HIGHLIGHT

TSH receptor gene mutations and familial gestational hyperthyroidism

Carmela Asteria

Istituto di Scienze Endocrine, Università degli Studi di Milano, Milan, Italy

'Gestational hyperthyroidism' is a clinical condition characterized by thyrotoxicosis and hyperemesis gravidarum and generally occurs in 1–2% of all normal pregnancies. It represents an extreme degree of morning nausea and vomiting in early pregnancy, accompanied by weight loss, ketonemia, acetonuria, and profound volume depletion.

Within the last decade, the association of abnormal thyroid function tests (suppressed thyrotropin (TSH) levels and high free thyroxine (FT₄) concentrations) with hyperemesis gravidarum has been increasingly recognized and the severity of the hyperemesis has been linked to the biochemical severity of the hyperthyroidism (1–3), even though a precise correlation between these two conditions is still unclear.

Gestational hyperthyroidism has been attributed to the thyrotropic action of choriogonadotropin (CG) (3–6). During early pregnancy, the high circulating levels of CG could be responsible for the transient thyroid stimulation leading to hyperemesis. The mechanism known as 'specificity spillover' could explain the ability of CG to stimulate the TSH receptor. The specificity spillover is related to the structural homology between CG and TSH molecules, and also between their mutual receptors. Using FRTL-5 cells, it was shown that highly purified CG increased iodide uptake and cAMP production (7), and induced thymidine incorporation and *c-myc* mRNA expression as indirect indices of cell growth (8). In addition, in cultured human thyroid follicles CG displaces TSH from its receptor and is able to stimulate adenylyl cyclase, iodide uptake, organification, and tri-iodothyronine (T₃) secretion (9). These data clearly indicate that CG possesses TSH-like activity. This characteristic of the CG molecule and the high degree of homology among glycoprotein hormone (TSH, follicle-stimulating hormone (FSH) and luteinizing hormone (LH)/CG) receptors, which belong to the family of closely related G-protein coupled receptors, is responsible for the hyperthyroidism found in trophoblastic diseases, as well as in CG-producing tumors, such as choriocarcinomas.

However, many but not all pregnant women with gestational hyperthyroidism have high serum concentrations of CG (6, 10), indicating that other factors, such as the glycosylation of the molecule, could contribute to the hyperthyroidism in pregnant women with normal CG circulating levels (11, 12). In this regard, it has been demonstrated that deglycosylation and/or

desialylation of CG enhances its thyrotropic potency to bind TSH receptor and stimulate cAMP production and growth response in FRTL-5 cells (13, 14).

More recently, Rodien and coworkers (15) have shown that another mechanism can be involved in the pathogenesis of hyperemesis gravidarum and hyperthyroidism associated with normal serum CG concentrations. These authors reported on a 10-week pregnant woman and her mother who had recurrent gestational hyperthyroidism and normal serum CG concentrations. The proband had two miscarriages accompanied by severe nausea and vomiting, and two full-term pregnancies characterized by hyperemesis and hyperthyroidism. On physical examination she presented weight loss of 5 kg, small and diffuse goiter, tachycardia, excessive sweating, tremors and absence of ophthalmopathy. Laboratory tests revealed the presence of suppressed TSH (<0.07 mU/l; normal value 0.2–6 mU/l) and elevated serum FT₄ and total T₃ (TT₃) concentrations (60 pmol/l and 9.8 nmol/l; normal value 11–24 pmol/l and 1.0–2.8 nmol/l respectively) associated with normal circulating levels of CG (70 U/ml; normal range for the first trimester of pregnancy, 38–173 U/ml). Anti-thyroid autoantibodies were negative. During both pregnancies, the patient was treated with propylthiouracil until the delivery and then the therapy was discontinued. She became rapidly euthyroid without symptoms or signs of hyperthyroidism out of the gestational period. Her mother reported a similar history of miscarriage followed by two full-term pregnancies characterized by hyperemesis gravidarum and recurrent hyperthyroidism.

The presence of familial gestational hyperthyroidism suggested a genetic defect transmitted by Mendelian inheritance. TSH receptor gene mutations were considered possible causes of the disease. In effect, a substitution of guanine for adenine at codon 183 on exon 7 of the TSH receptor gene was found in the proband and the mother. Both patients were heterozygous for this mutation, which results in the replacement of a lysine residue with an arginine (K183R) in the extracellular N-terminal domain of the TSH receptor. Functional studies in COS-7 cells demonstrated that the mutant receptor was more sensitive to CG (4-fold increase in cAMP production after stimulation by CG at the maximal dose of 1000 U/ml) than the wild-type receptor, thus accounting for the occurrence of hyperthyroidism despite the presence of normal CG

concentrations. Lysine at position 183 seems to be conservative and constitutes the putative surface of interaction with TSH. If it is replaced by arginine, as in this case, the stability of the complex between CG and TSH receptor may increase. Also LH can stimulate the mutant receptor *in vitro* but not at the physiological levels found *in vivo*, even after menopause. This latter finding is consistent with the euthyroidism showed by the patient's mother during menopause. FSH showed no effect on the stimulation of the mutant receptor activity *in vitro*.

This study seems to be relevant since it describes for the first time a genetic defect responsible for hereditary gestational hyperthyroidism, suggesting another mechanism, beside the glycosylation of the CG molecule, by which normal CG circulating levels can lead to gestational hyperthyroidism.

References

- 1 Mori M, Amino N, Tamaki T, Miyai K & Tanizawa O. Morning sickness and thyroid function in normal pregnancy. *Obstetrics and Gynecology* 1988 **72** 355–359.
- 2 Kennedy RL & Darnes J. The role of hCG in the regulation of the thyroid gland in normal and abnormal pregnancy. *Obstetrics and Gynecology* 1991 **78** 298–307.
- 3 Goodwin TM, Montoro M, Mestman JH, Pekar AG & Hershman JM. The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum. *Journal of Clinical Endocrinology and Metabolism* 1992 **75** 1333–1337.
- 4 Bouillon R, Naesens M, Van Assche EA, De Keyser L, De Moor P, Renaer M *et al.* Thyroid function in patients with hyperemesis gravidarum. *American Journal of Obstetrics and Gynecology* 1982 **143** 922–926.
- 5 Bober SA, McGill AC & Tunbridge WMG. Thyroid function in hyperemesis gravidarum. *Acta Endocrinologica* 1986 **111** 404–410.
- 6 Swaminathan R, Chin RK, Lao TTH, Mak YT, Panesar NS & Cochran CS. Thyroid function in hyperemesis gravidarum. *Acta Endocrinologica* 1989 **120** 155–160.
- 7 Hershman JM, Lee HY, Sugawara M, Mirell CJ, Pang XP, Yanagisawa M *et al.* Human chorionic gonadotropin stimulates iodide uptake, adenylate cyclase, and deoxyribonucleic acid synthesis in cultured rat thyroid cells. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 74–79.
- 8 Davies TF & Platzer M. hCG-induced TSH receptor activation and growth acceleration in FRTL-5 thyroid cells. *Endocrinology* 1986 **118** 2149–2151.
- 9 Kraim Z, Sadeh O, Blithe DL & Nisula BC. Human chorionic gonadotropin stimulates thyroid hormone secretion, iodide uptake, organification, and adenosine 3',5'-monophosphate formation in cultured human thyrocytes. *Journal of Clinical Endocrinology and Metabolism* 1994 **79** 595–599.
- 10 Depue RH, Bernstein L, Ross RK, Judd HL & Henderson BE. Hyperemesis gravidarum in relation to estradiol levels, pregnancy outcome, and other maternal factors: a seroepidemiologic study. *American Journal of Obstetrics and Gynecology* 1987 **156** 1137–1141.
- 11 Tsuruta E, Tada H, Tamaki H, Kashiwai T, Asahi K, Takeoka K *et al.* Pathogenic role of asialo human chorionic gonadotropin in gestational thyrotoxicosis. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 350–355.
- 12 Krentz AJ, Redman H & Taylor KG. Hyperthyroidism associated with hyperemesis gravidarum. *British Journal of Clinical Practice* 1994 **48** 75–76.
- 13 Hoerman R, Keutmann HT & Amir SM. Carbohydrate modifications transform human chorionic gonadotropin into a potent stimulator of adenosine 3',5'-monophosphate and growth responses in FRTL-5 thyroid cells. *Endocrinology* 1991 **128** 1129–1135.
- 14 Pekary AE, Jackson IMD, Goodwin TM, Pang XP, Hein MD & Hershman JM. Increased *in vitro* thyrotropic activity in partially sialylated human chorionic gonadotropin extracted from hydatiform moles of patients with hyperthyroidism. *Journal of Clinical Endocrinology and Metabolism* 1993 **76** 70–74.
- 15 Rodien P, Brémont C, Raffin Sanson ML, Parma J, Van Sande J, Costagliola S *et al.* Familial gestation hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. *New England Journal of Medicine* 1998 **339** 1823–1826.