Novel diagnostic procedure

Use of cetrorelix in the investigation of testosterone excess in a postmenopausal woman

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A 65-year-old woman presented to the endocrine clinic with increasing facial hirsutism over the past 6 months. She was noted to have excess hair on forearms, back and abdomen, along with some frontal balding. There were no abnormalities of the external genitalia, blood pressure was satisfactory and weight was stable. Biochemistry confirmed elevated testosterone (4.1 nmol/l). No abnormalities were seen on CT of abdomen and pelvis, nor by transvaginal ultrasound of the ovaries. Six months after her initial clinic visit, testosterone had increased to 6.0 nmol/l, rising to 7.3 nmol/l a few months later. Testosterone failed to suppress to low-dose dexamethasone suggesting excessive adrenal production was unlikely. Urine steroid profiling revealed no abnormality of adrenal steroid metabolites. Testosterone suppression was achieved with a rapidly-acting luteinizing-hormone-releasing hormone antagonist (cetrorelix), suggesting an ovarian source of excess production. Histology following bilateral salpingo-oophorectomy revealed a benign 6 mm diameter Leydig cell tumour in the right ovary.

BACKGROUND

Leydig (hilus) cell tumours of the ovary are an uncommon cause of hirsutism and virilisation. These are small tumours (typically <1 cm in diameter) which are difficult to visualise by CT or transvaginal ultrasound scanning.^{1–5} The diagnosis therefore largely relies on biochemical investigation.

Most androgen-producing ovarian tumours have been shown to express functional luteinizing hormone (LH) receptors, and thus respond to LH suppression or stimulation.⁶

Traditionally exogenous oestrogens or gonadotrophin-releasing hormone (GnRH) agonists have been employed as a means of gonadotrophin suppression. This approach however, necessitates administration of hormones over a period of several weeks.^{3–4 7}

A proposed practical alternative is the use of GnRH antagonists which have a more rapid onset of action. As this case demonstrates, the use of a rapidly-acting LH-releasing hormone antagonist (cetrorelix) can achieve gonadotrophin suppression within a few days, offering a more convenient diagnostic tool and enabling a more rapid diagnosis than traditional methods.

A few case reports describe the use of cetrorelix for this purpose, using protocols involving frequent blood sampling over a 2–4-day period.^{1 2} Based on information from these case reports, we established a protocol for cetrorelix administration which would allow investigation on an outpatient basis.

CASE PRESENTATION

A 65-year-old woman attended the local endocrine clinic for investigation of facial hirsutism. She reported increasing hair over her chin and cheeks over the previous 6 months, despite using facial hair removal cream twice a week. On

examination, she was also noted to have some excess hair on both forearms, upper back and lower abdomen, in addition to some slight frontal balding. The Ferriman–Gallwey score⁸ was 14. She reported that her voice had become slightly hoarse recently but not noticeably deeper. There were no abnormalities of external genitalia and blood pressure was satisfactory (on medication). Weight was stable at 61 kg.

She had a history of cerebrovascular accident, ischaemic heart disease and hypertension. She had three children having experienced no fertility problems. Her periods had been regular until menopause at the age of 49 years and she had not experienced any postmenopausal bleeding.

Regular medications included Tildium LA 300 mg daily, isosorbide mononitrate 20 mg twice daily, clopidogrel, lisinopril 10 mg daily, furosemide, simvastatin 40 mg, omeprazole 20 mg daily and co-codamol. She denied taking any over-the-counter or herbal preparations. She was a non-smoker and drank little alcohol.

INVESTIGATIONS

Initial biochemistry revealed menopausal gonadotrophin levels, however, testosterone was elevated at 4.1 nmol/l (table 1). Full blood count was normal.

CT of abdomen and pelvis showed normal adrenals. A 2 cm soft tissue mass was noted in the left adnexa, which was thought to represent either a normal ovary or fibroid. No significant abnormality was seen throughout the rest of the abdomen or pelvis. A subsequent transvaginal ultrasound was unremarkable except for the presence of some tortuous veins in the left adnexal region which may have created the abnormal appearance on CT. The left ovary appeared grossly normal, however, the right ovary could not be visualised.

The patient was commenced on Vaniqa cream for her facial hirsutism and serum testosterone was monitored over the next few months.

After 6 months, serum testosterone had increased further to 6.0 nmol/l, so a low-dose dexamethasone suppression test (0.5 mg four times a day for 2 days) was arranged to exclude adrenal production. Failure of testosterone suppression indicated its production was not adrenocorticotrophic hormone -dependent (figure 1). This was confirmed by a urine steroid profile which showed no abnormality of adrenal steroid metabolites, suggesting an adrenal source of excess testosterone production was unlikely.

Table 1 Baseline biochemistry results

Analyte	Concentration	Reference range
LH	45.5	16–64 U/l
FSH	>100	18–150 U/l
E2	<70	<100 pmol/l
Prolactin	383	<630 mU/l
Testosterone	4.1	<3.2 nmol/l
SHBG	50	20–155 nmol/l
FAI	8.2	<7.0

E2, oestradiol; FAI, free androgen index; FSH, follicle-stimulating hormone; LH, luteinising hormone; SHBG, sex hormone-binding globulin.

Table 2 Cumulative biochemistry results

	Testosterone (nmol/l)	SHBG (nmol/l)	FAI	Androstenedione (nmol/l)	DHAS (μmol/l)	17-OHP (nmol/l)
August 2007	4.0	54	7.4	5.8	1.4	3.0
March 2008	6.0	59	10.2			
May 2008	5.7	59	9.7			3.0
October 2008	7.3*	57	12.8	5.9*	1.8*	
April 2009	7.6	61	12.5			

*Results confirmed by TMS.

17-OHP, 17-OH progesterone; FAI, free androgen index; DHAS, dehydroepiandrosterone sulphate; SHBG, sex hormone-binding globulin.

Figure 1 Low-dose dexamethasone suppression test results (day 4 cortisol <25 nmol/l).

Over the next few months serum testosterone continued to rise, reaching a peak of 7.6 nmol/l (table 2). Androgen concentrations were confirmed by tandem mass spectrometry and a gonadotrophin suppression test was performed to determine whether the excess production originated from the ovaries.

Cetrorelix – gonadotrophin suppression test

A GnRH antagonist (cetrorelix) was used for suppression of gonadotrophins. Using information from case reports,^{1 2} we established a protocol for cetrorelix administration which would allow investigation on an outpatient basis.

Protocol

- ▶ 250 μg Cetrorelix daily for 5 days (administered by subcutaneous injection).
- ▶ Serum samples collected at baseline (day 1) and on day 5 for measurement of gonadotrophins and androgens.

Testosterone showed significant suppression following cetrorelix administration (figure 2), suggesting its production was under gonadotrophin control, thus was likely to be ovarian in origin.

Figure 2 Gonadotrophin suppression test results.

Figure 3 (A) Leydig cells in close proximity to blood vessel (medium power), (B) Leydig cells with inhibin staining, (C) Leydig cells (under higher power), arrow indicates Reinke crystalloid.

TREATMENT

The patient was referred to gynaecology for assessment and subsequently underwent bilateral salpingo-oophorectomy and hysterectomy. Histology revealed a well-defined, benign 6 mm diameter Leydig cell tumour in the right ovary (figure 3). Left ovary and both fallopian tubes were histologically unremarkable. No malignancy was noted.

OUTCOME AND FOLLOW-UP

At a follow-up appointment 6 months postsurgery, serum testosterone had fallen to 1.6 nmol/L, thereby confirming the tumour as the source of excess production. There was a marked reduction in facial hair growth and Ferriman-Gallwey score had decreased to 8.

The patient continues to be followed-up at 6-monthly intervals at the endocrine clinic with monitoring of serum testosterone levels.

DISCUSSION

Leydig cell tumours of the ovary are a rare cause of hirsutism and virilisation. They are usually benign, unilateral and mainly occur in peri or postmenopausal women. Approximately 75% are associated with signs of hyperandrogenism, although occasionally patients may have signs of hyperoestrogenism, such as postmenopausal bleeding, either alone or in addition to virilisation.^{2-3 9}

Due to their small size, Leydig cell tumours are difficult to visualise by CT or ultrasound scanning, therefore

biochemical investigations play an important role in their diagnosis.

Most testosterone-producing tumours express functional LH receptors.⁶ For this reason, these tumours are responsive to LH suppression or stimulation, which may explain their prevalence in postmenopausal women.

Gonadotrophin suppression testing has been successfully employed in identifying ovarian sources of excess testosterone production. Traditionally this is performed by administration of GnRH agonists or exogenous oestrogens.^{3–4 7} These approaches, however, necessitate prolonged hormone administration over several weeks in order to achieve complete gonadotrophin suppression. Cetrorelix, a GnRH antagonist, has a more rapid onset of action. As demonstrated above, cetrorelix can achieve gonadotrophin suppression within a few days.

The use of cetrorelix for gonadotrophin suppression has been illustrated by two previous case reports^{1 2} in the investigation of androgen-producing ovarian tumours.

Stephens *et al*¹ describe a 2-day inpatient procedure in the investigation of a 67-year-old woman with hirsutism and virilisation. Cetrorelix (0.5 mg) was given at baseline and 6 h, with serum samples for testosterone, LH and follicle-stimulating hormone collected at regular intervals over a 24-h period (n=8). Control samples were collected over the 24-h period prior to the test. Testosterone fell to normal levels within 9–12 h.

de Boer *et al*² report the use of cetrorelix in a 75-year-old woman with hirsutism and postmenopausal bleeding. Cetrorelix (250 µg) was administered by subcutaneous injection daily at 09:00 for 4 days. Serum samples were collected at 08:30, 12:00 and 16:30 on day 1, and at 08:30 and 16:00 on days 2–4. LH suppressed within 24 h, with androgen levels decreasing to normal within 48–72 h.

In both cases, the investigation protocol involved frequent blood sampling thus necessitating an inpatient stay. In contrast, the current case report demonstrates the successful use of the cetrorelix suppression test on an outpatient basis. This case confirms that cetrorelix is a convenient, rapid alternative to GnRH agonists or exogenous oestrogens for gonadotrophin suppression and provides a useful diagnostic tool in the investigation of ovarian sources of excess testosterone production.

Learning points

- ▶ Excess testosterone production in women may be adrenal or ovarian in origin.
- ▶ Leydig (hilus) cell tumours of the ovary are an uncommon cause of hirsutism and virilisation.
- ▶ These are small tumours which are difficult to visualise by CT or ultrasound scanning, therefore biochemical investigations play an important role in the differential diagnosis.
- ▶ Gonadotrophin suppression has been used to establish whether testosterone production is LH-dependent and thus likely to be of ovarian origin.
- ▶ Cetrorelix provides a rapid, convenient alternative to oestrogens or GnRH agonists for gonadotrophin suppression, and is suitable for use in the outpatient setting.

Competing interests None.

Patient consent Obtained.

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