

Pregnancy and thyroid cancer: ultrasound study of foetal thyroid

Gravidanza e carcinoma tiroideo: studio ecografico della tiroide fetale

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SUMMARY

Thyroid cancer is the most common endocrine malignancy, more frequently diagnosed in young women during childbearing age and approximately 10% of all thyroid cancers are diagnosed during pregnancy or in the early post-partum period. 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 cancer. Pregnancy after treatment of thyroid carcinoma requires both maternal and foetal controls. Of utmost importance is to ensure adequate maintenance of maternal levels of levothyroxine, needed by both the foetal central nervous system for its normal maturation and the mother to avoid possible recurrence or spread of the disease. In the present investigation, to confirm normal foetal growth and foetal thyroid development, an ultrasound study of the foetal thyroid was performed in 40 full term pregnancies in 32 women receiving levothyroxine treatment for previously treated thyroid cancer. In patients undergoing either suppressive or substitutive levothyroxine treatment, foetal thyroid growth was noted to be normal in all the cases, newborn thyroid status was always normal, and the incidence of maternal morbidity was not influenced. In the present study group, pregnancy does not appear to compromise mother's disease-free interval, nor to be compromised by thyroid cancer treatment. Results of the present study confirm that regular adjustment of levothyroxine treatment is of utmost importance for both maternal and foetal well-being and that foetal thyroid ultrasound study may add useful and reassuring data about child well-being.

KEY WORDS: Thyroid cancer • Foetal thyroid • Pregnancy • Ultrasound

RIASSUNTO

Il carcinoma della tiroide è la neoplasia endocrina più frequente, si presenta spesso in donne in età fertile, per questo motivo il 10% di tutti i carcinomi tiroidei viene diagnosticato durante la gravidanza o immediatamente dopo. I carcinomi tiroidei nei giovani presentano una prognosi eccellente e la sopravvivenza libera da malattia nelle donne cui viene diagnosticato durante la gravidanza non sembra differire da quella di pazienti non gravide con la stessa età e la stessa estensione di malattia, ma ovviamente la gravidanza dopo terapia per carcinoma tiroideo necessita un controllo duplice, sia per la madre che per il feto. Mantenere adeguati livelli di levotiroxina è di estrema importanza sia per la maturazione fetale, in particolare del sistema nervoso centrale, sia per proteggere la madre da possibili recidive di malattia. Le preoccupazioni maggiori riguardano gli effetti sul feto della terapia TSH-soppressiva e della terapia radio metabolica con I-131. Per confermare la sicurezza delle terapie sono state studiate anche con valutazione ecografica le tiroidi fetali in 40 gravidanze di 32 pazienti trattate con levotiroxina dopo chirurgia per carcinoma tiroideo. Sia per le pazienti sottoposte a terapia sostitutiva che per quelle in terapia TSH soppressiva lo studio ecografico della tiroide fetale si mostrò entro le curve di normalità. Per le pazienti di questo studio la gravidanza non sembra compromettere l'intervallo libero da malattia né essere compromessa dalle terapie utilizzate per il pregresso carcinoma tiroideo. Si conferma in questo studio che un regolare adeguamento della terapia con levotiroxina è di estrema importanza, e che lo studio ecografico della tiroide fetale può aggiungere informazioni rassicuranti sul benessere fetale.

PAROLE CHIAVE: Carcinoma della tiroide • Tiroide fetale • Gravidanza • Ecografia

Acta Otorhinolaryngol Ital 2009;29:339-344

Introduction

Maternal and foetal thyroid physiology

The thyroid is the first endocrine gland to appear during embryonic development and its hormones are major factors for normal foetal brain development. Until the end of the first trimester, when the hypothalamic-pituitary-thyroid axis becomes functional, the foetal brain is strictly dependent on the local de-iodination of maternal thyrox-

ine¹⁻⁶. During normal pregnancy HCG mimics TSH effects on the thyroid gland, resulting in a thyroid volume increase, and increase the total thyroxine pool as well as increases in thyroxine-binding globulin (TBG) and total T4, and reduced free fraction, that reaches a plateau at normal non-pregnant levels by the 16th to 18th week of gestation⁶⁻¹² (Fig. 1). In hypothyroid or thyroidectomized pregnant women, these physiological hormone variations obviously do not occur and pharmacological

levothyroxine (l-T4) requirements increase by 30-50% from baseline, also reaching a plateau after the 16th to 20th week of gestation. Untreated hypothyroidism during pregnancy may increase the incidence of maternal hypertension, preeclampsia, anaemia, spontaneous abortion, stillbirth and low birth weight. Thyroid hormone deficiency may cause severe neurologic disorders, as well as impaired intellectual and cognitive development in the offspring. It is therefore vitally important to avoid hypothyroidism in pregnant women^{4 7 13-15}.

Maternal hormone balance is the most practical index of foetal thyroid status and pregnancy requires greater care in l-T4 dosing to protect the foetus. Frequent monitoring and adjustment of l-T4 dosage are important, on account of substantial fluctuations in its absorption and metabolism^{1 10}.

Thyroid cancer and pregnancy

Thyroid cancer is the most common endocrine malignancy, more frequently diagnosed in young women of childbearing age; and approximately 10% of all thyroid cancers are diagnosed during pregnancy or in the early post-partum period.

As a result of physiologic changes in the structure and function of the thyroid gland, pregnant women with malignant thyroid nodules are twice as likely to be asymptomatic, but clinical and ultrasound (US) findings are often sufficient to suspect the presence of a malignancy or a relapse of previously treated disease. Skilled examiners and good quality images are more reliable than any other technique in detecting and differentiating malignant from benign solid thyroid nodules, especially for small lesions. US guided fine-needle

aspiration biopsy (US-FNAB) is the diagnostic tool of choice, because of its reliability and safety^{10 11}.

When thyroid cancer is diagnosed during pregnancy, surgery could be performed in the mid-trimester or after delivery, and there is no evidence that either maternal or foetal outcome are influenced by early or delayed surgery^{3 10 16-20}. Two main subsets of thyroid cancer patients exist with different biological tumour behaviour and treatment protocols (regardless of pregnancy status).

1. Differentiated Thyroid Cancer (DTC): papillary and follicular thyroid cancer, any histology

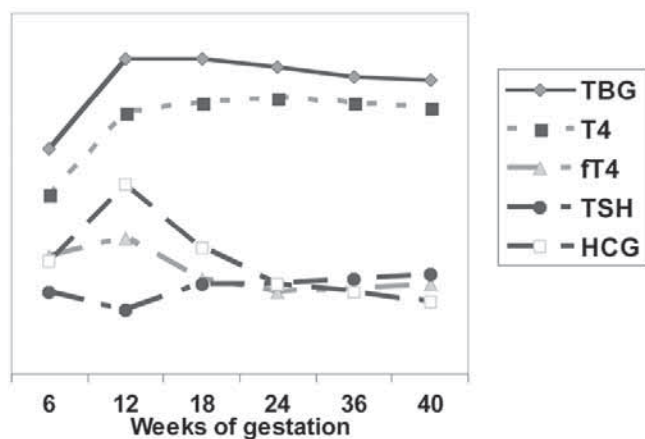
DTC is the most common endocrine malignancy with a pronounced female predilection especially during the 2nd to 4th (reproductive) decades. Thyroid cancer therefore ranks among the most common cancers during pregnancy, with a prevalence of 3.6-14 per 100.000 live births^{4 18 20-23}. For any patient treated on for follicular or papillary thyroid cancer, post-operative treatment consists in the administration of supra-physiologic "suppressive" oral doses of l-T4, to maintain low TSH levels. Suppression of endogenous TSH to serum levels < 0.05 mIU/l deprives TSH-dependent DTC cells of their most important growth factor. When caring for pregnant patients, keeping maternal free T4 level in the upper third of reference values should be the main goal. On the other hand, there is some concern regarding foetal well-being and the risk of miscarriage due to hyperthyroid status^{4 8}. Following delivery, the l-T4 dose is gradually reduced to the pre-pregnancy level, while TSH concentration should be constantly monitored^{2 3}.

Depending on the stage of the disease and prognosis the patient might have received post-operative radioiodide treatment prior to conception, and this is another cause for concern.

2. Medullary Thyroid Cancer (MTC): sporadic or familial or MEN 2 syndromes

Medullary carcinoma accounts for approximately 5-10% of thyroid cancers. More than 20% of MTC are hereditary diseases, and are observed both in the isolated form (familial MTC) or as part of the MEN 2 syndromes (MEN 2A and MEN2B). The clinical behaviour of MTC is extremely variable, and is somewhat more aggressive than papillary or follicular carcinoma. Patients with MTC (whose tumours derive from para-follicular C cells and are not TSH-dependent), do not require suppressive treatment, but only l-T4 replacement therapy after surgery, at the same dosages used in the treatment of hypothyroidism. C cells secrete a variety of peptides, with calcitonin being the most common, and calcitonin levels are thus elevated in MTC patients. Calcitonin and CEA are used as markers and are sensitive prognostic factors. Radioiodide treatment is not indicated in MTC therapy²⁴⁻²⁶.

Some concerns arise with regard to the safety of pregnancy following thyroid cancer surgical and medical treatments, therefore the aims of this study were:



TBG: thyroxin binding globulin; T4: thyroxin; FT4: free thyroxin; TSH: Thyroid-stimulating hormone (or thyrotropin); HCG: human chorionic gonadotropin.

Fig. 1. Thyroid hormones in pregnancy physiologic adaptation.

- 1) TBG (thyroxin binding globulin) increases due to stimulation from placental E2 and E3 (oestradiol and oestriol) and to reduced hepatic clearance. On account of this, maternal total T4 is very high, but FT4 is only moderately elevated.
- 2) HCG (human chorionic gonadotrophin) has thyrotropin-like activity and stimulates total T4 secretion.
- 3) TSH may decrease between week 8 to 14 of gestation, inhibited by increased T4.

1. to confirm that pregnancy is safe either for a previously treated mother and for her developing child, if adequate hormone supplementation is maintained;
2. to determine whether the foetal thyroid can develop and grow normally even with concomitant L-T4 suppressive therapy.

Materials and methods

Patients

From our female thyroid cancer population of child-bearing age, a restricted group was selected only on the basis of geographical proximity to our hospital to facilitate follow-up and US monitoring.

A total of 32 women with a diagnosis of thyroid neoplasia were followed. 31 patients previously treated with no evidence of recurrent or persistent disease ("cured" patients) and one patient who was diagnosed with thyroid cancer during the 6th week of pregnancy.

Overall, 40 full term pregnancies (2 twin and 8 repeated gestations) for a total of 42 babies, and 7 miscarriages were observed (Tables I, II). All patients received I-T4 treatment: 3 of 32 patients (one twin gestation) were diagnosed with MTC and underwent *substitutive* I-T4 therapy during gestation; 29 of 32 patients (one twin gestation) were diagnosed DTC and underwent *suppressive* I-T4 therapy. Of these, the only patient who was diagnosed during gestation and was submitted to thyroidectomy at the 16th week of gestation started I-T4 suppressive therapy after the diagnosis and before surgery.

Of the 29 patients with a diagnosis of DTC, 19 had also received previous I-131-treatment. (I-131-treatment is not administered to all patients, but is reserved only for patients in need on account of the risk score). One patient in the miscarriage group received repeated radioiodine therapy for a total dose of 12000 MBq 5 years before conceiving (Table II).

Gestational age was calculated on the basis of the last menstrual period and adjusted after the first US evaluation.

Patient Follow-up

Follow-up of pregnant patients was conducted as for any other thyroid cancer patient with clinical evaluation, neck US, TSH, fT4, thyroglobulin and Ab TG assay (or calcitonin and CEA assay for MTC patients), delaying I-131

Table II. Miscarriages: 6 patients, 7 miscarriages.

1)	8 wk abortion (trisomy 22) followed by full-term pregnancy healthy baby, in patient with previous trisomy 21, T1 NO papillary cancer, no I-131
2)	7 wk abortion, in 45 year-old patient after pT4 Hurtle cell cancer and I-131 therapy (total dose 3700 MBq)
3)	2 abortions at 7 th and 6 th week after pT1 papillary cancer, no I-131
4)	Blighted ovum in twin pregnancy, five years after surgery and I-131 (total dose 12000 MBq) for T2N1b papillary cancer
5)	7 wk abortion (followed by a full-term pregnancy) four years after surgery and I-131 (5400 MBq) for T4 N1 papillary cancer
6)	6 wk abortion (followed by a full-term pregnancy) two months after surgery for pT1NO papillary cancer, no I-131

scan and chest X-ray, when needed, after breast feeding. Free-T4 and TSH assays were repeated every 6 to 8 weeks, to adjust I-T4 dosage. Obstetric evaluations followed the usual protocol as in healthy pregnant women, with laboratory test and regular clinical and US monitoring, also with US study of foetal heart morphology and rhythm. After delivery monitoring was continued according to our regular non-pregnant schedule (follow-up ranges from 12 to 84 months after delivery).

Foetal thyroid ultrasound

Foetal thyroid growth was evaluated with US examinations performed by a single observer from the 16th week of gestation. The antero-posterior diameter of the foetal thyroid was measured on a transverse axial plane through the foetal neck at mid-level of the thyroid gland (Figs. 2, 3). The data obtained were compared to previously published normative data obtained in non-oncologic patients²⁷.

Results

In this study, 40 pregnancies were followed to term. Forty-one healthy newborns and 1 term death, due to umbilical cord prolapse were recorded. Seven patients (3 repeated gestations, for a total of 10 pregnancies, 2 of which twin) delivered their children via caesarean section (c-section). One patient developed hypertension near term. None of our patients developed pre-eclampsia or cardiac failure or arrhythmias needing specific treatment or I-T4 dosage reduction. No complications or preterm delivery nor disease recurrence were observed.

Table I. Pregnancy following thyroid cancer: 32 patients, 40 full term pregnancies, 42 babies.

	pT1	pT2	pT3	pT4	pN+	I-131	NO I-131	Term pregnancy	Abortion
29 DTC patients	9	7	1	12	15	19	10	35 pregnancies: 36 babies (6 repeated+ one twin)	7
3 MTC patients	1	1	1				//////	5 pregnancies: 6 babies (2 repeated+ one twin)	
Total	32 patients	40 full term pregnancy	42 babies	7 abortion					



Fig. 2. US image of foetal thyroid in a patient undergoing suppressive I-T4 treatment, previously treated with I-131 for papillary cancer (21st week).



Fig. 3. Foetal thyroid diameter in a patient undergoing substitutive I-T4 treatment after thyroidectomy for medullary cancer (22nd week).

Six patients, initially selected for the study, were excluded due to miscarriages; one of the 6 had 2 miscarriages for a total of 7 aborted gestations. However, 3 of them had also term pregnancies with healthy babies. Foetal demise resulted from chromosomal abnormalities in only one case: the mother had not been previously treated with radioiodine (Table II, pt. 1).

In patients undergoing either suppressive or substitutive I-T4 treatment, thyroid status in the newborn was always normal. One case of transient TSH suppression was recorded in a healthy newborn breast-fed during maternal suppressive I-T4 therapy. All APGAR scores were recorded as well as birth weight and length; all children were noticed to have normal values (weight ranging from 2750 g to 4080 g for single births and from 2500 g to 2800 g for twins babies). In the pregnancies followed for this study, the US measurements of foetal thyroid showed antero-posterior diameters within the normal or upper range of the normal data (Fig. 4).

Discussion

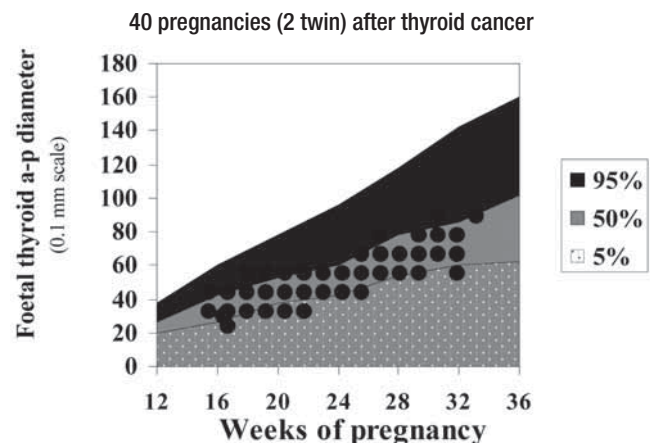
Pregnancy with or after thyroid cancer may cause considerable anxiety regarding the optimal timing of recommended treatments and especially about maternal and

neonatal morbidity. Current evidence suggests that proper management is, indeed, safe and that desired pregnancies should not be discouraged.

Effects of Pregnancy on Thyroid Neoplasia (Tumour growth, recurrence, morbidity)

Physiologic alterations such as hormonal modulation (mainly HCG surge during the first trimester) or associated immune tolerance intended to aid foetal development and survival have been thought to accelerate tumour growth and progression^{19,28,29}. However, the true impact of pregnancy seems to be minimal. An association between thyroid cancer, parity or full-term pregnancy has often been investigated but no significant or definitive conclusions have been drawn²². Recurrence rates or disease-free period do not differ in pregnant, versus non-pregnant, women affected by the same disease^{23,29-33}. Few cases of disease progression, during pregnancy, have been reported, but this would appear to be an exception rather than the rule^{31,34}. In a large retrospective study on 595 pregnancy-associated thyroid cancers, Yasmeen et al.²³ found no difference in outcome, disease-free survival and morbidity when compared to age-matched non-pregnant women. Unlike other pregnancy-associated cancers, no metastases of thyroid cancer to the placenta or the foetus have been reported to date.

The mutagenic effect of radiation and the theoretical possibility that I-131 may affect germ cells, causing miscarriages, congenital abnormalities or malignancy in the offspring, have raised concern about the use of radioactive iodine in childbearing age. Conventionally, patients who need post-surgical radioiodine (I-131) treatment are advised to postpone pregnancy until 6-12 months after treatment, in order to avoid the possible higher risk of miscarriage and to allow sufficient time to exclude recurrent disease requiring further treatment^{4,20,35}. All patients treated with any dosage of I-131 are at potential risk, but current information based on experimental evidence in animals and follow-up studies on humans, failed to reveal



Foetal thyroid antero-posterior diameter measurement, compared with growth curve in healthy women (95, 50, 5 percentiles on the right).

Fig. 4. Foetal thyroid growth and gestational age.

statistically significant effects of I-131 on chromosomal abnormalities, congenital malformation and childhood malignancy³⁶⁻³⁹. A possible increase in the rate of miscarriages has been reported to occur in the early period after treatment, but it remains uncertain whether abortion can be caused either by I-131 per se, or by thyroid autoimmunity, often associated with the disease, or by the hypothyroid-hyperprolactinemic status accompanying I-131 treatment. Only recently, a consensus has been reached on the fact that radioiodine treatment does not affect pregnancy outcomes 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 less favourable outcomes³⁹.

In agreement with published data, in our selected group of patients, thyroid cancer treatment does not appear to have a negative effect on the foetus. The miscarriages recorded in our series (Table II) appear to be due to non-oncological problems (such as maternal age or repeated chromosomal abnormalities) and 57% of those abortions occurred in patients who had not received I-131 treatment.

Effects of Oncologic Thyroid Therapies on Foetal Thyroid and Development of the Foetus

Adequate maternal thyroid function is essential for normal foetal thyroid development growth. Direct assessment of foetal thyroid status can be performed by means of invasive techniques such as amniotic fluid or foetal blood sampling that are not risk free for the mother and the unborn child. Imaging by means of ionizing radiation might lead to deleterious consequences for the foetus; other forms of imaging such as MRI are both expensive and technically difficult (unless an "open" machine is readily available) in pregnant patients. The optimal diagnostic tool should therefore be inexpensive, practical, safe and minimally invasive. US fulfils all these requirements and proven to be reliable^{8 10 27}.

Radaelli and Zamperini²⁷ demonstrated in more than 1.100 pregnancies, in women with a normal thyroid function, that the antero-posterior diameter of the foetal thyroid is consistent with progressive thyroid growth. In this study, we evaluated foetal thyroid growth with US examinations

performed by a single observer (P.Z.) and compared our findings with published normative data (Fig. 4). Regardless of whether the mother was submitted to substitutive or suppressive I-T4 treatment with adequate adjusted dosing, normal development of the child's thyroid was observed. In our study, the foetal thyroid US study simply confirms that adequate pharmacologic dosage can lead to normal gland development and function. Therefore optimal pharmacologic dosage and monitoring is absolutely essential during pregnancy and foetal thyroid US evaluation is recommended when a skilled examiner is available.

Our current and previous experience has shown that pregnancy after thyroid cancer has no significant effect on morbidity or disease-free period. Furthermore pregnant women with thyroid cancer have shown favourable outcomes regardless of the timing of oncologic diagnosis^{21 23 33 40}. Apart from "normal" maternal anxiety regarding previous disorder and treatment even in our restricted group of patients, we had no obstetrical or neonatal problem related to thyroid cancer. In our study group, no recurrence of disease has been detected even in patients treated for T4 cancer with node metastases and we had no adverse effects from I-T4 suppressive therapy. In agreement with published data, we are also of the opinion that pregnancy after thyroid cancer is possible and may be safe for both mother and child. Foetal thyroid US study may add useful and reassuring data concerning the child well-being, but meticulous I-T4 therapy adjustment as well as maternal and foetal control are of paramount and vital importance.

Pregnancy after thyroid cancer: take home messages

- Normal foetal growth, no IUGR (intra-uterine growth retard).
- No difference in outcome due to previous treatment (I-131 or not).
- More abortions due to non-oncological problems.
- Normal foetal thyroid growth either with replacement or suppressive I-T4 therapy.
- Maintain maternal fT4 in the upper third of normal range.

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Received: October 15, 2009 - Accepted: November 3, 2009

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