Recombinant Human Thyrotropin Use Resulting in Ovarian Hyperstimulation: An Unusual Side Effect

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What Is Known about This Topic

- Thyrogen® is commonly used for serum thyroglobulin testing, for radioiodine (¹³¹I) imaging in those patients unwilling to undergo thyroid hormone withdrawal, in patients unable to mount an adequate thyroid-stimulating hormone response to thyroid hormone withdrawal, in whom withdrawal was medically contraindicated and for ablation of thyroid remnants with ¹³¹I following near-total thyroidectomy for differentiated thyroid cancer having no metastatic disease. The most common side effects reported with Thyrogen use include upset stomach, headache, tiredness, vomiting, dizziness, prickling and tingling sensation, weakness, difficulty sleeping, and diarrhea.

What This Case Report Adds

- This case report highlights a hitherto unreported side effect of Thyrogen use in females of child-bearing age. Its use can result in transient ovarian hyperstimulation, especially in those patients needing Thyrogen administration for short time intervals.

Key Words

Recombinant human thyrotropin · Ovarian hyperstimulation · Positron emission tomography/computed tomography scan

Abstract

A 43-year-old female was administered recombinant human thyrotropin-α (Thyrogen®; Genzyme Corp., Cambridge, Mass., USA) before a fluorodeoxyglucose positron emission

tomography/computed tomography (PET/CT) scan as part of an evaluation of thyroid cancer recurrence. She was administered two doses of Thyrogen only 4 weeks before for stimulated thyroglobulin measurement. The PET/CT scan demonstrated enlarged ovaries which on subsequent conservative follow-up resolved. This transient hyperstimulated state of the ovaries was presumed to be related to Thyrogen injections received twice within a space of a month. Thyrogen is being increasingly used for raising the level of thyroid-stimulating hormone (TSH), besides thyroid hormone with-

drawal for suspected recurrence of differentiated thyroid carcinoma. Ovarian hyperstimulation has been reported as an iatrogenic complication for in vitro fertilization with the presence of human chorionic gonadotropin being invariably associated. Transient gestational thyrotoxicosis has been reported to be related to promiscuous activation of the thyrotropin receptor by chorionic gonadotropin. In our case it is possible that due to the promiscuous stimulation, thyrotropin caused a follicle-stimulating hormone (FSH)-like action resulting in ovarian hyperstimulation. The reason behind this could be the shared sequence identity of the hormone-binding domains of TSH and FSH receptors, or some mutation in the FSH receptor. In conclusion, our case highlights a potential side effect of administering Thyrogen in females of the reproductive age group.

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Introduction

Recombinant human thyrotropin- α (Thyrogen[®]; Genzyme Corp., Cambridge, Mass., USA) is increasingly being utilized in the management of differentiated thyroid cancer following thyroidectomy. It offers the advantage of avoidance of thyroid hormone withdrawal-induced hypothyroidism and its morbidity, and is employed as an adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without radioiodine (¹³¹I) imaging, and more recently as an adjunctive treatment for ¹³¹I ablation. We describe a 43-year-old female who underwent a Thyrogen stimulation protocol twice within 1 month and subsequently demonstrated transient enlarged hyperstimulated ovaries, and discuss possible physiologic mechanisms.

Case Report

A 43-year-old female with history of a follicular variant of papillary thyroid cancer after remote thyroidectomy and ¹³¹I treatment presented for ¹⁸F-2-deoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan for rising serum Tg levels. The patient had a long history of thyroid cancer and presented to us years after her initial diagnosis. In 1985, she was diagnosed with papillary thyroid cancer at age 16. She originally presented with an enlarging right-sided nodule in her neck and underwent a total thyroidectomy with removal of lymph nodes from the mediastinum and both sides of the neck. Pathology revealed a follicular variant of papillary thyroid cancer with metastasis to a single lymph node. Postoperatively and then again 6 months later, the patient received 138 and 136 mCi of ¹³¹I respectively and was main-

tained on thyroid hormone replacement. She underwent ¹³¹I scanning and neck ultrasound 5 years after the initial diagnosis and therapy which did not show any recurrence. The patient was recurrence-free in the ensuing 25 years, as indicated by periodic serum Tg measurements while on replacement thyroid hormone, negative neck ultrasounds, and lack of clinical disease. The anti-Tg antibody level was negative throughout.

In April 2011, she underwent Thyrogen stimulation according to the package insert, with serum Tg increase from 0.3 to 7.3 ng/ml. In July 2011, she underwent Thyrogen stimulation in combination with a ¹³¹I whole-body scan at another institution. The whole-body scan was negative and stimulated serum Tg was 3.8 ng/ml. Neck ultrasound was negative. Her endocrinologist suggested additional testing with an FDG PET/CT scan that time, which was not obtained when coverage was denied by her insurance. The patient had no complaints related to the Thyrogen stimulation procedure.

Meanwhile she had transvaginal ultrasound and MRI of the pelvis in December 2011 for menorrhagia, which revealed an enlarged lobular uterus with multiple fibroids, for which she underwent hysterectomy in January 2012. No other abnormalities were present and the ovaries were left at the time of hysterectomy. Of note, the patient did not report of any complications during her two previous successful pregnancies.

In September 2012 she underwent a Thyrogen protocol, with stimulated Tg 4.7 ng/ml, thyroid-stimulating hormone (TSH) measurements of 12.7 μ U/ml and Tg antibody level <20 IU/ml. Based on this and a prior positive rise in Tg following Thyrogen, she was referred for FDG PET/CT which was performed in conjunction with the Thyrogen stimulation protocol; she had received an intramuscular injection of Thyrogen 0.9 mg on the 2 preceding days before FDG injection and scan. She had received a total of four separate intramuscular injections of Thyrogen 0.9 mg during a 4-week period and remained asymptomatic.

The PET study did not reveal any abnormal FDG uptake or CT abnormality to suggest recurrent thyroid cancer. However, the scan demonstrated significantly enlarged bilateral ovaries at the pelvic inlet in a pattern that suggested a hyperstimulated state (fig. 1). We obtained the preoperative pelvic ultrasound and MRI from December 2011, which did not reveal any abnormality of the ovaries, indicating this was a new finding. We communicated the PET/CT findings to the referring endocrinologist at an outside facility and the patient underwent transabdominal pelvic ultrasound performed by her gynecologist 9 days after receiving Thyrogen, which confirmed enlarged bilateral ovaries. The right ovary measured 6.06 $\times$ 3.95 $\times$ 5.88 cm, corresponding to a volume of 73,696 mm³, and the left ovary measured 5.30 $\times$ 4.42 $\times$ 5.23 cm, corresponding to a volume of 54,150 mm³. The gynecologist conservatively followed her and repeated her transabdominal pelvic ultrasound 4 weeks later, which showed that both ovaries had returned to a normal size and appearance. We concluded that this transient change of the ovaries was related to Thyrogen injections received within an interval of a month. Of note, the patient did not report of any complications during her two previous successful pregnancies. We contacted Genzyme Corp. who then informed us that their database search did not find any reported case of ovarian hyperstimulation following Thyrogen administration.

Fig. 1. CT (a) and PET image in the axial plane (b) show enlarged bilateral ovaries at the pelvic inlet with no abnormal FDG uptake.

Discussion

This case demonstrates a relatively common management sequence for suspected recurrence of differentiated thyroid cancer that led to an unexpected discovery of ovarian stimulation. Patients with well-differentiated thyroid cancer generally undergo surgery, often thyroidectomy and long-term treatment with L-thyroxine at doses sufficient for suppression of pituitary production of thyrotropin (TSH) [1]. Eradication of iodine-avid tissue (benign or malignant) with radioactive iodine is not uncommon, as occurred in this patient. Despite the efficacy of surgery, ^{131}I ablation and L-thyroxine therapy for well-differentiated thyroid cancer, many patients suffer disease recurrence [2]. Measurements of serum Tg concentrations and neck ultrasound are used most frequently to monitor thyroid cancer patients for evidence of recurrence [1, 3]. ^{131}I whole-body imaging with TSH stimulation can localize sites of recurrence. The sensitivity of ^{131}I scanning and Tg measurement is limited by a small, relative amount of thyroid tissue present in patients treated by thyroidectomy and the potential for dedifferentiation and loss of iodine avidity of tumor cells compared to normal thyrocytes. For optimal sensitivity, both serum Tg measurement and ^{131}I imaging require stimulation of thyroid tissue by elevated TSH levels. This can be achieved either by thyroid hormone withdrawal for 4–6 weeks to achieve a TSH of ≥ 30 , or by stimulation of remaining thyroid cells by recombinant human TSH (rhTSH) [4]. FDG PET has been shown to be useful in patients after surgery and ablation, who have recurrent thyroid cancer as evidenced by elevated serum Tg values and negative ^{131}I scintigraphy [5, 6]. A meta-analysis exploring the role of TSH

for FDG PET in the diagnosis of recurrence and metastases of differentiated thyroid carcinoma with elevated Tg and negative scan concluded that TSH stimulation should be recommended for differentiated thyroid carcinoma patients undergoing PET scanning in such cases [7].

The initial use of exogenous TSH to augment ^{131}I uptake in thyroid cancer patients, using extracts from bovine pituitary glands, occurred over 60 years ago [8]. Between 1985 and 2000, thyroid hormone withdrawal to stimulate ^{131}I uptake became the norm with cessation of availability of bovine TSH in mid-1980s [9]. Pioneering work from the laboratories of Weintraub [10] and Kourides [11] in the late 1980s provided the primary sequence of the β -subunit of human TSH. The human pituitary α -glycoprotein subunit and the human TSH β -subunit were then separately cloned and co-expressed in human embryonal cells with recovery of rhTSH from the culture medium [12]. The process of rhTSH production was developed by Genzyme Corp. and was approved for use by the US FDA in December 1998 for serum Tg testing, for ^{131}I imaging in those patients unwilling to undergo thyroid hormone withdrawal and in patients unable to mount an adequate TSH response to thyroid hormone withdrawal or in whom withdrawal was medically contraindicated [9]. In December 2007, Thyrogen was additionally approved by FDA for ablation of thyroid remnants with ^{131}I following near-total thyroidectomy for differentiated thyroid cancer having no metastatic disease [13].

Ovarian hyperstimulation most often occurs as an iatrogenic complication of ovarian stimulation treatments for in-vitro fertilization, the incidence of severe forms ranging from 0.5 to 5% [14]. The clinical manifestations

vary from abdominal distention and discomfort to potentially life-threatening, massive ovarian enlargement and capillary leak with fluid sequestration in a third space [15]. The presence of human chorionic gonadotropin is invariably associated with this condition, though the pathophysiological mechanism remains undefined [16]. The overproduction of endogenous chorionic gonadotropin during pregnancy has been associated with spontaneous ovarian hyperstimulation syndrome, as well as with hyperemesis gravidarum and transient gestational thyrotoxicosis [17–20]. Transient gestational thyrotoxicosis appears to be due to promiscuous activation of the thyrotropin receptor by chorionic gonadotropin [21]. Follicle-stimulating hormone (FSH), luteinizing hormone, chorionic gonadotropin and TSH constitute the glycoprotein hormones made of a common α -subunit and specific β -subunits that share more than 40% amino acid sequence identities [22]. Although the corresponding glycoprotein hormone receptors (FSH receptor [23], luteinizing hormone/chorionic gonadotropin receptor [23, 24] and TSH receptor [25]) also display about 40% sequence identity in their hormone-binding domains, co-evolution of the hormone receptor couples resulted in the establishment of tight specificity barriers, preventing promiscuous activation under normal physiological conditions [26]. In this evolutionary context it is likely that the extremely high level of chorionic gonadotropin achieved during pregnancy in primates overrides the barrier of specificity and thus stimulates the TSH receptor in so-called promiscuous stimulation resulting in gestational hyperthyroidism.

There have been reported cases where mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin resulted in familial gestational hyperthyroidism [27]. In our case, it is possible that due to the promiscuous stimulation, thyrotropin caused FSH-like action resulting in ovarian hyperstimulation. The reason behind this could be the shared sequence identity of the hormone-binding domains of TSH and FSH receptors, or some mutation in the FSH receptor. There have been reported cases where ovarian hyperstimulation syndrome occurred due to mutation in the FSH receptor [28], which lends credence to our hypothesis. It is also plausible that in our case the repeated dose of Thyrogen within a 4-week period resulted in hyperstimulation of the ovaries through stimulation of FSH receptors. Because she remained asymptomatic and imaging was not performed when the patient had previously received Thyrogen, we cannot determine whether the stimulatory effect on the ovaries occurred occultly when she received a series of two rather than four injections.

This case highlights the need for awareness of potential physiologic effects beyond the thyroid, such as the ovaries, especially in patients who receive repeat Thyrogen doses for short intervals. In our case, conservative management and follow-up on ultrasound resulted in ovaries returning back to their normal size and the patient suffered no consequences. Also in our case, the raised Tg level in July 2011 (7.3 ng/ml) was probably false positive as it came down in September 2012 (4.8 ng/ml). However, the treating endocrinologists will continue to follow up her Tg levels.

Conclusion

In conclusion, our case highlights a potential side effect of administering Thyrogen in reproductive age group females, which has not been previously reported. All physicians involved in the care of female thyroid cancer patients who receive Thyrogen should be aware of this potential side effect, especially in those patients who might need Thyrogen administration for short time intervals. We emphasize the need for awareness of the potential physiologic effects of Thyrogen beyond the thyroid, especially the ovaries, and propose possible mechanisms which warrant additional investigation.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Singer PA, Cooper DS, Daniels GH, Ladenson PW, Greenspan FS, Levy EG, Braverman LE, Clark OH, McDougall IR, Ain KV, Dorfman SG: Treatment guidelines for patients with thyroid nodules and well-differentiated thyroid cancer. American Thyroid Association. Arch Intern Med 1996;156:2165–2172.
- 2 Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, Haugen BR, Ho M, Klein I, Ladenson PW, Robbins J, Ross DS, Specker B, Taylor T, Maxon HR: Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer 1998;83:1012–1021.
- 3 Ozata M, Suzuki S, Miyamoto T, Liu RT, Fierro-Renoy F, DeGroot LJ: Serum thyroglobulin in the follow-up of patients with treated differentiated thyroid cancer. J Clin Endocrinol Metab 1994;79:98–105.

- 4 American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer; Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167–1214.
- 5 Grunwald F, Kalicke T, Feine U, Lietzenmayer R, Scheidhauer K, Dietlein M, Schober O, Lerch H, Brandt-Mainz K, Burchert W, Hiltermann G, Cremerius U, Biersack HJ: Fluorine-18-fluorodeoxyglucose positron emission tomography in thyroid cancer: results of a multicentre study. *Eur J Nucl Med* 1999;26:1547–1552.
- 6 Helal BO, Merlet P, Toubert ME, Franc B, Schwartz C, Gauthier-Koelesnikov H, Prigent A, Syrota A: Clinical impact of ^{18}F -FDG PET in thyroid carcinoma patients with elevated thyroglobulin levels and negative ^{131}I scanning results after therapy. *J Nucl Med* 2001;42:1464–1469.
- 7 Ma C, Xie J, Lou Y, Gao Y, Zuo S, Wang X: The role of TSH for ^{18}F -FDG PET in the diagnosis of recurrence and metastases of differentiated thyroid carcinoma with elevated thyroglobulin and negative scan: a meta-analysis. *Eur J Endocrinol* 2010;163:177–183.
- 8 Benua R, Sonenberg M, Leeper R, Rawson R: An 18-year study of the use of beef thyrotropin to increase ^{131}I uptake in metastatic thyroid cancer. *J Nucl Med* 1964;5:796–801.
- 9 Robbins RJ, Robbins AK: Clinical review 156: recombinant human thyrotropin and thyroid cancer management. *J Clin Endocrinol Metab* 2003;88:1933–1938.
- 10 Wondisford FE, Radovick S, Moates JM, Usala SJ, Weintraub BD: Isolation and characterization of the human thyrotropin β -subunit gene. Differences in gene structure and promoter function from murine species. *J Biol Chem* 1988;263:12538–12542.
- 11 Guidon PT, Whitfield GK, Porti D, Kourides IA: The human thyrotropin beta-subunit gene differs in 5' structure from murine TSH- β genes. *DNA* 1988;7:691–699.
- 12 Wondisford FE, Usala SJ, DeCherney GS, Castren M, Radovick S, Gyves PW, Trempe JP, Kerfoot BP, Nikodem VM, Carter BJ: Cloning of the human thyrotropin β -subunit gene and transient expression of biologically active human thyrotropin after gene transfection. *Mol Endocrinol* 1988;2:32–39.
- 13 Haugen BR, Cooper DS, Emerson CH, Luster M, Maciel RM, Biscolla RP, Mazzaferri EL, Medeiros-Neto G, Reiners C, Robbins RJ, Robinson BG, Schlumberger M, Yamashita S, Pacini F: Expanding indications for recombinant human TSH in thyroid cancer. *Thyroid* 2008;18:687–694.
- 14 Delvigne A, Rozenberg S: Epidemiology and prevention of ovarian hyperstimulation syndrome: a review. *Hum Reprod Update* 2002;8:559–577.
- 15 Golan A, Ron-el R, Herman A, Soffer Y, Weinraub Z, Caspi E: Ovarian hyperstimulation syndrome: an update review. *Obstet Gynecol Surv* 1989;44:430–440.
- 16 Elchalal U, Schenker JG: The pathophysiology of ovarian hyperstimulation syndrome – views and ideas. *Hum Reprod* 1997;12:1129–1137.
- 17 Furneaux EC, Langley-Evans AJ, Langley-Evans SC: Nausea and vomiting of pregnancy: endocrine basis and contribution to pregnancy outcome. *Obstet Gynecol Surv* 2001;56:775–782.
- 18 Glinoe D: The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997;18:404–433.
- 19 Ludwig M, Gembruch U, Bauer O, Diedrich K: Ovarian hyperstimulation syndrome in a spontaneous pregnancy with fetal and placental triploidy: information about the general pathophysiology of OHSS. *Hum Reprod* 1998;13:2082–2087.
- 20 Wajda KJ, Lucas JG, Marsh WL: Hyperreactio luteinalis. Benign disorder masquerading as an ovarian neoplasm. *Arch Pathol Lab Med* 1989;113:921–925.
- 21 De Leener A, Montanelli L, Van Durme J, Chae H, Smits G, Vassart G, Costagliola S: Presence and absence of follicle-stimulating hormone receptor mutations provide some insights into spontaneous ovarian hyperstimulation syndrome pathophysiology. *J Clin Endocrinol Metab* 2006;91:555–562.
- 22 Dias JA, Cohen BD, Lindau-Shepard B, Nechamen CA, Peterson AJ, Schmidt A: Molecular, structural, and cellular biology of follicle-stimulating hormone receptor. *Vitam Horm* 2002;64:249–322.
- 23 Dufau ML: The luteinizing hormone receptor. *Annu Rev Physiol* 1998;60:461–496.
- 24 Ascoli M, Fanelli F, Segaloff DL: The lutropin/choriogonadotropin receptor, a 2002 perspective. *Endocr Rev* 2002;23:141–174.
- 25 Rapoport B, Chazenbalk GD, Jaume JC, McLachlan SM: The thyrotropin (TSH) receptor: Interaction with TSH and autoantibodies. *Endocr Rev* 1998;19:673–716.
- 26 Vassart G, Pardo L, Costagliola S: A molecular dissection of the glycoprotein hormone receptors. *Trends Biochem Sci* 2004;29:119–126.
- 27 Rodien P, Bremont C, Sanson ML, Parma J, Van Sande J, Costagliola S, Luton JP, Vassart G, Duprez L: Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. *N Engl J Med* 1998;339:1823–1826.
- 28 Smits G, Olatunbosun O, Delbaere A, Pierson R, Vassart G, Costagliola S: Ovarian hyperstimulation syndrome due to a mutation in the follicle-stimulating hormone receptor. *N Engl J Med* 2003;349:760–766.