REVIEW

Investigation of patients with atypical or severe hyperandrogenaemia including androgen-secreting ovarian teratoma

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Abstract

Approximately 7\% of women of reproductive age manifest polycystic ovary syndrome (PCOS) and <0.5\% have other causes of hyperandrogenism including congenital adrenal hyperplasia (CAH), androgen-secreting tumour of an ovary or an adrenal gland, Cushing’s syndrome or hyperthecosis. The presence of features atypical of PCOS should prompt more extensive evaluation than that usually undertaken. Features atypical of PCOS include the onset of symptoms outside the decade of 15–25 years, rapid progression of symptoms, the development of virilization and a serum testosterone concentration in excess of twice the upper limit of the reference range. Ethnic background, family history and specific clinical findings, e.g. Cushingoid appearance, may inform a focused investigation. Otherwise, patients should have measurement of 17-hydroxyprogesterone (17-OHP) under basal conditions ideally in the early morning, and if abnormal, they should have measurement of 17-OHP one hour after the administration of synthetic ACTH, 250 mg i.v. to screen for CAH, which is present in ~2\% of hyperandrogenic patients. The overnight cortisol suppression test employing 1 mg dexamethasone at midnight is a sensitive test for Cushing’s syndrome. Coronal tomographic (CT) scanning of the adrenals and transvaginal ultrasonography of the ovaries are the investigations of choice when screening for tumours in these organs. Less frequently required is catheterization and sampling from both adrenal and ovarian veins, which is a technically demanding procedure with potential complications which may provide definitive diagnostic information not available from other investigations. Illustrative case reports highlight some complexities in the investigation of hyperandrogenic patients presenting with features atypical of PCOS and include only the ninth case report of an androgen-secreting ovarian teratoma.

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Introduction

Hyperandrogenism is an essential component of polycystic ovary syndrome (PCOS), which is the most common endocrine disorder to affect young women. The term PCOS was defined at a meeting of experts in Rotterdam, 2003, to require two of the three following features: i) clinical or hormonal evidence of androgen excess; ii) oligomenorrhea or amenorrhea; iii) ultrasonographic evidence of polycystic ovaries (1). Therefore, the term PCOS covers a wide range of related presentations from the patient with hirsutism who continues to ovulate and menstruate and has polycystic ovaries through the non-hirsute, oligomenorrhoeic woman with polycystic ovaries to the hirsute patient with hyperandrogenaemia with or without polycystic ovaries and several other combinations. Approximately 7\% of women are affected by PCOS (2, 3). The diagnostic approach to the patients presenting with hirsutism should recognize that while PCOS and closely related disorders, such as idiopathic hirsutism, will be the diagnosis in >95\% of patients, alternative diagnoses exist which require specific and possibly urgent treatment, and this paper addresses their investigation and diagnosis (Table 1) (4, 5).

Patients with PCOS usually present between the ages of 15–25 years, and their symptoms are slowly progressive with over 1 year usually elapsing from the time the patients first notice the appearance of hair to seeking medical advice (6, 7). PCOS is rarely associated with evidence of virilization or severe hyperandrogenaemia (Table 1). Evaluation with a detailed history and clinical examination may be adequate to make the diagnosis of PCOS (8). However, measurement of serum testosterone, total or an index of free testosterone, is useful to screen for the rare patient with cryptic severe hyperandrogenaemia, which will prompt evaluation for diagnoses alternative to PCOS. Serum testosterone concentrations
which are greater than twice the upper limit of the reference range or indices of free testosterone which are over fivefold elevated suggest a diagnosis other than PCOS. While detection of polycystic ovaries by ultrasound examination is one of the criteria which may contribute to a diagnosis of PCOS according to the Rotterdam criteria, it is not essential, and indeed, the finding is non-specific since it is found in ~25% of young women (9) and may occur in other disorders included in the differential diagnosis of hirsutism, e.g. congenital adrenal hyperplasia (CAH) (10). Ovarian hyperthecosis presents similarly to PCOS, and the two diagnoses can be difficult to distinguish (11, 12). Features of hyperandrogenism in ovarian hyperthecosis persist beyond the menopause, and indeed, ovarian hyperthecosis may account for the majority of cases of post-menopausal hyperandrogeaemia. Women with hyperthecosis also have severe hirsutism and other clinical evidence of virilization not seen in PCOS such as cliteromegaly, temporal balding and deepening of the voice (11, 12).

The patient who presents with any features which are atypical of PCOS requires comprehensive evaluation. The investigations and their order will depend on the clinical setting and the finding of other abnormalities. Some ethnic groups have a high prevalence of CAH of the most frequently encountered type, 21-hydroxylase deficiency, including those of Hispanic origin, Askanesi Jews and Eskimos (13, 14). Patients with Cushing’s syndrome may have obvious signs of glucocorticoid excess. In rare cases, PCOS also co-presents as a manifestation of acromegaly (15). However, even in the absence of a suggestive family or ethnic history and/or in the absence of features of Cushing’s syndrome, screening for these disorders is warranted in the hirsute patient with features atypical for PCOS including severe hyperandrogeaemia (Table 2).

**Screening tests**

**Cortisol suppression test**

The dexamethasone, 1 mg overnight, cortisol suppression test is a widely used screening procedure for Cushing’s syndrome. In normal subjects, serum cortisol will be suppressed to <50–100 nmol/l in blood obtained 8–9 h following the administration of 1 mg dexamethasone by mouth at midnight (16–18). The cut-off point depends on the local assay characteristics and has been the subject of recent upward revision (16). False negative results are rare. False positive results have been reported to occur in up to 30% of patients tested, and they may be associated with anxiety, obesity, sleep deprivation, excessive alcohol intake or drugs which induce rapid clearance of dexamethasone, e.g. anticonvulsants (16). The 48-h ‘low-dose’ cortisol suppression test may be used if the overnight test produces a positive or equivocal result. However, a recent meta-analysis concludes that the performance of the frequently used screening tests for Cushing’s syndrome, including the overnight and ‘low-dose’ 48-h dexamethasone suppression tests, is similar (19, 20).

**Screening for CAH due to 21-hydroxylase deficiency**

Although 21-hydroxylase deficiency is not the only form of CAH that is associated with hyperandrogeaemia and its manifestations, it is by far the most frequently encountered (13, 14) accounting for 2% or less of patients with hirsutism in many western societies (4, 21). In this disorder, the spectrum of cortisol deficiency extends from profound to partially or completely compensated adrenal failure associated with virilization which may be present at birth. Depending on the extent of enzymatic compromise,
mild to severe hirsutism and menstrual disorders appear at various points from childhood to young adulthood. Significantly elevated early morning serum 17-hydroxyprogesterone (17-OHP), also associated with markedly elevated concentrations of serum testosterone and androstenedione, is highly characteristic of 21-hydroxylase deficiency, an autosomally recessive genetic disorder. Measurement of 17-OHP in serum 1 h after the administration of synthetic ACTH (1–24 ACTH), 250 μg i.v. or i.m., is particularly useful when access to early morning blood samples is not available. Figure 1 demonstrates the relationship of basal and ACTH-stimulated 17-OHP values in normal subjects, carriers (heterozygotes who are not affected in a clinically significant manner) and homozygotes for non-classical (mild) and classical 21-hydroxylase deficiency (22). It has been reported recently that basal serum 17-hydroxyprogesterone concentrations in excess of 5 nmol/l provide 100% sensitivity and 88.6% specificity in screening for 21-hydroxylase deficiency as confirmed by an ACTH-stimulated 17-OHP concentration in excess of 30 nmol/l (23). We recommend screening with an early morning baseline serum 17-OHP concentration and following up abnormal results with the ACTH stimulation test. The authors caution that each laboratory should establish local diagnostic values. Other enzymatic deficiencies accounting for CAH are very rare in most societies. CAH due to 11-hydroxylase deficiency is associated with hypertension and hypokalaemia and is characterized by elevated serum 11-deoxycortisol and 11-deoxycorticosterone concentrations (24). 11-hydroxylase deficiency has been reported with increased frequency in a Turkish population (25). CAH due to 3βol-dehydrogenase, δ4–5-isomerase is characterized by features of adrenal insufficiency, hirsutism, menstrual disorders, virilization and elevated δ5 steroids including DHEA, DHEAS, 17-hydroxypregnenolone and pregnenolone (26).

Screening for adrenal tumour
CT scanning and magnetic resonance imaging (MRI) scanning of the adrenal glands are sensitive tests for the presence of an adrenal adenoma or adenocarcinoma which is usually greater than 1 cm in diameter (27). Occasionally, iodocholesterol scanning, preformed under ACTH suppression using dexamethasone, 0.5 mg every 6 h for at least 5 days, may provide additional information where other imaging yields equivocal results (28). ACTH suppression is required to have only autonomous adrenal function picked up on scanning. In addition, measurement of androgens in serum after 5 days of adrenal suppression will distinguish between androgens maintained by suppressible ACTH stimulation as in the case of CAH and androgens secreted autonomously by tumours of adrenal glands or ovaries (29). Prolonged, 5-day adrenal suppression is necessary to allow time for the normal slow clearance of adrenal androgens, particularly DHEAS.

Screening for an ovarian tumour
Ultrasound examination is the procedure of choice when imaging ovaries in the evaluation of hyperandrogenaemia for polycystic characteristics or tumours. This is best performed using a combination of transabdominal ultrasonography and transvaginal ultrasonography (30). MRI scanning can also be used for the diagnosis of adnexal masses. However, this modality is most useful in differentiating an ovarian tumour from a uterine myoma or during pregnancy (31). Androgen-secreting ovarian tumours are frequently small solid masses with non-specific ultrasonographic or MRI appearances (32). Rarely extra-ovarian sources of androgens may also be detected by this examination (33).

Venous sampling to detect an obscure source of hyperandrogenaemia
In occasional hyperandrogenaemic patients who have normal results to the overnight cortisol suppression test, serum 17-OHP concentrations in the early morning or following synthetic ACTH administration and when CT and MRI scanning of the adrenals and ultrasound imaging of the ovaries have failed to detect a relevant abnormality, venous sampling may be helpful. This procedure should be undertaken by a radiologist highly experienced in the technique which is technically demanding and failure to catheterize one or more
vessels is common (34). A catheter is threaded into the femoral vein, which is then positioned if possible deep in both adrenal veins and both ovarian veins in sequence. When the catheter tip is in position, a sample of blood is obtained. At approximately the same time, a sample of blood is also obtained from a peripheral vein, e.g. arm. Measurement of the androgen or androgens present in excess, usually testosterone and/or androstenedione, in all samples will usually allow the identification of an exaggerated adrenal or ovarian vein to peripheral vein androgen concentration gradient. A >1–9 gradient from peripheral vein steroid concentration to concentration in a vein immediately draining either an adrenal gland or an ovary is highly indicative of the source of androgen excess (34–36). In this way, it is usually possible to locate the source of the androgen excess. Complications are infrequent but may include bleeding at the puncture site, rupture of a deep vein and thrombosis.

Illustrative cases

Case 1

A 30-year-old woman presented with recent onset of acne, mild hirsutism and irregularity of menstruation with intervals varying between 4 and 8 weeks in the preceding 12 months. She was noted to be hypertensive. On subsequent evaluation, she was noted to be hypokalaemic with serum potassium of 3.1 mmol/l. In addition, the serum testosterone concentration was markedly elevated, 7.5 nmol/l (reference range 0.5–2.0), as were those of androstenedione, 23.1 nmol/l (reference range 3.3–9.9), and DHEAS, 24.0 nmol/l (reference range 0.9–12). The early morning serum 17-OHP concentration was 3.4 nmol/l (reference range 1–5). Following the administration of 1 mg dexamethasone at midnight, serum cortisol concentrations fell from 351 to 27 nmol/l. CT scanning of the adrenal glands revealed a 5-cm right-sided adrenal mass. The right adrenal was resected and it revealed the presence of an adrenocortical tumour which apart from the large dimensions generally appeared to be benign. Absolute certainty of benignity or malignancy is not possible in the absence of metastases in the case of adrenal tumours or indeed most endocrine tissue tumours (37). Post-operatively, the patient was normotensive and normokalaemic, and after several months, acne cleared and regular menstruation resumed. Testosterone, androstenedione and DHEAS levels returned to normal, and at a 3-year follow-up visit, all features were maintained with no evidence of recurrence on CT scanning.

Comment

Although this patient’s presenting features were relatively mild, the late age of the first appearance of symptoms and the marked degree of hyperandrogenaemia prompted extensive evaluation, which was rewarded with the identification of an adrenal tumour. Unusual features in this patient were hypertension and hypokalaemia. The serum aldosterone and plasma renin activity and the aldosterone to renin activity ratio were normal, thus excluding primary hyperaldosteronism. It is tempting to suggest that the tumour also secreted an unusual mineralocorticoid. However, in that instance the plasma renin activity would be suppressed.

Case 2

A 25-year-old woman presented with a history of amenorrhoea for 21 months which had its onset following 3 months of treatment with a combined oral contraceptive pill for irregular menstruation. Menarche was at 16 years with regular menstruation occurring approximately at 31-day intervals and was associated with dysmenorrhoea. Mild hirsutism had been noted several years prior to presentation affecting the upper lip, inter-mammary region, lower abdomen and upper thighs. No treatment had been pursued by the patient. In addition to hirsutism, physical examination revealed cliteromegaly and anterior fusion of the labia. Investigations of steroid concentrations in serum are summarized in Table 3. The 0900 h serum 17-OHP concentration was 663 nmol/l, while serum cortisol concentration was 270 nmol (reference range 200–550 nmol/l). One hour following the administration of synthetic ACTH, 250 μg i.v., the serum 17-OHP value rose to 1108 nmol/l, while testosterone climbed to 13.7 nmol/l, androstenedione to 91 nmol/l and the cortisol response was to a concentration of

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Basal, ACTH-stimulated and dexamethasone-treated serum steroid and sex hormone-binding globulin (SHBG) concentrations in Case 2.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Testosterone (nmol/l)</td>
</tr>
<tr>
<td>Reference</td>
<td>0.6–2.0</td>
</tr>
<tr>
<td>Basal</td>
<td>9.5</td>
</tr>
<tr>
<td>Post-synacthen</td>
<td>13.7</td>
</tr>
<tr>
<td>Dexamethasone (6 weeks 0.5 mg at midnight)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

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416 nmol/l. A diagnosis of CAH of the 21-hydroxylase deficiency type was made (13, 14, 22). There was no family history of this disorder. Treatment with dexamethasone, 0.5 mg, at midnight was commenced. Five weeks later, the serum 17-OHP concentration was 10.1 nmol/l, while that of testosterone had fallen to 0.8 nmol/l and that of androstenedione was 3.6 nmol/l.

Ten weeks following the initiation of dexamethasone treatment, menstruation occurred and the subsequent day 21 serum progesterone level was 46 nmol/l (luteal phase reference range 20–60 nmol/l) with a simultaneous 17-OHP concentration of 10.3 nmol/l which is indicative of ovulation. Treatment with dexamethasone was continued long term, but the dosage was reduced to 0.25 mg each night and 0.1 mg fluoro cortisone was added daily. This patient subsequently became pregnant with twins without additional medical intervention.

**Comment** While this patient had mild hirsutism and onset of amenorrhoea in the age range of 15–25 years, the markedly elevated testosterone and the presence of virilization, indicated by cliteromegaly and anterior fusion of the labia, were atypical of PCOS and prompted comprehensive evaluation. Although the diagnosis of CAH was immediately suspected on finding a grossly elevated basal serum 17-OHP value and confirmed by the response to synthetic ACTH and long-term 17-OHP suppression with dexamethasone treatment, the clinical course was atypical. This is not the usual presentation of late onset or mild CAH because of the higher concentrations of 17-OHP than usually encountered in this form of the disorder and more typical of the classical form (Fig. 1). Likewise, anterior fusion of the labia is indicative of early intra-uterine, severe androgen excess. Reduced androgen sensitivity may be suggested by the mildness of the hirsutism, the late onset of menstrual disturbances and high normal sex hormone-binding globulin (SHBG) value, which is unusual for severe hyperandrogenaemia. As a result of the last feature, the free testosterone index, as indicated by the testosterone/SHBG ratio, was not proportionally elevated when compared to that of total testosterone. The relatively high serum concentration of SHBG may have been related to high levels of oestrone in the serum probably due to the conversion of markedly elevated androstenedione facilitated by the aromatase enzyme system (38).

**Case 3**

A nulliparous 25-year-old woman presented with amenorrhoea and hirsutism. Menarche occurred at 13 years and menstrual periods were irregular from that time with intervals of 2–3 months. At presentation, the patient had been amenorrhoeic for ~1 year. Onset of hirsutism was gradual and clinical examination demonstrated hair growth on the face, chest, lower back, thighs and upper arms. Local cosmetic measures were being used with minimal success. The patient was obese with a body mass index of 32 kg/m² and she smoked 20–30 cigarettes/day.

Initial investigation revealed significantly elevated androgen levels. The serum concentration of testosterone was 9.5 nmol/l. SHBG 26.3 nmol/l, androstenedione at 28.4 nmol/l and DHEAS 10.5 nmol/l. The free testosterone index was calculated at 36.1. The 17-OHP concentration in serum was mildly elevated above the reference range at 7.5 nmol/l. An ACTH stimulation test, however, was not associated with a 17-OHP response indicative of CAH as the maximum serum 17-OHP concentration was 15.2 nmol/l, and there was an appropriate cortisol response to 827 nmol/l 60 min after the administration of synthetic ACTH. 250 µg i.v. The serum cortisol concentration following the administration of dexamethasone. 0.5 mg, by mouth every 6 h for 24 h was <27 nmol/l. Serum androgen concentrations were also suppressed by ~50% following the low-dose dexamethasone suppression test with a drop in serum testosterone from 11.7 to 5.7 nmol/l and a fall in androstenedione from 24.3 to 11.2 nmol/l.

Transabdominal ultrasound examination showed a pattern which was typical of polycystic ovaries. However, in the light of the markedly raised serum testosterone value, selective venous sampling of the adrenal and ovarian veins was undertaken. This revealed abnormal central to peripheral steroid concentration gradients, >9, for serum testosterone.

**Table 4** Androgen and steroid concentrations drawn during selective venous sampling of the adrenal and ovarian veins in Case 3.

<table>
<thead>
<tr>
<th></th>
<th>Left adrenal</th>
<th>Left ovary</th>
<th>Right adrenal</th>
<th>Right ovary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central</td>
<td>Periph</td>
<td>C/P</td>
<td>Central</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>22</td>
<td>8.9</td>
<td>2.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>349</td>
<td>21.7</td>
<td>16.1</td>
<td>23</td>
</tr>
<tr>
<td>DHEAS (nmol/l)</td>
<td>6.3</td>
<td>5.2</td>
<td>1.2</td>
<td>5.9</td>
</tr>
<tr>
<td>17-OHP (nmol/l)</td>
<td>358</td>
<td>25</td>
<td>14.3</td>
<td>15.4</td>
</tr>
<tr>
<td>11-DOC (nmol/l)</td>
<td>307</td>
<td>18</td>
<td>17.1</td>
<td>21</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>7760</td>
<td>727</td>
<td>10.7</td>
<td>664</td>
</tr>
</tbody>
</table>

Centrally (Central) and peripherally (Periph) drawn samples. Gradients are expressed as central to peripheral serum concentrations (C/P). DHEAS, DHEA sulphate; 17-OHP, 17-hydroxyprogesterone; 11-DOC, 11-deoxycortic.
androstenedione and 17-OHP across the right ovary (Table 4). Transvaginal ultrasound examination was performed and showed a 2-cm, central, cystic lesion in the right ovary (Fig. 2).

Elective laparotomy and right oophorectomy were undertaken 3 years following the initial presentation. The patient had remained amenorrhoeic for this period other than occasional withdrawal bleeding in response to the administration of medroxyprogesterone acetate, 10 mg daily for 5 days. The patient elected to use cosmetic measures for the treatment of hirsutism in the intervening period. The right ovary at the time of surgery was enlarged, but a discrete lesion was not obvious on gross examination. Palpation of the left ovary and the broad ligament intra-operatively did not demonstrate any abnormality. Macroscopic examination of the right ovary following resection showed multiple cysts containing yellow and cream material. A benign ovarian teratoma, 2.2×2.0×2.1 cm, was described on histological examination to contain abundant diffuse Leydig cells (Fig. 3) in addition to mature skin, skin appendages, fat, bone and thyroid tissue. The surrounding ovarian stroma was normal and was not indicative of polycystic ovaries or hyperthecosis.

Following right oophorectomy, a significant reduction was seen in androgen concentrations with a fall in serum testosterone from 9.0 to 3.7 nmol/l and in the free testosterone index from 35.2 to 15.2, while serum androstenedione fell from 37.2 to 9.6 nmol/l. The post-operative fall in serum androgens was sustained, and 3 weeks following oophorectomy, the patient had her first spontaneous menstrual period in over 3 years. Regular menses followed this at monthly intervals. Measurement of mid-luteal phase serum progesterone yielded a value of 37.2 nmol/l indicative of ovulation. Ten months post-operatively, the patient became pregnant. Pregnancy was complicated by gestational diabetes, which was treated with insulin. Facial acne vulgaris was also noted at this time. A healthy female infant weighing 3.75 kg was delivered. The patient made a good post partum recovery and she decided not to breastfeed. Menstruation returned 6 weeks post partum.

Comment This report demonstrates the usefulness of venous catheterization and blood sampling in identifying the source of cryptic androgen excess and the superiority of transvaginal rather than of transabdominal ultrasonographic examination of the ovaries. It also highlights a number of other relevant issues. Confounding features include the spontaneous pulsatile nature of adrenal and to a lesser extent ovarian hormonal secretion, variable degrees of dilution of hormonal secretion depending on whether or not other veins have joined proximal to the point of sampling and anatomical variations in venous drainage. The finding of a significant gradient isolated to androstenedione across the left adrenal, 16.1, was probably due to the...
pulsatile nature of ACTH and adrenal steroid secretion. This is supported by the finding of serum cortisol concentration which was >10-fold higher in the venous blood draining the left adrenal than the right adrenal (Table 4).

We have reported previously of an 11-year-old girl who presented with signs of virilization and provided additional related lessons (33). In that patient, serum androgen concentrations were 3–5-fold elevated above the upper limits of reference ranges. There was a normal serum 17-OHP response to ACTH stimulation, 27.5 nmol/l, while cortisol was suppressed normally following the administration of dexamethasone. Ultrasound and MRI scanning of the pelvis and CT scan of the adrenals were all reported as normal. Bilateral ovarian and adrenal venous sampling demonstrated serum concentration gradients for testosterone, androstenedione and 17-OHP >9–1 across the left adrenal gland, which suggested that the source of excess androgen secretion originated from the left adrenal. Repeat multislice CT scan of the adrenal and radiolabelled iodonorcholesterol scanning showed no evidence of an adrenal tumour. Repeat pelvis ultrasound performed 5 years after presentation demonstrated a small mass within the broad ligament separate from the left ovary. At laparotomy, an extra-ovarian tumour was removed. Histological diagnosis was of a rarely reported extra-ovarian steroid cell tumour of the not otherwise specified category. Following tumour resection, serum androgen concentrations fell into the lower part of their reference ranges and the patient had her first menstrual bleed. It is likely that the apparent localization of androgen excess to the left adrenal gland was due to the venous drainage of the broad ligament tumour flowing into the renal vein close to the point at which the left adrenal vein also enters. As in that instance and in the present case, it is important to attempt to confirm the diagnosis suggested by the venous sampling study where possible.

There are only eight previous reports of apparently benign androgen-producing ovarian cystic teratomas with two occurring in pre-menopausal women and two that were bilateral (39). The observation that serum androgen concentrations did not return entirely into the normal reference ranges raises the possibility of co-existing PCOS in the remaining ovary although the non-tumourous ovarian tissue in the left ovary was normal. The possibility of bilateral teratomas is worthy of consideration although this was not apparent on ultrasonographic examination. Furthermore, trans-ovarian venous sampling studies did not identify the left ovary as a source of androgen excess. Therefore, the possibility of continuing androstenedione hypersecretion by the adrenal glands as suggested by partial suppression on treatment with dexamethasone may provide the explanation for the continuing mild androgen excess in this patient. Adrenal androgen excess is common in patients presenting with the clinical picture of PCOS (40, 41). Since this patient has resumed ovulation, further investigations are not immediately proposed but long-term observations and serum androgen review will be conducted.

These illustrative cases of investigation of patients with severe hyperandrogenaemia demonstrate the importance of interpreting all investigations within the context of all available information and with regard to the inherent limitations of each investigation.

Declaration of interest

The authors have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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