CASE REPORT

Total testosterone levels are often more than three times elevated in patients with androgen-secreting tumours

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SUMMARY

Hirsutism is present in up to 25% reproductive aged women and is most often caused by polycystic ovary syndrome. Less than 5% of patients with hirsutism are diagnosed with rare endocrine diseases including ovarian or adrenal androgen-producing tumours, but these tumours may be malignant and need surgery. Terminal hair growth on lip and chin gradually increases after menopause, which complicates distinction from normal physiological variation. Precise testosterone assays have just recently become available in the daily clinic. We present three women diagnosed with testosterone-producing tumours. Gold standard techniques were used to measure testosterone levels. All tumours originated from the ovaries. Based on the present cases and the existing literature, we suggest that androgen-producing tumours should be suspected in patients with rapid progression of hyperandrogen symptoms, particularly when total testosterone levels are above three times the upper reference limit.

BACKGROUND

Hirsutism affects 5–25% of premenopausal women and is defined as increased growth of terminal hair in a male pattern.^{1 2} More than 90% of hirsute women are diagnosed with idiopathic hirsutism (IH) or polycystic ovary syndrome (PCOS).^{1 2} IH can be defined as hirsutism with normal ovaries, testosterone levels within reference limits and regular ovulations.¹ The Rotterdam criteria define PCOS when two of the criteria are fulfilled: oligo/amenorrhoea, polycystic ovaries and clinical or biochemical hyperandrogenism.³ PCOS is a diagnosis of exclusion.³ Up to 5% of patients presenting with hirsutism may be diagnosed with serious endocrine disorders such as androgen-secreting tumours, 21-hydroxylase defects, Cushing's syndrome and hyperprolactinaemia.^{4 5} Androgen-producing tumours may be malignant, and surgery is the first-line treatment in contrast to treatment with oral contraceptives and life style intervention that are generally applied in hirsutism and PCOS. Therefore, it is critical to avoid delayed or incorrect diagnosis. Guidelines are needed to guide clinicians on when these relatively rare conditions should be suspected in patients presenting with symptoms of androgen excess and menstrual irregularities.

In postmenopausal women, the prevalence of androgen-producing tumours is probably low. It is generally recommended that postmenopausal women should be referred for endocrine

investigation when there is suspicion of androgen-producing tumours, but here, more specific guidelines would also be helpful. Clinical evaluation in postmenopausal women is especially complicated by a tendency to increased hair growth on the lips and chin.

Measurement of testosterone levels is recommended as part of the initial evaluation programme in patients with hirsutism.^{4 6} Furthermore, a medical history including androgenic and gynaecological symptoms, medications, physical examination and screen blood test of gonadotrophins, oestradiol, thyroid status, prolactin and 17-OH progesterone is appropriate.^{3 7} The gold standard method for measuring total testosterone is mass spectrometry, whereas commercially available direct assays generally overestimate the steroid concentration.⁸ Recent reported cases of androgen-producing tumours in patients with hirsutism may have applied imprecise testosterone assays, which could have affected results (table 1). We present three cases of androgen-producing tumours that occurred in our clinic. Gold standard techniques were applied to ensure correct measurement of testosterone levels. The literature was evaluated critically with the purpose of defining clinical symptoms and testosterone levels that indicate an androgen-secreting tumour.

CASE PRESENTATION

Case 1: A 39-year-old premenopausal woman was referred because of 2 years of progressive hirsutism and voice roughness. Previously, she had been pregnant three times. She was referred to an otorhinolaryngologist who recommended removal of her gestagen containing intrauterine device. Symptoms were unchanged and she still had amenorrhoea. The patient had no wish to preserve fertility.

The patient had a body mass index (BMI) of 25 kg/m², Ferriman-Gallwey score (FG-score) of 15, deep voice and no clitoromegaly.

Histological examination of the affected ovary showed an androgen-producing Sertoli-Leydig cell tumour without involvement of surrounding structures.

Case 2: A 61-year-old postmenopausal woman was referred because of 3 years of progressive facial hirsutism (figures 1 and 2). She had a known diagnosis of type 2 diabetes and medically treated hypertension.

The patient had a BMI of 35 kg/m², blood pressure of 130/80 mm Hg, facial FG-score of 8 and no signs of virilisation.

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Table 1 Published cases and abstracts on androgen-producing tumours 2009–2014

Reference, country, year	Study subject(s)	Symptoms	Histology	Testosterone values	Testosterone elevation
Agarwal and Trerotola, ⁹ USA, 2010	Postmenopausal age 58 years	Progressive androgen symptoms over 1 year including clitoromegaly	Leydig cell tumour in ovary—2 cm	Total testosterone 4.64 nmol/L (upper limit 1.30 nmol/L)	3.4 times
Di <i>et al</i> , ¹⁰ Italy, 2012	Postmenopausal age 67 years	Progressive, severe androgen symptoms over 6 months including clitoromegaly	Sertoli-Leydig cell tumour in ovary—3.5 cm	Total testosterone 12.6 nmol/L (upper limit 2.1 nmol/L)	6.1 times
Yetkin <i>et al</i> , ¹¹ Turkey, 2011	Postmenopausal age 60 years	Progressive androgen symptoms over 5 years including deepening of voice	Leydig cell tumour in ovary—5 cm	Total testosterone 46.4 nmol/L (upper limit 2.4 nmol/L)	19.5 times
Levens <i>et al</i> , ¹² UK, 2009	4 women age 90, 71, 62, and 12 years	Progressive androgen symptoms over years including deepening of voice and clitoromegaly	Ovarian hyperthecosis Stromal hyperplasia and ovarian hilus tumour—tumours were 1–2 cm	Total testosterone 7.5, 18.04, 27.76, and 20.82 nmol/L (upper limit not given)	3.8–13.9
Poduval <i>et al</i> , ¹³ USA, 2009	Age 15 years	Progressive androgen symptoms over 16 months including deepening of voice and clitoromegaly	Mature cystic teratoma in ovary with various cell types including Leydig cells—very large tumour of 20 cm	Testosterone 5.42 nmol/L (upper limit 2.60 nmol/L)	2.1 times
Chandrasekara <i>et al</i> , ¹⁴ UK, 2010	Postmenopausal age 52 years	Progressive androgen symptoms over 11 months including deepening of voice	Steroid-producing ovarian tumour with components of adrenal cortical cells—3 cm	Total testosterone 10.7 nmol/L (upper limit 2.9 nmol/L)	3.7 times
Dennedy <i>et al</i> , ¹⁵ Ireland, 2010	Premenopausal age 30 years	Progressive androgen symptoms over 1 year	Benign adrenocortical tumour—5 cm	Testosterone 7.5 nmol/L (upper limit 2 nmol/L)	3.8 times
	Premenopausal age 25 years	Progressive androgen symptoms over 21 months mild clitoromegaly	Ovarian teratoma with Leydig cells—2 cm	Testosterone 9.5 nmol/L (upper limit 2 nmol/L)	4.8 times
Paragliola <i>et al</i> , ¹⁶ Italy, 2009	Premenopausal age 42 years	Hirsutism	Sertoli-Leydig cell tumour in ovary—1.8 and 1.7 cm, respectively	Testosterone 11.6 and 28.9 nmol/L, respectively (upper limit not given)	7.7–19.2 times
	Postmenopausal age 54 years	Not given			
Amano <i>et al</i> , ¹⁷ Japan, 2011	Premenopausal age 31 years	Progressive severe androgen symptoms over 2 years	Androgen-secreting adrenocortical carcinoma—6 cm	Total testosterone 12.6 nmol/L (upper limit not given)	6.3 times
Rodriguez-Gutierrez <i>et al</i> , ¹⁸ Mexico, 2013	Premenopausal age 18 years	Progressive androgen symptoms over 10 years clitoromegaly, deepening of voice, and severe hypertension	Adrenal adenomas—9–10 cm	Testosterone 12.6 nmol/L (upper limit 2.4 nmol/L)	5.3 times
Finozzi <i>et al</i> , ¹⁹ Uruguay, 2012	Premenopausal age 18 years	Progressive severe androgens symptoms over 12 years including clitoromegaly	Adrenal carcinoma—15 cm	Total testosterone increased 10–25 times above reference interval	10–25 times

None of the articles reported in which testosterone assay was used.

Where no upper limits for testosterone were given in the articles, we used 2 nmol/L (0.69 ng/mL) as an arbitrary cut-off limit.

A macroscopic examination of the removed ovaries revealed a 1×1 mm yellow area in the right ovary but histological examination of both ovaries was normal without sign of malignancy.

Case 3: A 54-year-old postmenopausal woman was referred because of 2–3 years of progressive hirsutism and androgenous hair loss. She had passed an uneventful menopause at the age of

42 years. She had a history of type 2 diabetes of 12 years duration.

The patient had a BMI of 28 kg/m², blood pressure of 144/94 mm Hg, facial FG-score of 6 and scalp hair loss in a male pattern.

Figure 1 Picture of case 2. **Figure 2** Picture of case 2.

On macroscopic examination, both ovaries were of normal size without visible tumours but on the left ovary, small yellow areas were observed. Histology revealed a small steroid cell tumour, not otherwise specified, and no signs of malignancy.

INVESTIGATIONS

Routine evaluation in newly referred patients included medical history, clinical examination, transvaginal ultrasound (US) and fasting blood samples. Hirsutism was assessed by the FG-score²⁰ and transvaginal US was performed at the Department of Gynecology, Odense University Hospital.

Fasting blood samples were drawn during the morning in follicular phase (cycle days 2–8) in patients with a cycle length shorter than 3 months. Patients with cycle length >3 months and postmenopausal women had the blood samples drawn on a random cycle day. Blood tests included androgens (total testosterone, free testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), 17-hydroxyprogesterone (17OHP)), luteinising hormone (LH), follicle-stimulating hormone (FSH), prolactin and lipid profile. Two measurements of 24 h U-cortisol—or a short dexamethasone suppression test involving 2 days of using decadron 1 mg—were performed in patients with a clinical suspicion of Cushing's syndrome. Patients with elevated 17OHP levels had an adrenocorticotrophic hormone test performed according to recent guidelines.³

In case 1, serum total testosterone and SHBG were analysed using a specific radioimmunoassay (RIA) after ether extraction.²¹ This method shows close correlation with the determination of testosterone levels by using mass spectrometry.^{22–24} In cases 2 and 3, total testosterone was measured by mass spectrometry. The intra-assay coefficient of variation (CV) for total testosterone was 8.2% and for SHBG it was 5.2%. The interassay CV for total testosterone was 13.8%.

Reference intervals for premenopausal women were: total testosterone 0.55–1.8 nmol/L, free testosterone 0.006–0.034 nmol/L, SHBG 41–170 nmol/L, DHEAS 1200–9500 nmol/L.

Reference intervals for postmenopausal women were: total testosterone 0.52–1.7 nmol/L, free testosterone 0.005–0.019 nmol/L, SHBG 46–240 nmol/L, DHEAS 500–4500 nmol/L.

Prolactin levels were measured in the morning after a minimum of 2 h awakening time using a solid phase two-site commercial kit (AutoDelfia, Perkin Elmer, Wallac Oy, Turku, Finland). LH and FSH were analysed by time-resolved fluoroimmunoassay using commercial kits (AutoDelfia, Wallac Oy, Turku, Finland). 17OHP was analysed by RIA using a commercial kit (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, USA).

DHEAS was measured by RIA on diluted serum using specific antibodies.

Case 1: Total testosterone 15.0 nmol/L, SHBG 51 nmol/L, free testosterone 0.1957 nmol/L, DHEAS 6700 nmol/L. 17-OHP, FSH, LH, prolactin and oestradiol were within reference limits.

Transvaginal US showed a 6×7 cm ovarian tumour with cystic and solid changes. CT of the adrenals was normal.

Case 2: Total testosterone 5.3 nmol/L, SHBG 52 nmol/L, free testosterone 0.0925 nmol/L, DHEAS 5600 nmol/L. 17-OHP, androstenedione, FSH and LH were within reference limits.

Transvaginal US and adrenal MRI were normal and did not show any tumours.

Case 3: Total testosterone 15.4 nmol/L, SHBG 17 nmol/L, free testosterone 0.5088 nmol/L, DHEAS 1060 nmol/L. 17-OHP, androstenedione, FSH and LH were within reference limits.

Transvaginal US and adrenal MRI were normal and did not show any tumours.

DIFFERENTIAL DIAGNOSIS

Case 1: The presence of a unilateral adnexal mass, hirsutism, elevated testosterone levels and normal CT scan of the adrenals gave an indication of a testosterone-producing ovarian tumour requiring surgical intervention. There is at present no preoperative method to distinguish between Sertoli-Leydig cell tumours and other ovarian tumours with excess androgen production (eg, Sertoli cell tumour, Hilus cell tumour, gonadoblastoma) or to assess their malignant potential.²⁵

Cases 2 and 3: In these cases, ovarian origin of the androgen excess was deduced by a normal MRI of the adrenals. It was also taken into account that ultrasonic, radiological and macroscopic appearances of the ovaries are often normal in cases of excess ovarian androgen production.²⁵

TREATMENT

Case 1: The patient underwent hysterectomy, omentectomy and bilateral salpingo-oophorectomy with removal of the tumour.

Case 2: The patient underwent laparoscopic bilateral salpingo-oophorectomy, and hysteroscopic resection of endometrium and a benign endometrial polyp.

Case 3: The patient underwent laparoscopic bilateral salpingo-oophorectomy.

OUTCOME AND FOLLOW-UP

The surgical procedures were uncomplicated and, in all cases, testosterone levels were normalised during follow-up and no symptoms of relapse were present.

DISCUSSION

Hirsutism is a common clinical condition, whereas androgen-secreting tumours are rare.

General practitioners, gynaecologists and endocrinologists therefore need quick and reliable screening tools that clearly indicate when to suspect androgen-secreting tumours. These tools include medical history, clinical examination or biochemistry. The aim is to try to ascertain whether an androgen-secreting tumour can be suspected with a specific combination of clinical signs and test results.

Table 1 includes published cases of androgen-secreting tumours. Uniform evaluation programmes for patients with hirsutism were applied recently²⁶ and therefore only cases published within the past 5 years were included in the table.

Medical history and clinical examination

The FG-score is the most commonly used method to determine the degree of hirsutism.²⁰ In the daily clinic, use of the FG-score is complicated by interobserver variability²⁷ and the majority of patients applying cosmetic treatment.^{28 29}

Hirsutism is characterised by increased androgen activity in the hair follicles.^{1 2} The enzyme 5 α -reductase is responsible for the conversion of testosterone to the more potent androgen dihydrotestosterone and increased 5 α -reductase activity causes terminal hair growth in the dermal papilla.^{30 31} Individual variations in dermal 5 α -reductase activity may explain the often near-normal testosterone levels, and the lack of correlation between circulating testosterone levels and clinical hirsute manifestations.³¹ At menopause, the ovaries atrophy and increased levels of LH and FSH may stimulate ovarian testosterone secretion. Gradual increased growth of terminal hair on lip and chin may

therefore be seen around menopause and makes it difficult to evaluate the rate of symptom progression.

Androgen-producing tumours are often rapidly progressing. In our cases, the women experienced changed appearance during a rather short time period and the medical history, in combination with the clinical appearance, raised the suspicion of androgen-secreting tumours. These findings are in agreement with [table 1](#), where all patients had progressive hyperandrogen symptoms including, in some cases, clitoromegaly as a symptom of virilisation.

Biochemistry

Total testosterone: The cut-off limit for total testosterone above which an androgen-producing tumour should be excluded is usually set as more than two times above the upper reference limit.^{2–4} It is, however, important that a reliable method of testosterone measurement is used. The gold standard for measuring total testosterone is mass spectrometry, whereas most commercially available direct assays generally overestimate the steroid concentration.⁸ Overestimation of androgen levels increases the risk of ordering unnecessary US and MRI in healthy women, and incidentalomas may be diagnosed.³² In the three presented cases, testosterone levels were more than three times elevated. Despite reservations regarding assay use, these findings were in accordance with the cases reported in [table 1](#). One case in [table 1](#) had testosterone levels that were only two times elevated, but this patient had severe virilising symptoms that would lead to the suspicion of an androgen-producing tumour.

Free testosterone: All three presented cases had elevated levels of free testosterone. The majority of patients with PCOS have low levels of SHBG, which increase levels of free testosterone.³³ Therefore, in the daily clinic, elevated free testosterone is not a good predictor of androgen-secreting tumours. Salivary testosterone levels were increased in patients with androgen-secreting ovarian tumours, but the use of salivary testosterone to diagnose androgen-secreting tumours remains to be established.³⁴

DHEAS: DHEAS levels were normal in all three cases. DHEAS is, however, mainly produced in the adrenal glands and increased DHEAS can be used as a marker of increased adrenal activity.³⁵ High DHEAS levels may be seen in patients with adrenal tumours.³⁶ In patients with ovarian tumours, levels of DHEAS are most often normal or even decreased (34;36). DHEAS levels decrease with age.³⁵ We previously reported that 29/341 patients with hirsutism had DHEAS above reference interval, but none of those patients was diagnosed with an adrenal tumour.⁴ These results were in agreement with another cross-sectional study.³⁷ In the daily clinic, the use of DHEAS measurement to diagnose androgen-producing tumours is therefore limited by considerable overlap between patients and controls, and the need for age corrected reference intervals.

All diagnosed androgen-secreting tumours in our population of women with hyperandrogen symptoms were of ovarian origin. The cases in the present paper originated from two departments in collaboration; an endocrine and a gynaecological department. Three cases of androgen-secreting adrenal tumours were found during search of recent literature ([table 1](#)). All these cases were diagnosed in premenopausal women. These findings could suggest that androgen-producing tumours are most often of ovarian origin. Cases were retrieved from the literature with the help of a professional librarian. Publication bias could, however, be present and, therefore, published cases may not be representative of the presence of adrenal and ovarian tumours in the background population.

In agreement with previous studies, the functional ovarian neoplasms most frequently included Sertoli-Leydig cell tumours,

which represent less than 1% of all ovarian tumours. In many cases, ovarian tumours were very small or even undetectable. Cases 2 and 3 were postmenopausal and did not have visible tumours. Testosterone levels normalised during bilateral ovariectomy, which supported the correct diagnosis. Case 1 had an ovarian mass and did not want to preserve fertility. In our centre, we do not routinely perform ovarian and adrenal vein sampling, but this method may be relevant in women with no visible tumours or when fertility should be preserved if possible.³⁸ In premenopausal women, unilateral ovariectomy can thus be performed based on vein sampling.³⁸ Referral to a high specialist centre should therefore be considered in subgroups of patients to ensure the origin of androgen production.¹⁸ Fluorodeoxyglucose-positron emission tomography/CT could be an alternate method to diagnose very small ovarian Leydig cell tumours.³⁹

Gonadotropin-releasing hormone (GnRH)-agonist treatment efficiently decreases testosterone levels and may be an alternative to ovariectomy in postmenopausal women with no visible ovarian tumours.^{40–41} Owing to side effects including increased risk of osteoporosis, GnRH-agonist treatment is not indicated in premenopausal women. GnRH-agonist treatment for a limited time period may, however, be applied to confirm the diagnosis of ovarian androgen-secreting tumour.^{40–41} Close follow-up is needed during GnRH-agonist treatment to ensure low testosterone levels.⁴⁰ Laparoscopic ovariectomy is widely available and the risk of operative complications is generally low. Therefore, in our clinic, surgery is often preferred over long-term medical treatment with a GnRH-agonist.

The diagnosis of androgen-secreting tumours in postmenopausal women may be difficult given the tendency to increased hair growth after menopause. Severe hyperandrogenaemia in postmenopausal women needs treatment with surgery in the case of an androgen-secreting tumour or may, in some cases, be treated with GnRH-agonists.

Five per cent of all adrenal tumours are virilising and 50–70% are malignant with poor prognosis.^{42–43} In agreement with this, reported cases in [table 1](#) had very large tumours, which is a marker of malignancy. Furthermore, they were all young and premenopausal, which could be an additional marker of malignancy. The majority of androgen-producing adrenal tumours co-secrete cortisol, which may explain why many patients do not primarily present with PCOS-associated symptoms.⁴⁴ Only 6% of adrenal tumours secrete androgens alone.⁴⁴

The present data thus support that ovariectomy can be used as the first-line treatment in patients with markedly elevated testosterone levels and no visible adrenal tumour, who do not care to preserve fertility.

Some limitations may apply to the present case presentation and review. Data from the three cases were collected retrospectively and therefore no additional data on tumour pathology could be retrieved. Furthermore, the total number of postmenopausal women referred to our clinic due to hyperandrogen symptoms is not available. The strength of the present case presentation is the uniform evaluation of newly referred patients in our clinic and the use of precise hormone assays.

CONCLUSION

Testosterone levels should be measured with a reliable assay in women presenting with hyperandrogen symptoms. Androgen-secreting tumours should be suspected in patients with testosterone levels more than three times the upper reference limit or in patients with rapid progression of hyperandrogen symptoms.

Learning points

- Polycystic ovary syndrome is a diagnosis of exclusion.
- Medical history and precise androgen measurements are important to screen for androgen-secreting tumours in patients with hyperandrogen symptoms.
- Total testosterone is the biochemical marker that best predicts androgen-producing tumours.

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