Utilisation of gonadotrophin-releasing hormone (GnRH) analogue to differentiate ovarian from adrenal hyperandrogenism in postmenopausal women

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Summary

Postmenopausal hyperandrogenism is a relatively rare diagnosis resulting from excess androgen production from the adrenals or ovaries. The exclusion of malignant causes is a priority. Laboratory tests and imaging are utilised to help differentiate the source of excess androgens. We report two cases of postmenopausal hyperandrogenism in women aged 75 and 67 years. Both cases presented with clinical features suggestive of hyperandrogenism which had developed gradually over the previous 2 years. Laboratory investigations confirmed a significant elevation in their serum testosterone levels. In both cases, imaging did not reveal any abnormality of the adrenals or ovaries. To help differentiate an adrenal vs ovarian source a single-dose GnRH analogue was given with measurement of testosterone and gonadotrophin levels pre and post. The reduction in gonadotrophins achieved by the GnRH analogue resulted in suppression of testosterone levels which suggested an ovarian source. Both patients proceeded to bilateral oophorectomy. Histology revealed a benign hilus cell tumour in one case and a benign Leydig cell tumour in the other.

Learning points:

- A key part of the work-up of postmenopausal hyperandrogenism is to differentiate between an adrenal or an ovarian source of excess androgens;
- Imaging may not identify small ovarian tumours or hyperthecosis and may also identify incidental adrenal masses which are non-functioning;
- Current guidelines suggest ovarian and adrenal venous sampling when imaging is inconclusive but this requires technical expertise and has a high failure rate;
- GnRH analogue use can successfully confirm ovarian source and should be considered as a diagnostic tool in this setting.

Background

Postmenopausal hyperandrogenism is a rare but important diagnosis, particularly due to the possibility of an underlying malignant cause. Causes of postmenopausal hyperandrogenism can be divided into tumorous (benign or malignant) and non-tumorous. Even when the cause is benign the symptoms of hyperandrogenism may be distressing for the patient, and there is a possibility of increased cardiovascular morbidity due to long-term increased androgen exposure. Appropriate diagnosis and treatment is therefore essential. With an ovarian source of androgen excess determination of a benign diagnosis can typically only be made histologically.

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We report two cases of postmenopausal hyperandrogenism where imaging did not reveal an adrenal or ovarian abnormality. Response to GnRH analogue was successfully used to determine an ovarian source of hyperandrogenism in both cases. This was subsequently confirmed histologically post bilateral oophorectomy.

Case presentation 1

A 75-year-old lady was referred with a gradual history of male pattern baldness and hirsutism over the previous 2 years. The hirsutism primarily affected her chin and upper lip which she was waxing every 6 weeks. She underwent menopause at age 45 years and had a regular menstrual cycle prior to that. She had no previous pregnancies. She did not report any postmenopausal bleeding or weight loss. She had no other symptoms of note and was on no medications.

On physical examination significant temporal recession of the hairline was evident. Excess hair growth was noted over the chin and upper lip as well as over the lower abdomen and back. Clitoromegaly was not present. No abdominal masses were palpable.

Investigation

Initial laboratory results showed an elevated testosterone of 6.44 nmol/L, which was confirmed as elevated at 9.11 nmol/L on repeat. FSH and LH were elevated with a low oestradiol level, consistent with her postmenopausal state. Full blood count, renal and liver profiles, TSH, HbA1c, random cortisol and prolactin levels were all within normal limits. The patient was not formally screened for hypercortisolism. As seen in Table 1, other androgens, including DHEA-S level, were not elevated. Transvaginal ultrasound followed by contrast-enhanced

CT of abdomen and pelvis did not show an adrenal or adnexal mass.

Treatment

To help determine the likely source of excess androgen production we proceeded to give a single dose of GnRH analogue according to the following test method: Gonadotrophins and testosterone levels were measured pre and 1 month post administration of leuprorelin 3.75 mg intramuscularly. This drug is currently most commonly used in the treatment of metastatic prostate cancer and can also be used in women in the management of endometriosis. Hypersensitivity reactions can occur but long-term side effects would not be expected with a single dose. It is contraindicated in women who are, or may become, pregnant while using it. As seen in Table 1, the reduction in FSH and LH levels post GnRH analogue resulted in a normalisation of testosterone levels to 0.69 nmol/L. This confirmed an ovarian source of androgen excess and supported a decision to proceed with bilateral oophorectomy.

Outcome and follow-up

Histology showed a 4 mm hilus cell tumour of one ovary with no evidence of malignancy. The patient had an uneventful post-operative recovery. Testosterone level normalised to 0.55 nmol/L postoperatively and the patient had a progressive improvement in symptoms with regression of virilisation and hirsutism.

Case presentation 2

A 67-year-old lady reported an increase in hair growth on her face and abdomen during a routine clinic review for follow-up of her type 2 diabetes mellitus. The symptoms

Table 1 Hormonal profiles pre and 1 month post single-dose GnRH analogue.

Hormones	Reference range	Case 1		Case 2	
		Pre GnRH	Post GnRH	Pre GnRH	Post GnRH
Testosterone (nmol/L)	0.22–2.99	9.11	0.94	14.45	0.69
FSH (IU/L)	25.8–134.8	58.7	6.7	28.5	5.5
LH (IU/L)	7.7–58.5	30.8	1.7	13.7	1.4
Oestradiol (pmol/L)	91–533	57	39	194	75
Progesterone (nmol/L)	<0.16–0.40	0.3	–	2.0	–
DHEA-S (µmol/L)	0.90–2.10	1.09	–	4.10	–
Androstenedione (nmol/L)	2.44–12.22	4.89		6.63	
17 Hydroxyprogesterone (nmol/L)	0.24–3.90	3.62		1.81	
SHBG (nmol/L)	26–118	51.8		29.60	
Free androgen index (calculated)		17.59		48.82	

had been present for approximately 2 years, with more recent male pattern hair loss. She had no postmenopausal bleeding or weight loss. Her diabetes was well controlled on a basal-bolus insulin regime and metformin with a HbA1c of 51 mmol/mol. She had background retinopathy and treated hypertension and dyslipidaemia. She was obese with a BMI of 31.7 kg/m².

On physical examination, there was excess hair growth visible on her chin. Her abdominal hair had been waxed a couple of days before clinic so this was not visibly evident. A mild degree of temporal recession of the hairline was noted. Clitoromegaly was absent and there were no abdominal masses palpable.

Investigation

Her hormonal profile showed a markedly elevated testosterone at 14.45 nmol/L with elevated FSH and LH consistent with menopause. Repeat testosterone confirmed elevation at 11.14 nmol/L. Full blood count, renal and liver profiles, TSH, HbA1c, random cortisol and prolactin levels were all within normal limits. The patient was not formally screened for hypercortisolism. DHEA-S was mildly elevated at 3.89 µmol/L (0.9–2.1) with remaining androgen levels normal as seen in Table 1. Transvaginal ultrasound and contrast CT scans did not reveal any adrenal or adnexal abnormalities and the ovaries were reported as atrophic.

Treatment

A single dose of GnRH analogue was administered as per the method outlined in case 1. Her testosterone level suppressed significantly to 0.94 nmol/L following suppression of gonadotrophins. This supported an ovarian source of androgen excess and the patient proceeded to bilateral oophorectomy.

Outcome and follow-up

Histology showed a benign Leydig cell tumour of the left ovary with no evidence of malignancy. Testosterone level normalised to 0.88 nmol/L postoperatively and at further follow-up the patient noted a complete resolution of her hirsutism and improvement in her hairline.

Discussion

Androgen production in premenopausal women occurs in the adrenals, ovaries, and via peripheral conversion of prohormones (Table 2). Overall androgen production gradually declines with age with a marked decline in adrenal androgens from the third decade onward (1). Ovarian testosterone production does not decrease after menopause leading to an increase in the relative contribution of ovarian testosterone production in postmenopausal women. Hirsutism and alopecia are the most common clinical signs of androgen excess in postmenopausal women, with anabolic appearance, lowering of voice and clitoromegaly occurring with higher androgen levels.

One of the key steps in the evaluation of postmenopausal hyperandrogenism is to differentiate an adrenal from an ovarian source of excess androgens. While an ovarian source is more common in this age group, there are no reliable clinical features to help with this differentiation. Measurement of other adrenal androgens such as DHEA-S may be helpful if significantly elevated but are not diagnostic. Elevated DHEA-S levels have been reported in cases of ovarian androgen secreting tumours and non-tumorous hyperandrogenism, while normal levels can be seen in adrenal androgen-secreting tumours (2). DHEA-S levels may also be elevated in patients with diabetes due to dysregulation of the HPA axis. Recommended imaging modalities for the ovary are transvaginal ultrasound or magnetic resonance imaging (MRI) and for the adrenal are CT or MRI (3). As MRI was not readily available in our institution we performed transvaginal ultrasound and CT. In many cases, such as ours, imaging may not yield a definitive answer. This scenario may be more common in postmenopausal women where an ovarian tumour may be too small to be visualised. The possibility of a non-functioning adrenal adenoma being detected on imaging must also be considered and the presence of an adrenal mass on imaging does not guarantee that it is the source of androgen excess. In these cases ovarian and adrenal venous sampling has been recommended (3, 4). Our use of GnRH analogue as a diagnostic test is based on the principle that the secretion of androgens by ovarian tumours has been shown to be gonadotrophin dependent (5). Hence, the suppression of gonadotrophins by GnRH

Table 2 Source of androgen production in premenopausal women.

	Adrenal (%)	Ovarian (%)	Peripheral conversion (prohormone converted)
DHEA-S	95–100	0–5	
DHEA	50	20	30% (DHEA-S)
Androstenedione	50	50	
Testosterone	25	25	50% (androstenedione)

analogue administration will reduce ovarian androgen production but will not have any effect on adrenal androgen production.

Androgen-secreting ovarian tumours are most commonly sex-cord stromal tumours or steroid tumours (6). Sertoli-Leydig cell tumours are the most common androgen-secreting sex-cord stromal tumour accounting for 0.5% of all ovarian neoplasms. They are typically unilateral and rarely malignant. Pure Sertoli cell tumours are rare and 90% occur in the reproductive years. Hilus cell tumours are steroid tumours arising from Leydig cells in the hilus of the ovary. They are very rare, accounting for 0.02% of all ovarian neoplasms. They typically present with symptoms of hirsutism and virilisation and are most likely to occur in postmenopausal women. Malignancy is extremely rare in hilus cell tumours. The most common non-tumorous ovarian cause of postmenopausal hyperandrogenism is ovarian hyperthecosis (3). This is a benign condition characterised by elevated testosterone levels in absence of elevation of other androgens. Patients typically present with slowly progressive symptoms of hyperandrogenism and virilisation. The exact aetiology of this condition is unknown however postmenopausal elevated gonadotrophin levels and insulin resistance are thought to play a role. The diagnosis can only be confirmed histologically.

Previous case reports of postmenopausal hyperandrogenism have described a suppressive effect of short and long-acting GnRH analogue on testosterone secretion from ovarian tumours (7). A 50% reduction in testosterone levels was seen with short-acting GnRH analogue and a normalisation of testosterone levels with long-acting GnRH analogue. GnRH analogue use has also been described in the treatment of postmenopausal ovarian hyperandrogenism as a non-surgical alternative. Successful suppression of testosterone levels and normalisation of symptoms was achieved in three cases described by Vollard *et al.* in their case series (8). Consideration of its use was suggested by the authors in patients who may be poor surgical candidates due to comorbidities or in patients who are unwilling to undergo surgery. Although ovarian malignancies are rare in this setting the possibility needs to be borne in mind and ongoing follow-up would be required. Suppression of androgen production from an adrenal source with GnRH analogue use has been described in postmenopausal women with adrenal adenomas and bilateral adrenal macronodular hyperplasia (9). This raises the possibility of a false-positive response to a GnRH analogue test. Of note, many of these cases did have adrenal abnormalities evident on imaging.

There are no current recommendations for the use of GnRH analogue as a diagnostic tool to help confirm an ovarian source of androgen excess. Available algorithms have recommended combined adrenal and ovarian venous sampling if imaging is inconclusive (3, 4). This procedure is technically difficult however, and requires an experienced operator. Even in a specialist unit overall success rates for catheterisation of all four veins was only 27% in one study (10). Our cases add to the literature supporting the effectiveness of GnRH in suppressing ovarian hyperandrogenism (7, 8). We suggest that GnRH analogue use should be considered as the diagnostic test of choice in the setting of postmenopausal hyperandrogenism where imaging is inconclusive. It is non-invasive, does not require technical expertise and can be performed in an outpatient setting.

Patient consent

An informed consent has been obtained from the patients for publication of this case report

Author contribution statement

E Bahaeldein prepared the case report. M J Brassill reviewed and edited the manuscript and was the physician responsible for both patients care.

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