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Y-F Wu and others

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Thyrotropinoma with silent somatotroph and lactotroph adenoma during pregnancy

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Summary

Thyrotropinomas are an uncommon cause of hyperthyroidism and are exceedingly rarely identified during pregnancy, with limited evidence to guide management. Most commonly they present as macroadenomas and may cause symptoms of mass effect including headache, visual field defects and hypopituitarism. We present a case of a 35-year-old woman investigated for headaches in whom a 13 mm thyrotropinoma was found. In the lead-up to planned trans-sphenoidal surgery (TSS), she spontaneously conceived and surgery was deferred, as was pharmacotherapy, at her request. The patient was closely monitored through her pregnancy by a multi-disciplinary team and delivered without complication. Pituitary surgery was performed 6 months post-partum. Isolated secondary hypothyroidism was diagnosed postoperatively and replacement thyroxine was commenced. Histopathology showed a double lesion with predominant pituitary transcription factor-1 positive, steroidogenic factor negative plurihormonal adenoma and co-existent mixed thyroid-stimulating hormone, growth hormone, lactotroph and follicle-stimulating hormone staining with a Ki-67 of 1%. This case demonstrates a conservative approach to thyrotropinoma in pregnancy with a successful outcome. This highlights the need to consider the timing of intervention with careful consideration of risks to mother and fetus.

Learning points:

- Thyrotropinomas are a rare cause of secondary hyperthyroidism. Patients may present with hyperthyroidism or symptoms of mass effect, including headaches or visual disturbance.
- Thyrotropinoma in pregnancy presents a number of pituitary-related risks including pituitary apoplexy and compression of local structures.
- Hyperthyroidism in pregnancy raises the risk of complications including spontaneous abortion, preeclampsia, low birthweight and premature labour.
- Timing of medical and surgical therapies must be carefully considered. A conservative approach requires careful monitoring in case emergent intervention is required.

Background

Thyrotropinomas are rare, comprising 1–2% of all pituitary adenomas. They predominantly affect the 40- to 50-year age group with no gender predilection. The majority are macroadenomas at diagnosis. Patients may present with symptoms of mass effect such as headaches or visual disturbance (1) or hyperthyroidism. Compression can cause pituitary dysfunction, most commonly hypogonadotropic hypogonadism (2). Plurihormonal overproduction may also occur, most commonly co-secreting prolactin (3). Thyrotropinomas in pregnancy are very rare with only six reported cases at the time of this report (Table 1).

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Case presentation

A 35-year-old otherwise healthy woman of Filipino ancestry was found to have an incidental pituitary macroadenoma on imaging after investigation of headaches and sinusitis. There were no visual field abnormalities and no symptoms to suggest pituitary dysfunction. She had a history of gestational diabetes in her first pregnancy 3 years prior and a miscarriage 12 months prior. Menses were regular. There was no family history of pituitary adenoma or thyroid hormone resistance. On examination, she was clinically euthyroid and without a goitre. There were no features of acromegaly. She was overweight with a BMI of 25.9 kg/m^2.

Investigation

MRI revealed a 13 mm × 9 mm × 11 mm macroadenoma extending from the left side of the pituitary into the suprasellar cistern, contacting but not compressing the inferior surface of the optic chiasm (Fig. 1A and B). Biochemistry showed raised free T4 of 24 pmol/L (9–19) and free T3 of 6.8 pmol/L (2.6–6). Thyroid-stimulating hormone (TSH) was inappropriately elevated at 4.2 mIU/L (0.4–4), consistent with secondary hyperthyroidism. Insulin-like growth factor-1 was elevated at 46 nmol/L (11–38), but on repeat testing normalized to 36 nmol/L. A 75 g oral glucose tolerance test demonstrated growth hormone (GH) suppression down to 0.2 mIU/L (<1.0) at 2 h. Morning cortisol was 295 nmol/L (70–650), prolactin 517 mIU/L (85–500) and thyroid auto-antibodies were undetectable. Alpha subunit was 0.43 IU/L (0–0.6).

Endoscopic trans-sphenoidal pituitary surgery was planned; however, pre-operative evaluation identified the patient was pregnant at 5 weeks gestation. The case was reviewed in a multidisciplinary team meeting and options were discussed with the patient. A conservative approach was chosen with deferral of surgery and close monitoring with obstetrics, neurosurgery, endocrinology and neuro-ophthalmology. Medical therapy with octreotide was offered but declined by the patient.

Early pregnancy was complicated by hyperemesis gravidarum which was managed with metoclopramide. Gestational diabetes developed in the second trimester and was controlled with insulin. At 38 weeks, a healthy 3.4 Kg boy was delivered by planned induction. The delivery was complicated by post-partum haemorrhage with retained products of conception requiring transfusion, the patient was able to be discharged 1 week later. Glycaemic control normalized post-partum.

Treatment

A T3 predominant mild thyrotoxicosis persisted through the pregnancy and post-partum period (Table 2). Visual fields remained normal throughout pregnancy and no symptoms of mass effect developed. Repeat MRI pituitary showed no significant change in the size of the macroadenoma. At 3 months post-partum, carbimazole was commenced as a temporizing measure to control hyperthyroidism after declining somatostatin analogue therapy. At 6 months, she proceeded to an uncomplicated transsphenoidal resection of the macroadenoma with sparing of the normal pituitary. A postoperative MRI showed complete resection of the adenoma. Postoperative blood tests showed normal pituitary function, and no immediate hormone replacement was required.

Histopathology revealed an unusual double lesion with predominant expression of pituitary transcription factor-1 (PIT-1) and mixed staining for TSH, GH, prolactin and follicle-stimulating hormone with a Ki-67 of 1%. Steroidogenic factor-1 (SF1) was negative (Fig. 2A, B, C and D).

Outcome and follow-up

One week post discharge the patient developed nausea and vomiting. Hyponatraemia was identified with serum sodium of 123 nmol/L (135–145), low serum osmolality of 266 mOsm/kg (275–295), high urine sodium of 263 mmol/L (75–300) and urine osmolality of 682 mOsm/kg (50–1500), consistent with the syndrome of inappropriate anti-diuretic hormone secretion. A fluid restriction was commenced with a good resolution of hyponatraemia. Further testing showed an appropriately elevated cortisol at 814 nmol/L; however, thyroid function tests showed secondary hypothyroidism with a TSH of 0.02 mIU/L (0.4–4), free T4 of 10 pmol/L (9–19) and free T3 of 2.4 pmol/L (2.6–6). She was commenced on thyroxine 75 µg daily. Review 4 weeks later showed persistently low TSH <0.005 mIU/L (0.4–4) and improved free T4 15.5 pmol/L (9–19) and free T3 4.8 pmol/L (2.6–6).

Repeat MRI pituitary at 9 months post-op showed no residual or recurrent mass. 2 years on, our patient remains hypothyroid requiring replacement with no signs of recurrent tumour.

Discussion

This is an unusual case of thyrotropinoma coincident with pregnancy. At the time of writing just six other cases

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Table 1 Summary of published case reports of thyrotropinoma in pregnancy.

Reference	Clinical features	Biochemical features at diagnosis	Radiological features	Histological features	Co-secretion	Treatment	Outcome
Caron *et al*. 1996 (8)	31 year old Thyrotoxicosis, oligomenorrhea, galactorrhea, Visual field defect at 6 months gestation	TSH ↑ T4 ↑ T3 ↑ α-subunit normal Prolactin ↑ SHBG ↑	Macroadenoma with suprasellar extension	NR	-	Octreotide commenced 3 month pre-pregnancy and ceased in the first month of pregnancy Recommenced at 6 months gestation and continued postpartum	Elective caesarean section at 36 weeks No maternal or fetal complications
Blackhurst *et al*. 2002 (9)	21 year old Thyrotoxicosis, galactorrhea	TSH normal T4 ↑ Prolactin ↑	Macroadenoma 25 × 25 × 30 mm encasing the left internal carotid artery, filling the suprasellar cistern, displacing the third ventricle	TSH, PRL, α-subunit staining	PRL	Carbimazole (intolerant), propylthiouracil (resistant) and cabergoline TSS Octreotide Radiotherapy	Dizygotic twins delivered at 36 weeks No maternal or fetal complications
Chaiamnuay *et al*. 2003 (6)	39 year old Thyrotoxicosis, amenorrhea, galactorrhea Visual field defect at 27 weeks gestation	TSH normal T4 ↑ T3 ↑ α-subunit ↑ Prolactin ↑	Macroadenoma 20 × 20 × 17 mm extending to the suprasellar cistern Serial study at 27 weeks showed compression of the optic chiasm	TSH, chromogranin staining	PRL	Propylthiouracil and bromocriptine TSS at 27 weeks	Elective caesarean section at 39 weeks No maternal or fetal complications
Okuyucu *et al*. 2016 (11)	37 year old Exophthalmos	TSH ↑ T4 ↑ T3 ↑ Positive TRAb	Macroadenoma 13 × 11 mm adjacent to optic chiasm	TSH staining	-	Propylthiouracil Thyroidectomy TSS postpartum	Delivered full term No maternal or fetal complications
Perdomo *et al*. 2017 (3)	21 year old Thyrotoxicosis Recurrent thyrotropinoma	TSH ↑ T4 ↑ Positive Tg Ab and TPO Ab	Macroadenoma 28 × 19 × 17 mm encasing the right internal carotid artery, filling the suprasellar cistern, in contact with optic chiasm	TSH, PRL, GH staining	-	Carbimazole TSS Recurred 18 months post TSS Octreotide for 11 months, ceased once pregnant	Delivered at 38 weeks No maternal or fetal complications
Ng *et al*. 2021 (12)	32 year old Thyrotoxicosis	TSH normal T4 ↑ T3 ↑	Macroadenoma 10 mm	TSH, GH, FSH staining		Carbimazole TSS after pregnancy	Termination for social reasons at 12 weeks
Present study	35 year old Headache, euthyroid	TSH normal T4 ↑ T3 ↑ α-subunit normal	Macroadenoma 13 × 9 × 11 mm, extending into suprasellar cistern	TSH, GH, PRL, FSH staining	GH	Close observation during pregnancy TSS at 6 months postpartum	Induced labour at 38 weeks Post partum haemorrhage No fetal complications

FSH, follicle-stimulating hormone; GH, growth hormone; PRL, prolactin; SHBG, sex hormone-binding globulin; Tg Ab, thyroglobulin antibody; TPO Ab, thyroperoxidase antibody; TSH, thyroid-stimulating hormone; TSS, trans-sphenoidal surgery.

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have been reported (3, 4, 5, 6, 7, 8). This clinical scenario presents significant challenges with the need to balance the well-being of the mother and the fetus with limited evidence to guide therapy.

In other published cases, patients had symptoms or signs of hyperthyroidism, and three out of six had galactorrhoea (Table 1). In contrast to this, our patient presented with headaches likely secondary to mass effect leading to the identification of the pituitary adenoma.

In this case, thyrotoxicosis did not progress significantly during the pregnancy with downward trend in free T4 levels and a slow rise in free T3 (Table 2). Thyroid auto-antibodies were negative. The frequency of circulating anti-thyroid antibodies in thyrotropinoma reported is similar to the general population at 8% (6). See Table 1 for biochemistry summarized from published case reports. Hyperthyroidism in pregnancy increases the risk of a number of complications including stillbirth, low birth weight, pre-eclampsia and premature delivery (9). It is possible here that the earlier miscarriage may have been related to hyperthyroidism. Given hyperthyroidism did not progress significantly, the intervention was able to be delayed until post-partum without adverse outcomes.

We saw an initially normal α-subunit which rose during pregnancy and then normalized again post-partum. The normal pre-pregnancy alpha subunit in our patient is less common with α-subunit levels being increased in about 70% of patients with thyrotropinoma (10). We saw an elevated SHBG during pregnancy which normalized postpartum. Increase in SHBG can be expected during pregnancy. An increase in SHBG is also in keeping with thyrotropinoma as opposed to thyroid hormone resistance (2).

The normal pituitary gland enlarges by approximately a third during pregnancy due to hyperplasia of lactotroph cells. A significant concern with pituitary adenoma, and particularly macroadenoma, during pregnancy is the development of compression to surrounding structures leading to neurological compromise. Management varies depending on the adenoma type, as in the non-pregnant adults. In general, medical and surgical interventions are delayed until after delivery or timed to minimize adverse effects on the mother and fetus. Though development of symptoms suggesting compression may prompt urgent intervention (11).

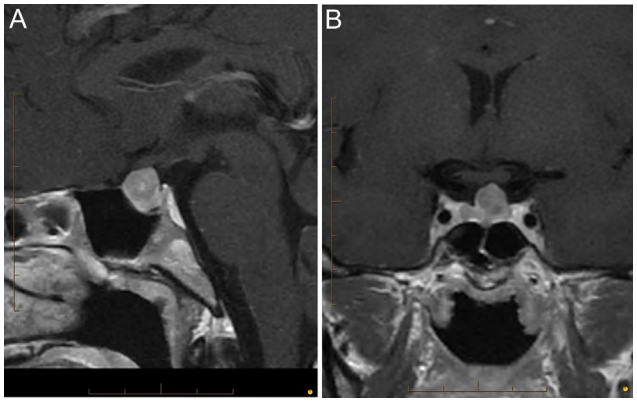

Figure 1
MRI of the pituitary with contrast enhancement. T1-weighted images showing a pituitary mass in sagittal (A) and coronal (B) planes.

First-line treatment for thyrotropinoma is surgical resection of the pituitary aiming for complete removal of tumour tissue. Surgery can be technically challenging due to frequent local invasion and characteristic tumour fibrosis. Macroadenomas are cured in less than 60% of cases (10). If surgery is declined or there is relapse, treatment with radiotherapy and/or medications can be considered. There is one published case report of transsphenoidal resection during pregnancy at 27 weeks gestation due to tumour enlargement with visual compromise despite propylthiouracil and bromocriptine medical therapies (5).

Somatostatin receptor subtypes 1, 2A, 3 and 5 have been described in thyrotropinomas. Somatostatin analogues (SSAs) show good efficacy for tumour shrinkage (40%), visual improvement (66%) and reversal of hypersecretion (>95%) in thyroptropinoma patients (12). They are generally well-tolerated and resistance is rare. Patients must be monitored for side effects such as hyperglycaemia and cholelithiasis. SSAs have been used in pregnancy in patients with acromegaly,

Table 2 Thyroid function tests, alpha subunit and sex hormone-binding globulin levels during pregnancy and post-partum.

Biochemistry	5 weeks gestation	23 weeks gestation	30 weeks gestation	1 month post-partum	3 months post-partum	6 months post-partum
TSH (pmol/L)	2.0 (0.4–3.2)	3.6 (0.3–2.9)	2.51 (0.3–2.9)	1.7 (0.4–3.2)	3.3 (0.4–3.2)	2.5 (0.4–3.2)
Free T4 (pmol/L)	18.8 (11–17)	15.4 (9–14)	16.5 (9–14)	18.6 (11–17)	19.4 (11–17)	18.1 (11–17)
Free T3 (pmol/L)	6.0 (2.6–6)	6.9 (2.6–6)	7.2 (2.6–6)	6.6 (2.6–6)	6.6 (2.6–6)	5.8 (2.6–6)
Alpha subunit (IU/L)	0.43 (0–0.6)			0.84 (0–0.6)		0.40 (0–0.6)
SHBG (nmol/L)	380 (30–110)			37 (30–110)		

Trimester-specific normal ranges for thyroid function tests are shown.

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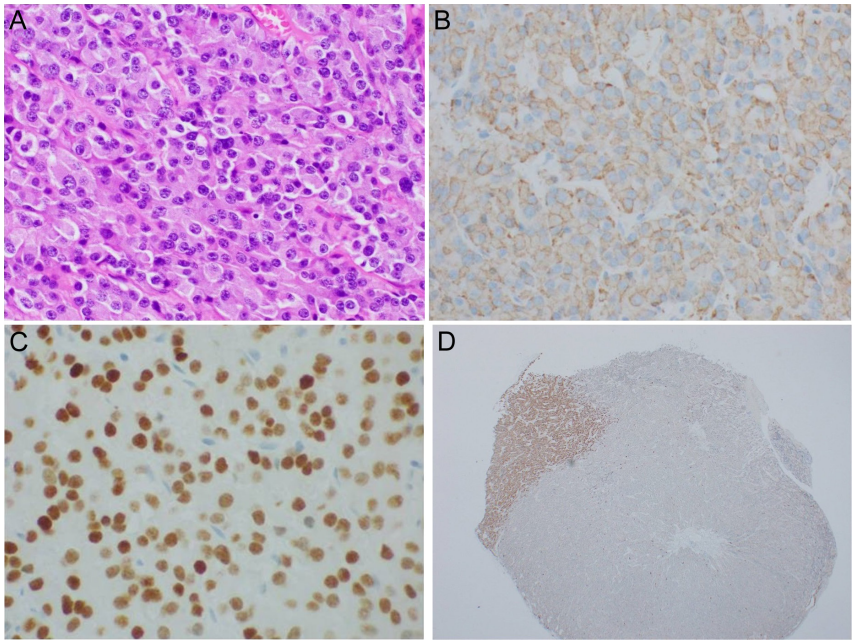

Figure 2
Histopathology of resected pituitary tissue. (A) Hematoxylin and eosin stain showing predominance of polygonal cells. (B) Diffuse moderate granular staining for thyroid-stimulating hormone (TSH) and growth hormone (GH). (C) Transcription factor-1 (PIT-1) positive nuclear staining throughout the adenoma. (D) Prolactin staining.

with no reports of fetal malformations. However, SSAs cross the placenta and there are somatostatin receptors in the fetal pituitary gland leading to the theoretical risk of growth inhibition (11). All three published cases of thyrotropinoma in pregnancy that were treated with octreotide had a good response, demonstrated by reduction in tumour mass and biochemical euthyroidism. All three patients, including one presenting with subfertility, achieved natural conception several months later (3, 6, 7).

Thionamides may be used in thyrotropinoma to optimize patients pre-operatively to a euthyroid state. These agents are commonly used in pregnancy and in five of the six published cases with thyrotropinoma were used prior to delivery or further intervention. In this case, carbimazole was commenced 3 months after delivery prior to trans-sphenoidal resection.

Twenty-five percent (25%) of thyrotropinomas co-secrete other anterior pituitary hormones; the most common being GH (17.9%), followed by prolactin (10.2%) and thereafter gonadotropins (1.8%). The features of GH excess can occasionally be the prominent presenting complaint in GH co-secreting tumours, rather than thyrotoxicosis symptoms. Menstrual irregularities are present in all prolactin co-secreting tumours (10) and 33% of thyrotropinomas. Partial or total hypopituitarism has been reported in 25% of cases (2).

Tumour recurrence postoperatively appears to be uncommon. A systematic review of 536 patients with thyrotopinoma showed overall biochemical remission in 86% of patients, which included patients undergoing medical therapy alone, surgery alone, surgery plus adjuvant radiotherapy or surgery plus combined medical therapy with SSAs and/or dopamine agonists. Long-term follow-up was defined in this review as >24 months and was reported in 474 patients (13). Somewhat surprisingly, two of the six reported thyrotropinomas in pregnancy had recurrences post-surgery requiring medical therapy (3, 6) indicating close surveillance is needed.

Thyrotropinoma in pregnancy is an exceedingly rare entity in part because of the scarcity of this tumour but also likely due to subfertility secondary to the presence of a macroadenoma. Early diagnosis is important as there are risks from tumour mass effect and a hyperthyroid state. This case demonstrated a conservative approach with close monitoring was able to yield an excellent outcome. Medical and surgical options were successfully delayed until after delivery reducing both maternal and fetal risk.

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 consent was obtained from the patient for publication of the submitted article and accompanying images.

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Author contribution statement
Y F W, H Y N, D N and D L contributed equally to this paper as first authors. V P supervised this manuscript.

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