An undiagnosed TSH-secreting pituitary macroadenoma found during pregnancy

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Summary
Thyroid stimulating hormone (TSH)-secreting pituitary adenoma (TSHoma) is an uncommon cause of thyrotoxicosis, and is even rarer when found during pregnancy. Our patient presented with thyrotoxicosis accompanied by an inappropriately normal TSH level at 10 weeks of gestation during work-up of surgical termination of pregnancy (STOP). Subsequent investigations performed after STOP confirmed the presence of a TSH-secreting pituitary macroadenoma. She was initially treated with anti-thyroid drugs for biochemical control, followed by trans-sphenoidal surgery after STOP had been performed. Her thyroid function completely normalized after the trans-sphenoidal surgery. Our case illustrated the importance of recognizing the syndrome of inappropriate TSH secretion and highlighted several pregnancy-related aspects in the diagnosis and management of TSHoma during pregnancy.

Learning points:
• This case report illustrates the need to raise awareness in recognizing the syndrome of inappropriate TSH secretion.
• Illustrate the different hormone tests available for reaching the diagnosis of TSH-secreting pituitary adenoma.
• Highlight the physiological changes in the thyroid status during pregnancy and the importance of using trimester-specific reference ranges for assessment of thyroid function during pregnancy.
• Describe the challenges in the management of TSH-secreting pituitary adenoma during pregnancy.

Background
Thyroid stimulating hormone (TSH)-secreting pituitary adenoma (TSHoma) is an uncommon cause of thyrotoxicosis. The incidence is around 0.015 to 0.03 per 100 000 person-years (1). It is even rarer to present during pregnancy, and with only limited cases reported to date (2). Here we describe a patient who was found to harbor a TSHoma during her first trimester of pregnancy. We illustrated the importance of recognizing the syndrome of inappropriate TSH secretion, which can be due to the use of concomitant medications such as amiodarone or heparin, assay interference, thyroid hormone resistance, as well as the presence of a TSHoma, an uncommon yet important cause of thyrotoxicosis. Our report also highlighted a few pregnancy-related aspects during the diagnosis and management of TSHoma during pregnancy.

Case presentation
A 32-year-old pregnant lady was referred to our unit for recurrent thyrotoxicosis. She was at 10 weeks of gestation and was planning surgical termination of pregnancy (STOP) due to social reasons.

Upon further questioning, her first episode of thyrotoxicosis occurred in five years ago, when she presented with hand tremor, heat intolerance and palpitations. Her thyroid function test (TFT) at that time showed a free thyroxine (fT4) level of 30.7 pmol/L (normal
range (NR): 9.5–18.1) and a TSH level of 2.73 mIU/L (NR: 0.35–3.8). She had no family history of thyroid diseases or abnormal TFT. She was managed by her general practitioner for primary hyperthyroidism and was treated with carbimazole for 3 years until her fT4 levels eventually normalized. Her TSH remained between 1.3 and 2.45 mIU/L (NR: 0.35–3.8) while on carbimazole. As her symptoms improved with anti-thyroid medications, she then defaulted follow-up without further TFT checking until this pregnancy.

During this pregnancy, her TFT at 10 weeks of gestation revealed elevated fT4 and free triiodothyronine (fT3) levels with an inappropriately normal TSH based on the gestation-specific reference ranges (Table 1). She complained of heat intolerance and mild hand tremor but was otherwise well without significant weight loss or vomiting. Physical examination showed a small diffuse goiter without thyroid bruit or thyroid eye signs. Her pulse was regular at 98 b.p.m. and she had sweaty palms. Visual field was full by confrontation test.

Since STOP had to be performed by 12 weeks of gestation, it was decided to stabilize her thyroid function first with oral carbimazole 10mg twice daily and propranolol 10mg thrice daily, and to investigate the cause of thyrotoxicosis after the procedure. STOP was performed uneventfully two weeks later, and her carbimazole was stopped. A repeat TFT 4 weeks after discontinuation of carbimazole however still showed elevated fT4 level with an inappropriately normal TSH (Table 1).

Investigation

Further investigations were performed to evaluate the cause of fT4 elevation with an inappropriately normal TSH. Her fT4 result was verified using a two-step assay on Architect (Abbott). Her anti-thyroglobulin, anti-thyroid peroxidase and anti-TSH receptor antibodies were all normal. Alpha subunit was checked and was within the normal range. However, the alpha subunit-to-TSH molar ratio (defined as alpha subunit divided by TSH and multiplied by 10) was abnormally elevated. The thyrotropin-releasing hormone (TRH) test showed a blunted TSH response, and the T3 suppression test demonstrated a failure of TSH suppression with T3 administration (Table 2). Her serum prolactin and age- and sex-matched insulin-like growth factor-1 (IGF-1) levels were 189 mIU/L (NR: 60–620 mIU/L) and 205 µg/L (NR: 53–331 µg/L), respectively. The other anterior pituitary hormones including morning cortisol and random growth hormone (GH) were all within normal ranges.

A MRI of her pituitary gland revealed a 1 cm well-defined hypo-enhancing lesion on the left pituitary gland, which caused deviation of the pituitary stalk to the right without optic chiasmal compression (Fig. 1A).

Treatment

The patient subsequently underwent a trans-sphenoidal surgery with gross total removal of her pituitary tumor. The histology confirmed a pituitary adenoma with weakly positive immunostaining for GH, TSH and, follicle-stimulating hormone (FSH), while negative for adrenocorticotropic hormone (ACTH). The Ki67 was less than 3%.

Outcome and follow-up

Her immediate post-operative TSH and fT4 levels were 0.03 mIU/L (n: 0.35–3.8) and 17 pmol/L (n: 12–23), respectively. A repeat TFT 6 months later showed completely normalized TSH and fT4 levels and her post-operative MRI did not reveal any tumor recurrence (Fig. 1B).

Discussion

Among the pituitary tumors, TSHomas are rare. Only several cases managed during pregnancy had been reported (2) and, to our knowledge, this is the first TSH-producing pituitary macroadenoma diagnosed during pregnancy. Here we discuss the potential issues in the diagnosis and management of this unusual cause of thyrotoxicosis during pregnancy, including those encountered in women

Table 1 Thyroid function tests of the patient at her initial presentation, 10 weeks of gestation and 4 weeks postpartum.

| Initial presentation (2012) | At 10 weeks of gestation (2017) | 4 weeks postpartum (2017) | Reference ranges (3) |
|---------------------------|-------------------------------|--------------------------|---------------------|
| TSH (mIU/L)               | 2.73                          | 0.7                      | 0.35–3.8            |
| fT4 (pmol/L)              | 30.7                          | 48.0                     | 9.5–18.1            |
| fT3 (pmol/L)              | –                             | 12                       | 3.2–6.5             |
| Non-pregnant              | 10–11 weeks gestation         |                          | 0.01–2.53           |
| 10–11 weeks gestation     |                               |                          | 11.1–22.9           |
| 10–11 weeks gestation     |                               |                          | 3.0–5.7             |

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Interpretation of TFT can be challenging during pregnancy, owing to the normal physiological changes that occur as gestation advances. Human chorionic gonadotropin (hCG) shares an identical alpha subunit with TSH, which in turn stimulates the production and release of thyroid hormones during pregnancy (3). Free thyroxine levels peak at week 10, followed by a gradual decrease to 10–30% below non-pregnancy level in the late third trimester. Therefore, the use of a trimester-specific reference range is thus recommended (3). In general, in the first trimester, the lower and upper end of reference range of TSH are reduced by 0.4 and 0.5 mU/L respectively, and the level should gradually return toward non-pregnancy range in the second and third trimesters (6). TSH level during pregnancy may also be affected by geographic and ethnic variability, and hence population-specific reference ranges should be used whenever available. In our patient, however, even after accounting for the physiological changes during pregnancy using gestational specific reference ranges, the TSH level was inappropriately normal with the level of fT4 elevation, suggesting a pathology other than primary hyperthyroidism.

TSH-secreting adenoma (TSHoma) is an uncommon pituitary adenoma. The majority of patients have a long history of thyroid dysfunction, and the thyrotoxic symptoms are usually milder than expected given the circulating thyroid hormone levels. Most patients have goiter, as in our patient, but cardiac involvement related to thyrotoxicosis is usually less frequent (7). Some TSHomas may co-secrete other hormones, which are commonly growth hormone and prolactin (7). In addition to thyrotoxic symptoms, patients with TSHoma may also present with symptoms of tumor expansion including visual field impairment, headache, partial or complete pituitary insufficiency.

Our case highlighted the importance of recognizing an inappropriate TSH response in the context of an elevated fT4 level. Before a diagnosis of TSHoma is made, other more common causes of inappropriate TSH secretion should also be excluded. These include the use of concomitant medications such as amiodarone or heparin, or assay interference due to the presence of heterophile antibodies. The latter condition can be resolved by verifying the TFT with a different laboratory technique.

### Table 2

| Test                          | Results | Normal ranges         |
|-------------------------------|---------|-----------------------|
| Alpha subunit (IU/L)          | 0.21    | <0.9*                 |
| Alpha subunit-to-TSH molar ratio | 2.36    | <1.0 (4)              |
| TRH test                      |         |                       |
| Basal TSH, mIU/L              | 0.89    | ≥2-fold†              |
| Peak TSH at 180 min, mIU/L    | 0.89    |                       |
| T3 suppression test           |         | Suppression to <10% of baseline |
| Basal TSH, mIU/L              | 0.86    |                       |
| Nadir, mIU/L                  | 0.77†   |                       |

*1.8-fold increase; †after T3 suppression; ‡for premenopausal women; † increase in TSH levels from baseline (5).

TRH, thyrotropin releasing hormone.

who, unlike our patient, would like to continue with the pregnancy.

Figure 1
Pre-operative (A) and post-operative (B) MRI of pituitary of the patient.
using a two-step analog method, which entails a wash step immediately after capture to avoid the interference from circulating autoantibodies. After the exclusion of the above analytic issues, further investigations should be performed mainly to distinguish the presence of TSHomas from thyroid hormone resistance, which could be challenging during pregnancy. For instance, serum alpha subunit is a glycoprotein hormone that might be increased in patients with TSHomas (7). However, the substantial increase in serum alpha subunit contributed by raised HCG levels during pregnancy may pose a problem with the interpretation of the alpha subunit to TSH ratio. Moreover, although the demonstration of absent or impaired TSH responses to both the stimulatory TRH test and the inhibitory T3 suppression test would also favor the diagnosis of TSHomas, T3 suppression test is generally avoided during pregnancy. TRH test, on the other hand, can still be performed. However, it should be noted that exaggerated response has been observed in normal pregnant mothers (8).

With regards to imaging modality, plain MRI is not contraindicated during pregnancy, although some would prefer to defer the scan to postpartum to avoid the theoretical teratogenic risk and acoustic damage, especially if patients do not report visual field problems. Notably, gadolinium is generally avoided during pregnancy due to safety concerns for the fetus (9). TSHoma usually presents as a hypointense macroadenoma on MRI pituitary, and microadenomas are increasingly being identified, accounting for around 20% of all cases (7, 10). However, there is still chances that the pituitary tumors could further increase in size during pregnancy, especially if the pituitary tumor also co-secretes prolactin, which would also be difficult to ascertain during pregnancy.

Trans-sphenoidal surgery is usually the first-line treatment in TSHoma after delivery (10). However, unless early surgical intervention is indicated, for instance, in case of severe visual impairment, it is a common practice to postpone definitive management until after delivery (11). Anti-thyroid drugs are usually given to stabilize the thyroid function before definitive treatment, although the choice of agents depends on gestation, due to differences in teratogenic effects between carbimazole/ methimazole and propylthiouracil. Medical therapy with somatostatin analogues may also normalize the thyroid function, but monitoring of side effects, including cholelithiasis and hyperglycemia, is crucial. Indeed, in the few case reports on TSHomas during pregnancy, medical treatment with octreotide and bromocriptine had been given with successful control of thyroid function and good pregnancy outcomes (12). Given the limited number of patients with TSHoma presenting during pregnancy, there is insufficient evidence to suggest which may be the best treatment modality in this group of patients. Nonetheless, since our patient responded well to anti-thyroid drugs before her STOP, she did not require somatostatin treatment for further stabilization.

In summary, our case demonstrated that early recognition of the syndrome of inappropriate TSH secretion is important for timely diagnosis and optimal management of TSHomas.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement
Chi-Hong Ng – Primary author, conceived the ideas of the study. Wing-Sun Chow – Conceived the ideas of the study, provided revision to the scientific content of the manuscript, provided stylistic grammatical revisions to the manuscript. Karen Siu-Ling Lam – Provided revision to scientific content of manuscript, provided stylistic grammatical revisions to the manuscript. Chi-Ho Lee – Named physician, conceived the ideas of the study, provided revisions to scientific content of the manuscript, provided stylistic grammatical revisions to the manuscript.

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