Chapter 8
A Case of Gestational Thyrotoxicosis

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Objectives
TSH levels may be suppressed in pregnancy, and it is important to determine the cause so that appropriate action can be initiated. This case aims:

1. To draw attention to the need for measurement and careful assessment of low TSH values in pregnancy.
2. To advise not to introduce antithyroid drugs in pregnancy unless one is sure they are needed.

Case Presentation

History This was a 27-year-old female teacher from the Upper West Side of New York City who was referred by a careful high-risk obstetrician from a group called Maternal-Fetal Medicine Associates. The patient had been found to have a very low TSH of 0.012 uU/mL and an increased FT4 of 2.23 ng/dL at a reliable commercial laboratory (see Table 8.1 for normal ranges). She was at 11 weeks with her first pregnancy and was reported to have normal fetal development on ultrasound.

The patient had a family history of Hashimoto's thyroiditis in a maternal grandmother and an aunt. Her history also included the current use of daily Lovenox injections because of factor 5 Leiden deficiency. She had no history of biotin intake which is well known to interfere with the TSH assay in many laboratories. And she had no history of taking thyroid hormone replacement or abusing such treatment which would have explained her low TSH.

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Table 8.1 Thyroid function studies

	Ref. range	11/9/2020
T3, total	Normal ref range: 71–180 ng/dL	298 (H)
T4, free	Normal ref range: 0.82–1.77 ng/dL	2.24 (H)
Thyroglobulin antibody	Normal ref range: 0.0–0.9 IU/mL	<1.0
Thyroid peroxidase (TPO) AB	Normal ref range: 0–34 IU/mL	<9
TSH	Normal ref range: 0.450–4.500 uIU/mL	<0.005 (L)
TSH receptor antibody (TBII)	Normal units: U/L	<0.3

Table 8.2 Pregnancy testing

	Ref. range	11/9/2020 11:00
hCG total, quant.	Units: mIU/mL	254,056

Presentation The patient was not in distress. At her initial visit, she was complaining of recurrent nausea but not sufficient to suggest hyperemesis gravidarum, and there was no weight loss and no dehydration. She had a normal clinical examination apart from a slightly enlarged soft thyroid. Her BMI was 22.0. She had no tremor, no tachycardia, no eye signs, and a normal BP.

Investigations My thyroid ultrasound at the visit showed a normal homogeneous thyroid with no evidence of nodules or heterogeneity suggestive of thyroiditis. Her repeat thyroid function testing confirmed the reported suppressed TSH with no thyroid autoantibodies detectable including TSH receptor antibodies (Table 8.1).

It was now unlikely that the patient had Graves' disease which was the initial thought on referral to endocrinology. The absence of TSH receptor antibodies would be very unusual. On review of her hCG levels, it became clear that the high levels were compatible with gestational thyrotoxicosis (Table 8.2). This result was further confirmed on dilution of the sample and re-assayed for hCG and was significantly higher than found in many women with a normal singleton pregnancy (Table 8.3). However, it was not as high as may be seen in multiple pregnancies and hydatidiform moles.

Outcome The decision not to treat was made, and the patient was followed up to see how she progressed since time confirms many diagnoses. By 3 months, at week 25 of pregnancy, she then had a normal TSH of 0.7uU/mL and normal FT4 0.95 ng/dL, and her pregnancy was progressing normally.

Differential Diagnosis The possibility of an active thyroid nodule was excluded very early by an immediate thyroid ultrasound examination at presentation. Graves' disease was excluded by the lack of TSH receptor antibodies since cases of antibody negative Graves' disease are very unusual although much talked about. Alternative diagnoses that were considered included either the "Hashitoxicosis" phase of autoimmune thyroiditis, which was unlikely in the absence of thyroid antibodies, or the acute thyrotoxic phase of subacute (DeQuervain's) thyroiditis, also unlikely without any thyroid tenderness although painless thyroiditis occurs and could not be instantly ruled out.

Table 8.3 The normal range of hCG (mIU/mL) in pregnancy

Female	(Non-pregnant)	0–5
	(Postmenopausal)	0–8
Female	(Pregnant)	
	Weeks of gestation	
	3	6–71
	4	10–750
	5	217–7138
	6	158–31,795
	7	3697–163,563
	8	32,065–149,571
	9	63,803–151,410
	10	46,509–186,977
	12	**27,832–210,612**
	14	13,950–62,530
	15	12,039–70,971
	16	9040–56,451
	17	8175–55,868
	18	8099–58,176

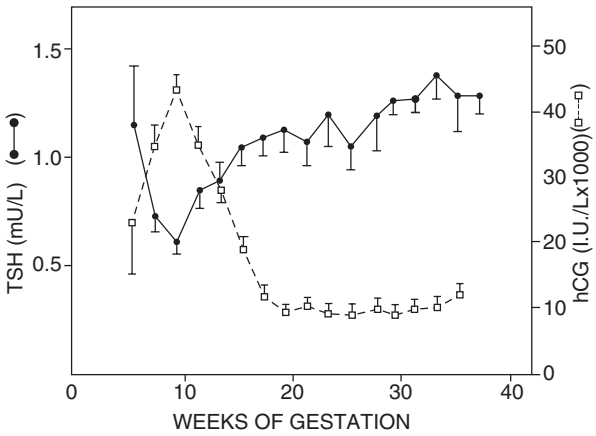

Fig. 8.1 The fall of TSH as hCG levels increase. (From Ref. [2])

Review of the Diagnosis

Hyperthyroidism in early pregnancy can quickly spin out of control and result in miscarriage [1]. It is, therefore, imperative that a clear diagnosis be made as soon as possible and severe cases of hyperthyroidism in pregnancy may require ICU admission. This was not the case with this patient who had a normal physical examination. The repeat measurement of her hCG level quickly suggested her diagnosis. The range for hCG in early pregnancy reaches a peak at 12 weeks, just when this patient presented, and correlates well with the suppression of TSH as emphasized by Glinoer [2] (Fig. 8.1). Serum levels of hCG in singleton pregnancies can vary

Table 8.4 Examples of hCG levels with low TSH concentrations

		TSH (mU/L)		hCG (U/L) (mean ± SEM)		
Trimester	*N*	≤0.20 N (%)	0.21–4.00 N (%)	in women with TSH ≤ 0.20	in women with TSH 0.21–4.00	*P*
I	338	62 (18%)	276 (82%)	52,400 ± 3900	34,900 ± 1200	<0.001
II	249	13 (5%)	236 (95%)	20,400 ± 5300	12,600 ± 1000	<0.001
III	102	2 (2%)	100 (98%)	ND	13,000 ± 1400	ND

From Glinoer [2]

considerably from 28,000 up to 210,000 mIU/mL in our laboratory and sometimes even higher (Tables 8.3 and 8.4). This patient's hCG was especially high and in keeping with the clinical suspicion for gestational thyrotoxicosis and supported by the lack of thyroid antibodies. If the patient was not pregnant, then this might well have been a case of silent subacute thyroiditis which would have been diagnosed by a radioactive iodine uptake of less than 1% although I would also have expected heterogenous changes on her thyroid ultrasound.

Lessons Learned

The commonest cause of a suppressed TSH in clinical practice is probably excessive intake of T4 medication directed by a physician. Outside this phenomenon, overt hyperthyroidism affects only 0.1–0.4% of pregnancies and is associated with poor maternal and fetal outcomes [3]. The problem for the clinician is that 10% or more of normal women show a low TSH in early pregnancy. This is usually secondary to the highly variable influence of hCG on the thyroid and is referred to as gestational thyrotoxicosis [1]. There are no data, yet, to suggest this phenomenon has adverse effects and such pregnancies progress normally as in the case discussed.

The thyrotropic action of hCG is explained by the structural homology between hCG and TSH molecules and between LH/CG and TSH receptors. Thus, hCG is able to bind to the TSH receptor of thyroid follicular cells [4] and exert its stimulatory effects by activating intracellular messengers, such as cAMP [5]. However, the thyroid-stimulating ability of hCG varies from person to person and appears to be secondary to the degree of glycosylation which not only lengthens its half-life but also enhances its "specificity cross-over" with the TSH receptor [6]. To date, two cases of a TSH receptor mutation have been reported that endow increased sensitivity to hCG, and these cases presented with hyperemesis gravidarum, the hallmark of which may be severe weight loss and dehydration except in such cases the hCG level may be normal for pregnancy [7].

Multiple-Choice Questions (There May Be More than One Correct Answer)

1. A suppressed TSH in a young female may be due to:

   (a) Biotin intake for "strong nails"
   (b) Excess "synthroid" tablets from her mother
   (c) Japanese food excess
   (d) Kosher salt use
   (e) A laboratory error

2. An enlarged thyroid in a pregnant woman indicates:

   (a) A normal thyroid expansion of pregnancy
   (b) Possible underlying Hashimoto's thyroiditis
   (c) The certain development of Graves' disease
   (d) A likely multiple pregnancy
   (e) Iodine deficiency in New York City

3. The TSH action of hCG is:

   (a) Secondary to the high TBG level in pregnancy
   (b) Related to the glycosylation pattern of T4
   (c) May vary intrinsically between patients
   (d) Indicative of a likely miscarriage
   (e) Can be assessed with a qualitative pregnancy test

4. Gestational thyrotoxicosis requires:

   (a) Immediate admission to the ICU for impending "storm"
   (b) Initiation of antithyroid drugs and possible corticosteroids
   (c) A clear diagnosis and reassurance to the parents
   (d) A sign that Graves' disease is likely to develop in the postpartum
   (e) An assessment of changes in serum hCG levels

5. Profuse and recurrent vomiting with weight loss in pregnancy and a suppressed TSH may be a sign of:

   (a) Hyperemesis gravidarum
   (b) Gestational thyrotoxicosis
   (c) An LH/CG mutation highly sensitive to hCG
   (d) Anorexia nervosa

Answers

1. (a), (b), (e)
2. (a), (b)
3. (b), (c)
4. (c), (e)
5. (a), (c)

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