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Recombinant human thyrotropin to help confirm lack of evidence of radiation-induced differentiated thyroid cancer in young women seeking pregnancy

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Abstract

BACKGROUND: Women with a history of differentiated thyroid carcinoma who are contemplating pregnancy may wish reassurance regarding apparent remission. However, the thyroid hormone withdrawal needed to obtain serum thyroglobulin testing (Tg) results in weeks-long biochemical and clinical hypothyroidism, which could increase miscarriage and fetal death rates if pregnancy occurred during withdrawal of thyroxine or soon thereafter. Recombinant human thyrotropin (rhTSH) elevates thyrotropin exogenously, allowing uninterrupted thyroid hormone therapy and avoids hypothyroidism.

MATERIAL AND METHODS: Thirty female radiation-induced papillary thyroid carcinoma survivors who had undergone total- or near-total thyroidectomy and who were now seeking pregnancy (mean age 23.9 ± 1.8 years), and who were considered cancer-free by local standards, underwent rhTSH-aided Tg testing to help confirm remission. At the time of rhTSH testing, mean follow-up after primary surgical treatment was 11.1 ± 3.9 years, and all patients had negative neck ultrasonography, undetectable unstimulated serum Tg (< 0.2 ng/mL) and no interfering anti-Tg antibodies. However, based on T3, N1 or M1 status, 28/30 (93.3%) patients had high recurrence risk.

RESULTS: rhTSH produced no serum Tg increase in 27/30 women (90.0%). Serum Tg increases to 0.4-0.9 ng/ml were observed in 3 women, but careful neck ultrasonography found no lymphadenopathy. Reassured about their remission, 14/30 women (46%) have become pregnant and delivered healthy children in the 3 years since rhTSH-aided testing.

CONCLUSIONS: rhTSH-aided Tg testing is useful in confirming absence of tumor in female patients with a history of radiation-induced thyroid cancer who are seeking pregnancy, but who also have a high risk of thyroid cancer recurrence.

KEY words: radiation-induced differentiated thyroid carcinoma, serum thyroglobulin testing, recombinant human thyroid-stimulating hormone, pregnancy, remission, recurrence

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Background

Dramatically increased differentiated thyroid carcinoma (DTC) incidence in the young was the greatest public health consequence of the 1986 Chernobyl nuclear reactor disaster. By 2006, nearly 5,000 DTC cases had been diagnosed among the population that was ≤ 18 years old at the time of the accident. Fortunately, although radiation-induced DTC shows aggressive properties including frequent metastasis, even in young patients with advanced tumors, treatment has been highly effective and cure frequent [1–3].

Therefore, a unique situation occurs in Belarus, where a large number of young reproductive-age women is under endocrinologists' observation because of a DTC history. Because of the high recurrence risk in patients apparently cured of advanced disease, these women receive long-term follow-up generally including periodic physical examination, neck ultrasonography (US), serum thyroglobulin (Tg) measurement using modern assays and whole-body scintigraphy (WBS). For optimal sensitivity, the latter two procedures require serum thyrotropin elevation [3–5]. In this (near) totally-thyroidectomized population, such elevation is attained through thyroid hormone withdrawal (THW) rather than through recombinant human thyroid-stimulating hormone (rhTSH) administration which, due to limited financial resources, has not been readily available in Belarus [3].

Pregnancy appears to stimulate normal thyroid growth as well as Tg production, and is a state of reduced immune function [6–9]. Additionally, although data on this possible relationship are conflicting [3, 7, 9–13], increased estrogen concentrations have been postulated to play a role in thyroid cancer growth [14]. It thus is reasonable for DTC survivors planning to have children, as well as their physicians, to be concerned that pregnancy may be associated with an increased risk of DTC recurrence or progression [7, 15].

Reports [6, 8] exist that DTC survivors who are apparently free of recurrence can become pregnant without any unfavorable impact on their course. Therefore, it is desirable in patients planning pregnancy to obtain reassurance of cure, or to detect and eliminate any residual disease, before pregnancy is attempted. However, the THW needed to stimulate Tg testing and WBS results in weeks-long biochemical and most often also clinical hypothyroidism, and even minimal hypothyroidism can increase miscarriage and fetal death rates and also may adversely affect the offspring's cognitive development [6, 12, 16, 17].

As an exogenous source of TSH, rhTSH prevents from interruption of thyroid hormone therapy, and hence, hypothyroid metabolic impairment or morbidity, entailed by raising TSH endogenously with THW. Therefore when the manufacturer donated 30 rhTSH kits to our center, the concept emerged to apply those kits to aid follow-up examinations confirming the disease-free status of young Chernobyl-induced DTC survivors who were attempting to become pregnant. Although rhTSH has been used in hundreds of thousands of adults [10, 11, 18, 19] and some juveniles [20], limited data have been published regarding rhTSH use in young patients with radiation-induced DTC. For that reason, we undertook this retrospective analysis of our single-center experience with rhTSH stimulation of diagnostic procedures to rule out disease in members of this group who were planning pregnancy.

Table 1. Selected characteristics of 30 female thyroid cancer patients

Characteristic	Value
Age at rhTSH-aided testing, years	
Mean ± SD	23.9 ± 1.8
Median (range)	23.6 (20–29)
Age at time of Chernobyl accident, years	
Mean ± SD	1.6 ± 1.6
Median (range)	1.2 (0–7)
T stage[a]	
T1	20
T2	7
T3	3
N stage[a]	
N0	2
N1a	9
N1b	19
M stage[a]	
M0	27
M1	3
Number of prior radioiodine therapies, % (n) of patients	
1	27% (8)
2	47% (14)
3	17% (5)
≥ 5	10% (3)
Cumulative therapeutic radioiodine activity, GBq	
Mean ± SD	8.9 ± 6.1
Median (range)	7.2 (2.2–29.3)
Daily LT4 dose at time of study entry	
Mean ± SD, μg/kg	2.6 ± 0.6
On >3 μg/kg, % (n)	10% (3)
On calcium therapy, % (n)	50% (15)
Interval disease-free at time of rhTSH-aided testing, years	
Mean ± SD	7.7 ± 3.6
Median (range)	7.8 (3.5–17)
Live births before rhTSH-aided testing, % (n) of patients	
0	77% (23)
1	23% (7)

DTC — differentiated thyroid carcinoma; LT4 — levothyroxine; SD — standard deviation; TNM — tumor, nodes, metastasis; [a]TNM according to the American Joint Committee on Cancer/Union Internationale Contre le Cancer classification of 2002

Materials and methods

Patients

This cohort analysis involved 30 consecutive eligible patients followed at the National Dispensary of Medical Rehabilitation and Hydrotherapy in Minsk, Belarus. Selected patient characteristics are seen in Table 1; based on T3, N1 or M1 status, 28/30 patients (93.3%) were considered to be at high recurrence risk. Inclusion criteria for the rhTSH-aided diagnostic

procedures were: near-term plans to become pregnant; history of histologically-proven, radiation-induced DTC; (near-) total thyroidectomy with neck lymph node dissection; and > 1 yr interval since the last therapeutic radioiodine activity. Moreover, patients had to have no evident residual DTC according to these criteria: no pathological uptake outside the thyroid bed on WBS performed ≤ 1 yr before the rhTSH-aided procedures; undetectable (< 0.2 ng/mL) unstimulated serum Tg or stimulated serum Tg levels < 1 ng/ml ≥ 6 months before the procedures; absence of interfering Tg antibodies (TgAb) at the time of the procedure; no clinical or US signs of residual disease at the time of the rhTSH-aided testing.

Patients were given rhTSH (Thyrogen, thyrotropin alfa, Genzyme, Cambridge, MA, USA), 0.9 mg, by intramuscular injection on 2 consecutive days while on levothyroxine therapy. Blood samples were drawn on day 1 ("baseline," immediately before the first rhTSH injection), day 3 (1 day after the second rhTSH injection) and day 5 (3 days after the second rhTSH injection) for determination of serum TSH, Tg, TgAB, and anti-thyroperoxidase (TPO) antibody levels.

TSH was quantified by radioimmunoassay (DPC, Biermann, Germany; normal range in healthy adults: 0.3–4.0 mIU/l). Serum Tg was measured with an immunoradiometric assay (Thermo Fisher B.R.A.H.M.S., Henningsdorf, Germany). The assay has a functional sensitivity of 0.2 ng/ml; results lower or equal to this level were considered undetectable, but were reported as 0.2 ng/ml. TgAb and anti-TPO autoantibodies were evaluated by enzyme immunoassay (Phadia Pharmacia, Freiburg, Germany), with negative values defined as < 100 IU/ml. Quality control of all biochemical testing was done at the Department of Nuclear Medicine, Wurzburg University, Würzburg, Germany.

All patients gave informed consent for rhTSH-aided testing, and the protocol for such testing was approved by our Institutional Review Board.

Results

Table 2 presents mean values for all tested analytes.

TSH

Twenty-seven of 30 patients (90%) had suppressed baseline TSH (0.01-0.09 mIU/l); the remaining three had TSH of 1.6 – 4.0 mIU/l. TSH rose on average nearly 1600-fold the day after the rhTSH course, ranging from 46.0-227.2 mIU/l; 2 days later, the analyte had sharply decreased (by 90.9%) from the day 3 elevations, and ranged from 10.2 ± 4.3 mIU/l.

Tg

All 30 patients had undetectable baseline Tg (≤ 0.2 ng/ml). Serum Tg increased slightly after rhTSH stimulation in 3 patients (Figure 1):

— patient A, age 24 yr, had a 3.5-yr follow-up after apparent cure of T3/N1/M1 disease, and stimulated Tg of 0.9 ng/ml on day 5 (Cumulative therapeutic radioiodine activity 6,2 GBq);

— patient F., age 23 yr, had T1/N1/M0 disease, a 15.5-yr follow-up, and stimulated Tg of 0.7 ng/ml on day 5 (Cumulative therapeutic radioiodine activity 5,2 GBq);

Table 2. Serum TSH, Tg, TgAb and anti-TPOAb levels before and after rhTSH stimulation in 30 radiation-induced DTC survivors planning pregnancy

Analyte	Day 1	Day 3	Day 5
	(baseline; immediately before 1st rhTSH injection)	(1 day after 2nd rhTSH injection)	(3 days after 2nd rhTSH injection)
	Mean ± SD		
TSH, mIU/l	0.07 ± 0.1	111.5 ± 37.1	10.2 ± 4.3
Tg, ng/ml	0.2[a] ± 0.0	0.2[a] ± 0.0	0.2[a] ± 0.1
TgAb, IU/l[b]	36.0 ± 20.8	Not measured	9.4 ± 14.5
TPOAb, IU/l[b]	18.6 ± 15.3	Not measured	18.7 ± 13.1

DTC — differentiated thyroid cancer; rhTSH — recombinant human thyroid-stimulating hormone; SD — standard deviation; Tg — thyroglobulin; TgAb — anti-thyroglobulin autoantibodies; TPO — thyroperoxidase; TPOAb — anti-thyroperoxidase antibodies; TSH — thyroid-stimulating hormone; [a]undetectable values (< 0.2 ng/ml were reported as 0.2 ng/ml, the functional assay sensitivity; [b]titers < 100 IU/l were considered undetectable

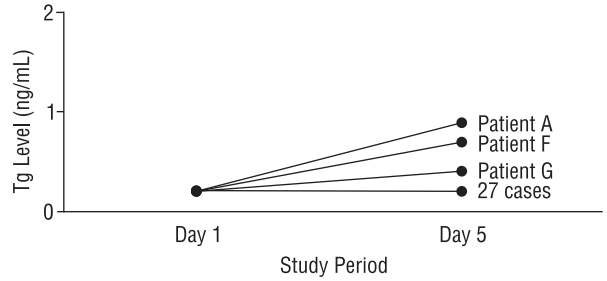

Figure 1. Individual serum Tg levels before and after rhTSH stimulation in 30 female radiation-induced DTC survivors

— patient G. age 23 yr, had T3/N1/M1 disease, a 15-yr follow-up, and stimulated Tg levels 0.4 ng/ml on day 5 (Cumulative therapeutic radioiodine activity 20,1 GBq).

None of these three patients had lymphadenopathy on neck US, and an additional measurement of serum Tg (on levothyroxine) in next 3 months was recommended.

TgAb and anti-TPO antibodies

In all 30 patients, TgAb and anti-TPO antibody titers were well below levels considered detectable both before and after the rhTSH course.

rhTSH tolerability

RhTSH-aided testing had no serious side effects, however 2 patients complained of some headache during investigation and 2 others had nausea.

Patients' courses and pregnancies since rhTSH-aided testing

The entire cohort has been re-evaluated regularly by physical exams, US, and unstimulated Tg testing during the 3 years after the rhTSH test. No patient demonstrated any evidence of disease in the time since the rhTSH-aided testing. Only one patient showed elevated titer TgAb antibodies after delivery of an infant.

In that interval, 16/30 (53.3%) women became pregnant, of whom 14/30 (46.6%) delivered a healthy child after an uneventful pregnancy, 2/30 (6.6%) had a miscarriage during early gestation, and 2/30 (6.6%) had a tubal pregnancy. Note that numerators add to more than 30 due to two events in some women. Among the live births, no congenital malformations or first year neonatal mortality was observed.

Regarding 3 patients with slightly increased serum Tg after rhTSH stimulation, none demonstrated any elevated Tg level (on levothyroxine) during subsequent follow-up. Two women delivered a healthy child. Patient A experienced a tubal pregnancy followed by a pregnancy that resulted with a healthy child. Patient G experienced a miscarriage in early gestation followed by a pregnancy that resulted with a healthy child. Patient F is still seeking pregnancy.

Two women underwent surgical intervention because one of them had ovarian cysts and endometriosis, while the other was diagnosed with craniapharyngioma and developed hypopituitarism after surgery.

Two additional women were under treatment for infertility. The other 8 women are still trying to become pregnant.

Discussion

The peak in radioinduced thyroid cancer incidence occurred in the early 1990's in Belarus, Ukraine and Russia after environmental contamination with radioactive iodine from the 1986 Chernobyl nuclear power plant catastrophe [1–3]. The accelerated onset of thyroid cancer may be attributable to radiation dose rate effects, sensitivity to the effects of ionizing radiation during early childhood, screening activity that enhanced case finding, and to endemic iodine deficiency in Eastern Europe [1, 11, 21].

The cohort of children and adolescents with radiation-induced thyroid cancer is currently entering the period of reproductive activity and child-bearing age [22]. Because of the propensity of juvenile DTC to spread aggressively, such patients are usually at high relapse risk and have been exposed to radioiodine therapy [2, 3]. These cancer survivors should have special medical considerations as they contemplate pregnancy. It would be valuable in young women believed likely to be free of thyroid cancer to confirm the absence of tumor before they become pregnant, and to perform this assessment without a long period of hypothyroidism during the time of pregnancy planning [6]. Prolonged hypothyroidism is related to exacerbation of concomitant illnesses or stimulation of tumor growth. Use of rhTSH to provide TSH stimulation exogenously allows to avoids many of these problems [4, 10, 18].

Recent studies suggest that in patients without apparent recurrence, pregnancy has no unfavorable health impact [6, 8, 15]. No restriction concerning seeking pregnancy exists when the following criteria are met: last iodine-131 treatment ≥ 12 months prior, normal clinical exam, normal neck US within 6 months prior, stimulated Tg < 2 ng/mL in the absence of known persistent or recurrent disease, or a > 50% decrease from peak Tg in conjunction with negative imaging in patients previously treated for metastases, TSH < 2.0 mIU/L [8, 10, 12]. In addition, ideally a woman will have favorable socioeconomic conditions that permit specialized follow-up, among other reasons to titrate the levothyroxine dose as needed to avoid hypothyroidism should pregnancy occur. Assuring that these criteria are met is particularly important in many young women who have persistent subclinical disease detected by highly sensitive Tg assays and neck US. Such low levels of serum Tg can be difficult to eradicate with additional radioactive iodine therapy or surgery [8].

The experience reported here demonstrates the effectiveness of using rhTSH to obtain further reassurance of the disease-free status of young women with a history of radiation-induced DTC who are planning pregnancy, while avoiding the hypothyroidism of THW. To confirm apparent cure, one should not rely simply on unstimulated Tg levels, since false negative Tg measurements using second-generation assays have been reported in about 20% of patients with isolated neck lymph node metastases and in 5% with small distant metastases, mainly in the lungs and not visible on X-rays [12, 14, 15].

In this study we observed that in period of 3 years (2009–2011) 14 of 30 women delivered a healthy child (46.6%) and 4/30 (13.3%) lost their pregnancy. We should emphasize that the majority of our patients (28 of 30) belonged to high risk group regarding possible tumor recurrence. Thus, testing of these women to be more certain of their tumor-free status prior to pregnancy was important.

In conclusion, rhTSH-aided Tg testing is useful in helping to better confirm absence of thyroid cancer in female thyroid cancer survivors who are seeking pregnancy. This might be particularly important in women with a history of radiation-induced thyroid cancer who are thought to have a high risk of thyroid cancer recurrence.

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