery, safely in the second trimester. Cases diagnosed in the second and third trimesters should be treated in puerperium. There are no data to support the termination of pregnancy in these patients.

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