Management and follow-up of thyroid cancer in pregnant women

Neoplasie maligne della tiroide in gravidanza: management e follow-up

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SUMMARY

Thyroid cancer, the most common endocrine malignancy, is often detected in young female patients. Therefore, pregnancy following thyroid cancer is not infrequent, and about 10% of thyroid cancers occurring during the reproductive years are diagnosed during pregnancy or in the early post-partum period. Differentiated thyroid cancer (DTC) in young people generally has an excellent prognosis, and disease-free survival among women with DTC diagnosed during pregnancy may not differ from that in age-matched non-pregnant women with similar disease. However, thyroid cancer detected during pregnancy may cause anxiety about the optimal timing of recommended treatments and about both maternal and neonatal morbidity, as weel as pregnancy following a diagnosis of thyroid cancer obviously needs both maternal and foetal management. The main objectives in clinical monitoring of pregnant thyroid cancer patients are: 1) to reach an adequate balance of maternal calcium and thyroid hormones that is absolutely required by the foetal central nervous system for normal maturation; 2) to maintain optimal levels of maternal thyroxin to avoid possible recurrence or spread of disease; and 3) to perform safe follow-up visits for the mother and to plan further therapy when needed. Data from a review of the literature and the authors' own experience show that in patients undergoing either suppressive or substitutive thyroxine therapy foetal thyroid growth is normal at ultrasound study, newborn thyroid status is normal, and the incidence of maternal morbidity is not influenced by the pregnancy. In this review, the authors underline that regular adjustment of levo-thyroxine and calcium therapy is of outmost importance for both maternal and foetal well-being and offer some insight, very interesting from a practical point of view, to provide a clear and simple pathway for the management of pregnancy-associated thyroid cancer.

KEY WORDS: Pregnancy • Thyroid cancer • Thyroxin therapy

RIASSUNTO

I carcinomi tiroidei sono la neoplasia endocrina più frequente, si presentano facilmente in età giovanile e nelle donne, quindi una gravidanza in seguito ad un tumore tiroideo non è un evento raro, e circa il 10% delle neoplasie tiroidee diagnosticate in età fertile si colloca nel periodo della gravidanza o dell'immediato post-partum. I tumori differenziati della tiroide (DTC) hanno in genere una eccellente prognosi, e la sopravvivenza libera da malattia nelle donne con DTC diagnosticato durante la gravidanza non sembra differente da quella di pazienti non gravide della stessa età e con malattia simile per estensione locale e indici di rischio. Nonostante ciò un tumore diagnosticato in corso di gravidanza è ovviamente fonte di ansia non solo per la scelta delle modalità e dei tempi di trattamento, ma anche per la valutazione dei rischi materno - fetali associati sia al tumore che alla terapia stessa. Una gravidanza che invece inizi dopo il trattamento per carcinoma della tiroide richiede accurati controlli del feto e della madre sia dal punto di vista oncologico che biochimico. Nel monitoraggio di una paziente in gravidanza con diagnosi di carcinoma tiroideo o già trattata per carcinoma tiroideo gli obbiettivi principali sono: 1) raggiungere un buon compenso calcio-vitaminico ma soprattutto un ottimale livello di levo-tiroxina, assolutamente indispensabile per la maturazione del sistema nervoso centrale del feto; 2) mantenere livelli di levotiroxina adeguati per evitare possibili recidive di malattia; 3) attuare controlli di follow-up sicuri per madre e feto e adatti a pianificare ulteriori terapie se necessario. Dall'analisi dei dati di letteratura e dall'esperienza personale degli autori emerge che lo sviluppo fetale è regolare nelle pazienti trattate con levotiroxina sia a dosaggio sostitutivo che a dosaggio TSH-soppressivo, la tiroide risulta normale all'esame ecografico nel feto e alla valutazione neonatale, e la patologia materna non è influenzata dalla gravidanza. In questa review gli autori ricordano con semplici spunti pratici che un'attenta modulazione della terapia calcio-vitaminica e della terapia con levotiroxina siano di estrema importanza per il benessere sia della madre che del feto.

PAROLE CHIAVE: *Gravidanza • Carcinoma tiroideo • Terapia con tiroxina*

Introduction

Thyroid cancer, the most common endocrine malignancy, is often detected in young patients and is more frequently diagnosed in women. The median age at diagnosis is low, below 40 years in most populations. For these reasons, differentiated thyroid cancer (DTC) is one of the most common cancers in women in the reproductive age. Hence, thyroid cancer ranks among the most common cancers during pregnancy, with a prevalence of 3.6-14 per 100,000 live births, mirroring the its incidence [1-4].

Therefore, pregnancy in thyroid cancer patients is not unusual, and about 10% of thyroid cancers occurring during reproductive years are diagnosed during pregnancy or in the early post-partum period.

Some data suggest the importance of growth factors (mainly TSH, but also HCG) in growth, progression and spread of papillary tumours. In vitro oestrogens have been shown to down-regulate the NIS (sodium iodide symporter) gene and promote the production of thyroglobulin (HTG), increasing HTG-gene expression via oestrogen receptors present in thyroid tissue, without stimulating rapid cell proliferation [1 4 5]. This could support the hypothesis that sex hormones and, therefore, menstrual and reproductive events, may modify thyroid cancer risk in women [6], although these associations – which could indicate either a causal link or a surveillance bias – may reflect an aetiology shared by both the above-mentioned factors and by thyroid cancer. However, such a relation has not yet been confirmed.

The diagnosis of a tumour during pregnancy obviously causes anxiety about the optimal timing of recommended treatments and about both maternal and neonatal morbidity. However, thyroid cancer in young people has generally an excellent prognosis, and survival among women with thyroid cancer diagnosed during pregnancy may not differ from that in age-matched non-pregnant women with similar disease.

Pregnancy is a special situation in oncology: we need to control two patients at the same time, and both are vulnerable. In addition, each situation must be considered in development, nothing is static, mainly in the first trimester. Finally, thyroid cancer patients often undergo total thyroidectomy and thus need adequate supplementation of both calcium and thyroxine.

Thus, pregnancy following thyroid cancer needs both maternal and foetal control. The main problems are: i) to reach an adequate balance of maternal thyroid hormones that is absolutely required by the foetal central nervous system for normal maturation [7], ii) to maintain maternal levels of l-thyroxin to avoid possible recurrence or spread of disease, and iii) to perform safe follow-up controls for the mother and to plan further therapy when needed.

Physiology of pregnancy

1. Thyroid hormones and foetal development

The first endocrine structure to appear during embryonic development is the thyroid gland. At 10-12 weeks of embryo development, follicles containing colloid become visible, and the thyroid is able to incorporate iodine into thyroid hormones. Thyroid hormones are major factors for the normal development of foetal brain, and until the end of the first trimester, when the hypothalamic-pituitary-thyroid axis becomes functional, the foetal brain is strictly dependent on local deiodination of maternal thyroxine [7-12]. Thyroid hormone deficiency may cause severe neurologic disorders, resulting from defects in neuronal cell differentiation and migration, axonal and dendritic outgrowth, myelin formation and synaptogenesis [7 9 13]. The offspring of women with a serum-free thyroxine (fT4) concentration in the lowest decile of the reference range at 12 weeks of gestation may have significant delays in neurodevelopment. The mother is the only source of foetal thyroid hormones from conception to approximately 13 weeks of gestation, when foetal thyroid function has developed [14-16].

During pregnancy, the mother's thyroid physiology undergoes many well-defined changes, leading to an increase in thyroid volume which is often associated with higher urinary iodine excretion. It is also associated with the formation of new thyroid nodules with the histological features of nodular hyperplasia. Very early in pregnancy, the increase in oestrogen levels causes an approximate doubling in thyroxine-binding globulin (TBG) that can lead to an increases in total T4 concentration and a reduced free fraction (Table I). In healthy women, the final effect consists of a significant increase in the total thyroxine pool, mainly in the first trimester [17-19]. This increment may be brought about largely by thyroid stimulation induced by human chorionic gonadotropin (HCG) through its structural affinity with thyrotropin (TSH). It can be observed that a slight increase in fT4 and a reduction in TSH occur between the 9th and 12th weeks of gestation; subsequently, HCG levels decrease and TSH reaches normal non-pregnant levels. The TSH concentration generally lies within the normal range after the 16th to 18th week [11 17 19 20]. In

Table I. Physiological changes in thyroid function during pregnancy.

Increase	Decrease
HCG (TSH–like effect)	TSH
TBG, serum total T 4 and T3, T3 and T4 pool size	
HTG	
Type III 5-deiodinase, iodine clearance, T3 and T4 degradation	
Thyroid volume	

hypothyroid or thyroidectomized pregnant women, such physiological changes obviously cannot occur. Both during suppressive or substitutive therapy, L-T4 requirement increases very early during pregnancy, reaching a plateau after 16th to 20th weeks of gestation, with a required L-T4 dosage approximately 30 to 50% higher than that administered before pregnancy.

Besides the well-known association between gestational hypothyroidism and impaired intellectual and cognitive development in offspring, untreated or inadequately treated and subclinical hypothyroidism is associated with foetal loss, anaemia, gestational hypertension and pre-eclampsia, abruption placentae, increased risk of miscarriage, foetal growth retardation, perinatal mortality and neonatal morbidity [9 13 15-17 21 22]. Finally, for thyroid cancer patients, hypothyroidism can rise the maternal risk of recurrence.

Thus, hypothyroidism must be absolutely avoided in all pregnant woman, especially in thyroid cancer patients, and therefore correct supplementation of thyroxine is of extreme importance.

2. Vitamin D requirement during pregnancy

Thyroidectomised patients often need calcium and D vitamin supplementation, and the treatment needs frequent adjustment during the pregnancy to prevent maternal and neonatal hypocalcemia. During pregnancy vitamin D and calcium metabolism undergo significant changes to provide the calcium needed for maternal skeletal preservation and foetal skeletal formation. Increased intestinal calcium absorption seems to be the primary mechanism for obtaining extra calcium in physiological pregnancy, but frequent nausea and vomiting or sometimes diarrhea reduce the amount of calcium absorbed by the mother [23].

Vitamin D does not occur naturally in foods. Moreover, the usual recommendations to avoid sun exposure reduces dermal synthesis of vitamin D_3 Although vitamin D is undoubtedly important for foetal bone development, we know that it plays a much wider role in health and disease prevention.

Not really a vitamin, D3 is a pro-prehormone made in the skin in response to ultraviolet-B light exposure. It is the precursor to form 25-hydroxyvitamin D_3 [25(OH)D_3], a prehormone, which is ultimately converted to 1,25-dihydroxyvitamin D_3 [1,25(OH)2D_3], one of the most potent steroid hormones known. 1,25(OH)$_2$D may interfere with many functions beyond calcium metabolism, such as foetal "imprinting" that may affect neurodevelopment, immune function and chronic disease susceptibility later in life, as well as soon after birth [24 25].

The active metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)$_2$ D] increases intestinal calcium absorption and decreases renal calcium excretion, thus increasing the pool of calcium available both for mother and foetus. Vitamin D and calcium deficiency can lead to maternal anorexia with poor weight gain, and impaired bone ossification or osteopenia among newborn infant.. Neonatal hypocalcemia with seizures is not uncommon in D-vitamin deficient mothers.

Vitamin D is likely safe during pregnancy and breast feeding when taken by mouth in recommended amounts, that is 10 mcg (400 USP units) of vitamin D daily in normal pregnancy. but sometimes thyroidectomised women need more. Dosage in excess of 50 mcg (2000 units) per day are not recommended, thus the treatment of postsurgical hypoparathyroid patient calcium supplementation may be required at dosage as high as 4 g/day together with D vitamin.

The range between therapeutic and toxic doses is narrow, and vitamin D toxicity, when it occurs, is a serious problem. The first sign is a rise in the ratio of calcium to creatinine in the urine, which precedes hypercalcemia. Hypervitaminosis D is thought to be associated with a rare infant disease with supravalvular aortic stenosis, elfin facies and mental retardation.

Thus doses of D vitamin and calcium supplementation, which may differ from those recommended in normal pregnancy, need to be carefully tailored in thyroidectomised patients.

Thyroid cancer and pregnancy

Treatment and follow-up of thyroid cancer in pregnant women are the same as in non-pregnant patients except for the use of radioactive iodine. There are some differences in the management of the two most important histotypes: DTC (differentiated thyroid cancer: follicular and papillary cancer) and MTC (medullary thyroid cancer) just as for non-pregnant patients [Boxes 1-2].

Thyroid nodules in pregnancy are often misdiagnosed because of physiological thyroid increases during pregnancy, but clinical and ultrasound findings are sufficient to suspect malignancy. Skilled examiners and good quality images with grey-scale and power Doppler US seem more reliable than other techniques in detecting and differentiating malignant and benign solid thyroid nodules, especially for small lesions. Even during pregnancy, US guided fine-needle aspiration biopsy (FNA) is the investigation of choice, thanks to its reliability and safety [19 26].

Papillary thyroid cancer is the most common histological type detected in pregnant women, and in most series 90% to 95% of thyroid carcinoma diagnosed are Stage I disease, with the majority found in the first trimester of pregnancy during the first antenatal visit. The predominance of papillary cancer may be an important factor favouring localized disease, as these cancers metastasize slowly, and mostly in the lymphatic system, whereas less common follicular cancers tend to spread via angio-invasion with a higher frequency of distant metastasis. Although thyroid cancer during pregnancy may have a faster growth [27 28] since hormonal factors (mainly HCG) may ac-

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Box 1.

Differentiated Thyroid Cancer (DTC) – cancer arising from follicular thyroid cells

Mostly diagnosed in young people, DTC usually has a good prognosis with an overall 90-95% long-term disease-free survival for early stage or low risk tumours, which represent the vast majority of tumours diagnosed below 40-45 years of age. According to the current staging score, DTCs of any dimension, even with nodal invasion, for patients below 45 years of age, are classified as Stage I tumours, and usually pregnant patients are below 45 years of age. Genetic alterations activating a common pathway of the RET-RAS-BRAF signalling cascade and other chromosomal rearrangements have been identified in most DTC. The existence of common genomic changes between DTC and anaplastic carcinoma may provide convincing proof of the multi-step carcinogenesis hypothesis in which cancer cells are produced from well-differentiated benign cells by transformation caused by accumulating damage to their genome

Although gene expression in thyroid cancer reveals highly consistent profiles, a second hypothesis has been proposed, which can possibly explain other "non-RET" tumours: namely foetal cell carcinogenesis, according to which cancer cells are derived from the remnants of foetal thyroid cells, or from stem cells instead of differentiated follicular cells. Both hypotheses can be valid and coexist, and the second (foetal-cell carcinogenesis) could explain some cases of unusual, rapidly growing DTC. Both hypotheses would suggest a higher thyroid neoplasm proliferation in stimulated thyroid tissue during pregnancy or adolescence, though even in growing tissues these cancers show a very good prognosis.

The best treatment for nearly all identified malignant thyroid neoplasm is surgery. The aim of the primary treatment is an adequate excision of the primary tumour and any loco-regional extension. Considerable controversy still exists over the optimal extent of primary surgical resection. According to the extent of the disease, hemithyroidectomy or radical thyroidectomy is performed. As nodal spread is relatively common, initial surgical exploration should include careful examination of the central compartment nodes (paratracheal and tracheoesophageal) as well as dissection of clinically suspicious nodes for frozen section examination. Nodes in the jugular chains should also be carefully examined with US before surgery and, when suspicious, FNAB should be obtained. If nodal involvement is confirmed, total thyroidectomy and modified radical neck dissection are indicated.

Adjuvant therapies

Thyroid hormones – Endocrine therapy: post-operative oral administration of supraphysiologic oral doses of levothyroxine are used assuming that the suppression of endogenous production of TSH deprives TSH-dependent DTC cells of an important growth-promoting influence and the goal for basal serum TSH should be in the 0.1 to 0.4 mIU/L range.

When radical thyroidectomy is performed, the second most frequently used post-operative adjuvant therapy for non-pregnant patients with DTC is radioactive iodine (RAI, I-131) administered to eradicate persistent neck disease or distant metastatic lesions. This adjunctive therapy is supposed to destroy occult microscopic carcinoma within the thyroid remnant by being actively trapped both by normal and pathological thyroid cells, and to facilitate follow-up because serum thyroglobulin (HTG) measurements are more reliable after the destruction of residual normal thyroid tissue.

Follow-up

Follow-up is planned according to the stage of the disease and to the extent of the surgery performed. All patients should undergo neck ultrasound and serum assay for HTG, HTG antibodies, fT4 and TSH. For thyroidectomized high-risk, non-pregnant patients, I-131 scan is also indicated, and serum HTG measurements – performed both with thyroxine deprivation or under rTSH (recombinant human TSH) stimulation – is a useful and reliable marker of disease progression or persistence.

In our experience, the best follow-up method to detect loco-regional recurrences is, without question, neck sonography, followed by a meticulous physical examination by experienced personnel and, when indicated, ultrasound-guided FNA to confirm clinical suspicion of neck recurrence [41-45].

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celerate tumour progression, the real impact of pregnancy seems to be minimal. In fact, the rates of recurrence or the disease-free period do not differ between pregnant and non-pregnant women affected by the same disease [2 27 29-32]. Hod et al. reported a single case of accelerated tumour growth during pregnancy, but this would appear to be an exception rather than the rule [29].

In a large retrospective study on 595 pregnancy-associated thyroid cancers, Yasmeen et al. detected no difference in outcome, disease-free survival and morbidity when compared to age-matched non-pregnant women [2]. Differently from what is observed in other pregnancy-associated cancers, no metastasis of DTC to placenta or foetus has been reported. An association between thyroid cancer and parity or full-term pregnancy has been assessed in many studies without significant or conclusive results [6].

During pregnancy, cellular immunity undergoes changes, as reflected by a decrease in T-cell number. Pregnancy-associated immune tolerance, designed for foetal survival, might enhance disease progression. However, according to literature data and our own experience pregnancy after thyroid cancer has been shown to have no significant

effect on morbidity, disease-free period or survival time. Pregnant women with thyroid cancer have been shown to have favourable outcomes regardless of the timing of diagnosis [1 32 33].

Guidelines for evaluation and treatment of thyroid cancer must consider the gestational age but also the patients' desires. Detecting a thyroid cancer during pregnancy should not be a reason for termination of pregnancy, and in the large majority of cases it does not require urgent surgery [4].

The problem of pregnancy-associated thyroid cancer can affect three groups of patients:

1. New diagnosis
Patients with no prior history of cancer, in whom a malignant thyroid nodule is suspected or diagnosed during pregnancy.

For these patients, surgery could be safely performed during the mid-trimester or delayed until delivery without worsening prognosis [30 34]. Thyroidectomy during pregnancy has not been associated with adverse maternal or neonatal outcomes [35 36]. There are no indications for ter-

Box 2.

Medullary Thyroid Cancer (MTC) – cancer arising from parafollicular thyroid cells

Medullary carcinoma of the thyroid (MTC) constitutes approximately 5-10% of thyroid cancers, although there are no precise figures for incidence and survival rates because of the large geographic variations, mainly due to its familial pattern. Although uncommon, MTC is interesting because of its biochemical and genetic features and clinical association, both in autosomal-dominant inherited syndromes with incomplete penetrance (MEN IIA and IIB), and in the non-MEN forms.

Familial cases account for about 30% of MTCs. The occurrence of MTC in both sporadic and familial forms makes the clinical approach to this tumour different from that to other thyroid tumours. First, patients with MTC should always be suspected of carrying the genetic form of the disease. Secondly, the possible presence of associated conditions, such as pheochromocytoma, should be recognized before submitting patients to thyroidectomy. Lastly, since the clinical behaviour of MTC is extremely variable, this tumour represents a true therapeutic challenge.

MTC arises from C cells secreting calcitonin, a 32-amino acid peptide. Calcitonin is the most clinically useful biochemical marker for these tumours, and C cell hyperplasia represents a pre-cancerous stage. These neuroendocrine cells are believed to be of neural crest origin, thus having a separate lineage from the endoderm-derived follicular thyroid cells. For this reason, in addition to calcitonin-gene products, such as calcitonin CGRP (calcitonin-gene-related-peptide) and C-CAP (katacalcin), MTC cells express several other biochemical markers that reflect the features of diffuse neuroendocrine system, implicated in the pathogenesis of the symptoms (flushing, diarrhoea, carcinoid syndrome or Cushing's syndrome) that may occur in patients with advanced disease. These cells can also produce prostaglandins and other neuroendocrine markers such as chromogranin A, sometimes used together with calcitonin and CEA in MTC patients during follow-up.

When dealing with MTC, we should always bear in mind that these patients may be the index-case for one of the familial forms of the disease: pre-symptomatic screening of relatives of MTC patients enables early diagnosis of this malignancy. Early diagnosis rather than more extensive surgery may improve survival and reduce recurrences, mostly in the MEN IIB form of MTC, which is highly aggressive.

Biochemical screening of familial disease consists of serum calcitonin evaluation, and genetic screening of individuals with a RET mutation may also be performed. In inherited forms, the initial germline mutation produces multiple foci of cells – the so-called C-cell hyperplasia – that are susceptible to tumour formation, and each MTC is the result of a second cell transformation in one of these susceptible clones.

Primary MTC lesions become visible at echography as solid masses, often with calcifications. Fine needle aspiration shows a mixture of round, polyhedral and spindle-shaped cells that may seem undifferentiated, and look like a variable amount of extra-cellular amyloid.

MTCs, like other neuroendocrine tumours, can express somatostatin receptors. Follow-up of MTC patients suspected for recurrence can therefore be performed by using the somatostatin analogue octreotide (octreoscan). The presence of somatostatin receptors provides the basis for treatment with long-acting analogues of somatostatin or with Y-octreotide (DOTATOC) in some patients.

MTC is somewhat more aggressive than papillary or follicular carcinoma. It locally extends into lymph nodes and into the surrounding muscles and trachea, and may invade lymphatic and blood vessels and metastasize in lungs, bones and liver. Sporadic MTC tumours are often monolateral with a single localization, while familial forms are mostly bilateral and often multifocal or diffuse. For these reasons, total thyroidectomy appears to be the appropriate approach to MTC. Central neck and upper mediastinum clearance and, in addition, mono or bilateral node dissection (depending on the extent of nodal involvement) is also advisable. The most appropriate treatment for clinical N0 tumours is still a matter of debate, but most surgeons prefer prophylactic node dissection because MTC metastasize in regional lymph nodes at a very early stage.

Surgery is the only treatment which is considered potentially curative for metastatic or recurrent medullary carcinoma. The role of radiotherapy is controversial as MTC is generally not believed to be radio-sensitive. Therapy with long-acting somatostatin analogues has been tested in metastatic disease, with some positive benefots in most patients. Radioactive iodine is ineffective because I-131 uptake by MTC cells is negligible. No reliably effective chemotherapeutic regimen has been identified. New drugs with anti-angiogenetic, anti-tyrosine kinase and anti-VEGF effects are currently under observation.

In conclusion, there are several ways to expedite the diagnosis of MTC and to follow-up patients after surgery: biochemical markers (e.g. CEA, calcitonin, katacalcin, chromogranin-A according to tumour staining), and scanning with specific ligands such as octreotide. Furthermore, there are new therapeutic approaches under validation for advanced or recurrent disease [46-48].

mination of pregnancy [4]. When surgery is planned during pregnancy, it is important to consider both gestational age and the type of general anaesthesia. Whenever possible, the operation should be performed during the second trimester or after delivery [37]. During the first trimester, which is the organogenesis period, general anaesthetic agents may have some teratogenic potential or may increase the risk of miscarriage. In the third trimester, surgery may induce premature labour. Physiological changes of pregnancy, such as increased heart rate and blood volume, may complicate general anaesthesia, and hypotension caused by *vena cava* compression of the uterus during a long period in the supine position may cause foetal hypoperfusion [1]. Postponing surgery to at least 6-7 months after diagnosis of DTC in the first trimester does not adversely affect prognosis; on the other hand, thyroidectomy can be safely performed in the second trimester of pregnancy or after delivery [15]. Thyroxin therapy should be started immediately after surgery because untreated hypothy-

roidism may expose the mother to a higher risk of disease recurrence and may have an adverse effect on cognitive function and regular growth of the offspring. Regular assessments of TSH and fT4 levels every 6/8 weeks during pregnancy and breast-feeding are required to ensure an adequate dose of levothyroxine. Follow-up may be carried out on a regular basis with ultrasound techniques and thyroglobulin assay, as in non-pregnant women. Radioiodine therapy, when needed, can be safely postponed until after breast- feeding.

2. "Cured" patients
Pregnant patients with a history of previously treated DTC with no evidence of recurrent or persistent disease by imaging and by thyroglobulin measurement.
Whether women treated for thyroid cancer should become pregnant was once a matter of concern, but current evidence suggests that DTC should not discourage intended pregnancy, with the usual recommendation to postpone it

to at least 6 months after radioiodine therapy. In spite of the theoretical proliferative stimulation caused by HCG and placental growth factors, published data indicate that there is no evidence that thyroid cancer can be influenced by pregnancy. In addition, follow-up studies have shown no significant increase in risk. Usually, patients are recommended to postpone pregnancy to 6-12 months after radioiodine (I-131) treatment to avoid a potentially higher risk of miscarriage in the first few months after radioiodine therapy and to allow time enough to exclude residual disease requiring further treatment [4 14 38]. Miscarriages or premature birth have raised concern about the use of radioactive iodine in a childbearing age due to the known mutagenic effect of radiation and the theoretical possibility that it may affect germ cells, thereby causing genetic damage, congenital abnormalities and malignancy in offspring. Virtually any person treated with any dosage of I-131 is at potential risk, but experimental evidence in animals and follow-up studies in humans has failed to reveal any statistically significant effects of I-131 on chromosomal abnormalities, congenital malformation or childhood cancers. In a large retrospective study, Dottorini et al. evaluated fertility and the long-term effects of I-131 therapy in 815 women. Among those children born from I-131 treated women, the authors found only one case of ventricular septal defect and patent ductus arteriosus [22 39 40]. A possible increase in the rate of miscarriages has been reported to occur in the early period after therapy, but it remains uncertain whether abortion can be caused either by I-131 itself, by the thyroid autoimmunity often associated with disease or by the hypothyroid-hyperprolactinaemic status accompanying I-131 therapy. At present, consensus has been reached on the fact that radioiodine treatment of DTC does not affect pregnancy outcome and does not appear to be associated with any genetic risk, with the usual recommendation to delay pregnancy for 6-12 months after radioiodine exposure, even if there is no evidence that pregnancy before this period could lead to a less favourable outcome [22 38].

3. Persistent or recurrent disease

Pregnant patients with the evidence of persistent disease despite therapy.
Management of these patients and providing evidence-based advice are obviously extremely difficult tasks. Patients with active DTC can be reassured that, as mentioned above, pregnancy itself does not appear to increase disease progression, and therefore a gap in treatment during pregnancy is not contraindicated. When a simple increase in serum Htg levels is observed, further therapy is not necessary. For patients with local recurrent disease, ultrasound controls by skilled hands is of outmost importance, both to help surgeons in selecting tissues for excision and to perform local therapy, such as alcoholization

of small lesions. For patients with advanced disease, ultrasound control of tissue growth can help in therapeutic decisions, such as timing of surgery. Whenever possible, surgery should be carried out during the second trimester or after delivery, as for newly diagnosed thyroid cancer.

For any patient, both with first diagnosis or recurrent disease, post-operative therapy for DTC is based on the administration of supraphysiologic "suppressive" oral doses of levothyroxine. This treatment has been widely used for more than 40 years, with the assumption that suppression of endogenous TSH deprives TSH-dependent DTC cells of the most important growth factor. Therefore, thyroxine therapy aims at suppressing pituitary secretion of TSH, as indicated by serum TSH levels below 0.05 mIU/L. In univariate analyses, thyroxine therapy apparently helps decrease cancer-related death rates among patients with PTC. Many series have reported reduced rates of tumour recurrence both in PTC and in FTC. Doses of L-thyroxine greater than 150/200 µg (at least 2 µg/kg/day) are usually needed to maintain maternal serum-free thyroxin concentrations within the upper third of the reference range and to suppress TSH levels. Usually the dosage needs to be increased as early as during the fifth week of gestation, and fT4 TSH monitoring is recommended every 6 weeks for adequate adjustment of dosage. After delivery, thyroxine dose can be gradually reduced to pre-pregnancy levels, while TSH levels should be constantly monitored [10 15].

Patients with MTC whose tumours deriving from C cells are not TSH-dependent do not require suppressive therapy, but only thyroxine replacement therapy after surgery, and the dosages are the same as those used for hypothyroidism.

Pregnancy status requires much more accuracy in assessing levothyroxine dosage to protect the foetus from maternal hypothyroidism because, as mentioned above, the mother is the only source of thyroid hormones for the embryo in the first trimester of pregnancy. With regards to pharmacokinetics, oral dosing produces therapeutic effects within 3-5 days. Approximately 40-80% of the oral dose is absorbed, with peak serum levels measured within 2-4 hour, and the half-life of the administered dose is approximately 1 week. The extent of absorption is increased in fasting status and decreased if there is inadequate intestinal absorption, often caused by other drugs, such as ferrous sulphate. Therefore, during pregnancy, thyroxin and ferrous sulphate doses should be spaced by at least 4 hours. There is limited but still important placental transfer of maternal T4 to the foetus [18], while placental type III deiodinase catalyzes the conversion of T4 to the more active form reverse-T3, which crosses the placental barrier, and to the less active 3,3'-diiodothyronine (T2), representing a homeostatic mechanism for maintaining T_3 production in the placenta when maternal serum T_4 concentrations are modified [18].

Frequent monitoring and adjustment of L-T4 dosages are very important because of large fluctuations of T4 me-

tabolism during pregnancy; calcium and D vitamin supplementation, often indispensable, must be carefully tailored [23] [24].

Conclusions

When treating thyroid cancer in pregnancy, 3 factors should be considered:

1. *The effect of cancer on pregnancy*: No metastasis to placenta or foetus – no IUGR.
   Pregnancy does not seem to be compromised by thyroid cancer.
2. *The effect of pregnancy on cancer: In vitro* accelerated cell growth, no effect seen *in vivo*.
   Survival and disease-free intervals identical in pregnant and non-pregnant women
3. *The effects of management modalities on pregnancy outcome*: No I-131, tailored therapy.
   Critical monthly adjustment of levothyroxine therapy: maintain fT4 in the upper third of reference range.

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