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 well 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 thyroxin 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 gravidiche 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

Acta Otorhinolaryngol Ital 2011;31:358-365
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. 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. This could support the hypothesis that sex hormones and, therefore, menstrual and reproductive events, may modify thyroid cancer risk in women, 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 thryiodectomy 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, 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. 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. 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.

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. 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 T4 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. In summary, Table I presents the changes in thyroid function during pregnancy. The changes in Table I can be explained by the increase in oestrogen levels, which stimulates the production of TBG and reduces the free fraction of T4, as well as the increase in HCG levels, which stimulates the production of TSH and reduces the free fraction of T4. Additionally, the changes in Table I can be explained by the increase in oestrogen levels, which stimulates the production of TBG and reduces the free fraction of T4, as well as the increase in HCG levels, which stimulates the production of TSH and reduces the free fraction of T4.

| Table I. Physiological changes in thyroid function during pregnancy. |
|-----------------|-----------------|
| Increase         | Decrease        |
| HCG (TSH–like effect) | TSH            |
| TBG, serum total T4 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, abruptio placentae, increased risk of miscarriage, foetal growth retardation, perinatal mortality and neonatal morbidity. 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. Vitamin D does not occur naturally in foods. Moreover, the usual recommendations to avoid sun exposure reduces dermal synthesis of vitamin D. 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, a prehormone, which is ultimately converted to 1,25-dihydroxyvitamin D, one of the most potent steroid hormones known. 1,25(OH)2D 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.

The active metabolite of vitamin D, 1,25-dihydroxyvitamin 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 infants. 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. 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.

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 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 radio-active 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.

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. Different 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.

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.

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.

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. Thyroidectomy during pregnancy has not been associated with adverse maternal or neonatal outcomes. There are no indications for ter-
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. 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 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. 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. Thyroxin therapy should be started immediately after surgery because untreated hypothyroidism 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. A miscarriage 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 ven-tricular septal defect and patent ductus arteriosus 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. 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.

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 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. 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, 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’-diodothyronine (T2), representing a homeostatic mechanism for maintaining T3 production in the placenta when maternal serum T3 concentrations are modified.

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. 21, 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.

References

1. Bradley PJ, Raghavan U. Cancers presenting in the head and neck during pregnancy. Curr Opin Otolaryngol Head Neck Surg 2004;12:76-81.
2. Yasmeen S, Cress R, Romano PS, et al. Thyroid cancer in pregnancy. Int J Gynecol Obstet 2005;91:15-20.
3. Hay I. Nodular thyroid disease diagnosed during pregnancy: how and when to treat. Thyroid 1999;9:667-70.
4. O’Connell TB, O’Doherty MJ. Differentiated thyroid cancer and pregnancy. Nucl Med Commun 2000;21:127-8.
5. Furlanetto TW, Nguyen LQ, Jameson JL. Estradiol increases proliferation and down-regulates the sodium/iodide symporter gene in FRTL-5 cells. Endocrinology 1999;140:5705-11.
6. Truong T, Orsi L, Dubourdieu D, et al. Role of goiter and of menstrual and reproductive factors in thyroid cancer: a population-based case-control study in New Caledonia (South Pacific), a very high incidence area. Am J Epidemiol 2005;161:1056-65.
7. Patel J, Landers K Li H et al. Thyroid hormones and fetal neurological development. J Endocrinol 2011;209:1-8.
8. Pop VI, Brouwers EP, Vader HL, et al. Maternal Hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. Clin Endocrinol (Oxf) 2003;59:282-8.
9. Moreale de Escobar G, Obregon MJ, Escobar del Rey F. Is neuropsychological development related to maternal hypothyroidism or to maternal hypothyroxinaemia? J Clin Endocrinol Metab 2000;85:3975-87.
10. Glimoer D. Management of hypo- and hyperthyroidism during pregnancy. Growth Horm IGF Res 2003;13(Suppl A):S45-54.
11. Shah MS, Davies TF, Stagnaro-Green A. The thyroid during pregnancy: a physiological and pathological stress test. Minerva Endocrinol 2003;28:233-45.
12. Alexander EK, Marqusee E, Lawrence J, et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004;351:241-9.
13. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med 1999;341:549-55.
14. Lazarus JH. Thyroid disorders associated with pregnancy etiology, diagnosis and management. Treat Endocrinol 2005;4:31-41.
15. Lao TT. Thyroid disorders in pregnancy. Curr Opin Obstet Gynecol 2005;17:123-7.
16. Obregon MJ, Calvo RM, Escobar del Rey F, et al. Thyroid hormones and fetal development. In: Pinchera A, Mann K, Hostalec U, editors. The thyroid and age. Stuttgart, Germany: Schattauer Verlagsgesellschaft mbH; 1998. pp. 49-73.
17. Glimoer D. Thyroid disease during pregnancy. In: Braverman LE, Utiger D, editors. Werner & Ingbar’s The Thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 1086-108.
18. Burrow GN, Fisher DA, Larsen PR. Maternal and fetal thyroid function. N Engl J Med 1994;331:1072-8.
19. Neale D, Burrow G. Thyroid disease in pregnancy. Obstet Gynecol Clin N Am 2004;31:893-905.
20. Santisteban P. Development and anatomy of the hypothalamic-pituitary-thyroid axis. In: Braverman LE, Utiger D, editors. Werner & Ingbar’s The Thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 8-26.
21. Blazer S, Moreh-Waterman Y, Miller-Lotan R, et al. Maternal hypothyroidism may affect fetal growth and neonatal thyroid function. Obstet Gynecol 2003;102:232-41.
22. Krassas GE. Thyroid disease and female reproduction. Fertil Steril 2000;74:1063-70.
23. Speker B. Vit D requirement during pregnancy. Am J Clin Nutr 2004;80(Suppl):1740-7.
24. Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern CMAJ 2006;174:1287-90.
25. McGrath J. Does “imprinting” with low prenatal vitamin D contribute to the risk of various adult disorders? Med Hypotheses 2001;56:367-71.
26. LeBeau SO, Mandel SJ. Thyroid disorder during pregnancy. Endocrinol metab Clin North Am 2006;35:117-36.
27. Rosen IB, Korman M, Walfish PG. Thyroid nodular disease in pregnancy: current diagnosis and treatment. Clin Obstet Gynecol 1997;40:81-9.
28. Kobayashi K, Tanaka Y, Ishiguro S, et al. Rapidly growing thyroid carcinoma during pregnancy. J Surg Oncol 1994;66:61-4.
29. Hod M, Sharon R, Friedman S, et al. Pregnancy and thyroid carcinoma: A review of incidence, course and prognosis. Obstet Gynecol Surv 1989;44:774-9.
30. Chlo W, Mc Dougall IR. Thyroid cancer in pregnant women: diagnostic and therapeutic management. Thyroid 1994;4:433-5.
31. Mestman JH, Goodwin M, Montoro MM. Thyroid disorders of pregnancy. Endocrinol metab Clin North Am 1995;24:41-71.
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32 Zamperini P, Gibelli B, Gilardi D, et al. Pregnancy and thyroid cancer: ultrasound study of foetal thyroid. ACTA Otorhinolaryngol Ital 2009;29:339-44.

33 Moosa M, Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metab 1997;82:2862-6.

34 Tan GH, Gharib H, Goellner JR, et al. Management of thyroid nodules in pregnancy. Arch Intern Med 1996;156:2317-20.

35 Hamer CL, McCready VR. Thyroid cancer: differentiated carcinoma. Cancer Treat Rev 1996;22:161-77.

36 Vini L, Hyer S, Pratt B, et al. Management of differentiated thyroid cancer diagnosed during pregnancy. Eur J Endocrinol 1999;140:404-6.

37 Nam KH, Yoon JH, Chang HS, et al. Optimal timing of surgery in well-differentiated thyroid carcinoma detected during pregnancy. J Surg Oncol Sep 2005;91:199-203.

38 Schlumberger M, De Vathaire F, Ceccarelli C, et al. Parmenier C. Exposure to radioactive iodine-131 scintigraphy or therapy does not preclude pregnancy in thyroid cancer patients. J Nucl Med 1996;37:612-5.

39 Bal C, Kumar A, Tripathi M, et al. High-dose radioiodine treatment for differentiated thyroid carcinoma is not associated with change in female fertility or any genetic risk to the offspring. Int J Radiat Oncol Biol Phys 2005;63:449-55.

40 Dottorini ME, Lomuscio G, Mazzucchelli L, et al. Assessment of female fertility and carcinogenesis after I-131 therapy for differentiated thyroid cancer. J Nucl Med 1995;36:21-7.

41 Takano T, Amino N. Fetal cell carcinogenesis: a new hypothesis for better understanding of thyroid carcinoma. Thyroid 2005;15:432-8.

42 Thomas T, Nowka K, Lan L, et al. Expression of endoderm stem cell markers: evidence for the presence of adult stem cells in human thyroid glands. Thyroid 2006;16:537-44.

43 Zhang P, Zuo H, Ozaki T, et al. Cancer stem cell hypothesis in thyroid cancer. Pathol Int 2006;56:485-9.

44 Gibelli B, El-Fattah A, Giugliano G, et al. Thyroid stem cells – danger or resource? Acta Otorhinolaryngol Ital 2009;29:290-5.

45 Kondo T, Ezzat S, Asa SL. Pathogenic mechanism in thyroid follicular-cell neoplasia. Nat Rev Cancer 2006;6:292-306.

46 Gagel RF, Hoff A, O, Cote GJ. Medullary thyroid carcinoma In: Braverman LE, Utiger D, editors. Werner & Ingbar’s The Thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. pp. 967-89.

47 Gim O, Dralle H. Therapy for medullary thyroid cancer. In: Biersack HJ, Grunwald F, editors. Thyroid Cancer. Berlin: Springer Verlag; 2005. pp. 335-47.

48 Raue F, Raue FK. Diagnosis of medullary thyroid cancer. In: Biersack HJ, Grunwald F, editors. Thyroid Cancer. Berlin: Springer Verlag; 2005. pp. 297-310.

Received: March 20, 2011 - Accepted: May 15, 2011

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