Case 13

Diagnosis and Management of Polycystic Ovary Syndrome (PCOS)

Ioannis Kyrou, Martin O. Weickert, and Harpal Singh Randeva

Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-age women (5–15 %). All PCOS definitions include hyperandrogenism and oligo/anovulation in the proposed diagnostic criteria. Polycystic ovary morphology on ultrasound was not part of the initial definition and is not considered necessary for diagnosis if the patient meets the other two criteria. PCOS remains a diagnosis of exclusion and other disorders which are associated with symptoms/signs of androgen excess in women must be excluded. The clinical expression of PCOS is variable with hirsutism representing the most common clinical manifestation (65–75 %). Moreover, there is a strong link between PCOS and metabolic syndrome manifestations, including obesity, insulin resistance, type 2 diabetes mellitus (T2DM), dyslipidaemia, hypertension and non-alcoholic fatty liver disease (NAFLD). PCOS women exhibit increased incidence of obesity (30–75 %) and central adiposity even within the normal BMI range (50–70 %). In the spectrum of PCOS phenotypes, presence of hyperandrogenism is associated with a more adverse cardiometabolic profile, whereas menstrual irregularity and polycystic ovary morphology are more closely linked to infertility problems. Oral contraceptives are recommended as first-line treatment for hirsutism/acne in PCOS. Lifestyle modifications for weight loss are also essential in overweight/obese PCOS women. Metformin therapy may improve metabolic and reproductive outcomes in selected PCOS women and is recommended in PCOS patients

I. Kyrou, MD, PhD • M.O. Weickert, MD, FRCP
Endocrinology and Metabolism (WISDEM),
Warwickshire Institute for the Study of Diabetes,
University Hospitals Coventry and Warwickshire
NHS Trust, Coventry, UK

Division of Metabolic and Vascular Health,
Warwick Medical School,
University of Warwick, UHCW, Coventry, UK

H.S. Randeva, MBChB, PhD, FRCP (✉)
Endocrinology and Metabolism (WISDEM),
Warwickshire Institute for the Study of Diabetes,
University Hospitals Coventry and Warwickshire
NHS Trust, Coventry, UK
e-mail: Harpal.Randeva@warwick.ac.uk

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with T2DM or impaired glucose tolerance who are failing lifestyle modification. Clomiphene citrate is mainly used for ovulation induction in anovulatory PCOS women without other infertility factors. The long-term management plan for the care of PCOS women must include regular screening and follow-up in order to prevent, diagnose and treat T2DM, cardiovascular risk factors, NAFLD, obstructive sleep apnea, eating disorders, depression/anxiety, endometrial hyperplasia/cancer and pregnancy complications.

Keywords

Polycystic ovary syndrome (PCOS) • Hyperandrogenism • Hirsutism • Anovulation • Oligomenorrhea • Amenorrhea • Infertility • Central obesity • Insulin resistance

Case: Female Patient with Hirsutism and Oligomenorrhea

A 21-year-old white Caucasian woman presents to clinic after a referral from her primary care physician due to hirsutism and oligomenorrhea. Her main complaint is excessive growth of coarse dark hair on her face and to a lesser degree on her chest, midline abdomen and thighs.

How would you proceed?

A detailed history is needed, initially establishing the severity/progression of her hirsutism and obtaining a thorough menstrual history.

She mentions that her hirsutism has been gradually worsening over the last year and that she has tried waxing and shaving, but without lasting results. Moreover, she noted facial acne recently for the first time since her teenage years. She also finds very distressing that her frontal hairline appears to be thinning in the temporal areas.

In addition, she mentions that her menstrual periods have been irregular since stopping her oral contraceptive pill more than a year ago. Since then she has been menstruating once every 2–3 months. Her last period was 2 months ago without significant premenstrual symptoms. She reports that this did not alarm her because she had irregular menses during most of her teenage years (menarche at age 13; followed by irregular menses for the next 3 years which became regular when she was prescribed an oral contraceptive pill). A home pregnancy test which she recently did was negative. She has not noticed any nipple discharge. She got married about a year ago and at that time she stopped her oral contraceptive pill, but she admits that she is not planning to become pregnant in the near future.

What other questions would you ask?

Given that polycystic ovary syndrome (PCOS) is a common cause of menstrual irregularities, the patient should be also asked about changes in her weight and other features that can be associated with this condition.

She reports that her weight has increased by 12 kg over the past 3 years which she attributes to poor dietary habits and a sedentary lifestyle. Overall, she describes that it has been a stressful period with finishing her studies and applying for jobs. She also notes that she often tends to get tired easily and feel sleepy during the day. Furthermore, her husband has mentioned to her that she has been snoring on several occasions over the past few months.

Her past medical history is unremarkable, she has never smoked or used recreational drugs and her alcohol intake is less than 10 units/week.

Family history includes type 2 diabetes mellitus (T2DM) in both her parents and a myocardial infarction in her father aged 50 years. She further

mentions that, her mother did not have menstrual problems but had a history of miscarriages and was diagnosed with gestational diabetes mellitus (GDM) when she was pregnant with her. She has no siblings.

What would you do next?

The patient requires a full physical examination.

She is 169 cm tall, weighs 92 kg (body mass index [BMI]: 32.2 kg/m^2) and her waist circumference is 98 cm. Her resting blood pressure was 120/80 mmHg with regular pulse. She has dark hair and a light skin tone. Excessive growth of terminal dark hair was noted on her face, chest, midline abdomen, lower back and upper thighs, with a Ferriman-Gallwey hirsutism score of >7 (total score calculated by assessing nine androgen-sensitive body areas [i.e., upper lip, chin, chest, arms, upper abdomen, lower abdomen, upper back, lower back and thighs] each with a score ranging from 0 [no terminal hair] to 4 [frankly virile]); however, it was not possible to obtain an accurate total score due to previous hair removal from some of these areas with cosmetic measures. Mild degree of acne vulgaris was also present on the face and upper back. There was no diffuse hair loss, but slight thinning of the hairline was noted in the temporal areas of the scalp. Breast exam was remarkable only for periareolar hair growth bilaterally without expressible galactorrhoea. Mild acanthosis nigricans was evident in her axillae bilaterally. Her thyroid was not palpable. On abdominal exam, central adiposity was noted with a few silver/white coloured, narrow (<1 cm wide) striae scattered at her lower abdomen and hips, while there were no palpable masses or hepatomegaly. The rest of the physical examination was unremarkable.

Summarise the Pertinent Symptoms/Signs

This young woman presents with clinical hyperandrogenism, oligomenorrhea and central obesity. Clinical hyperandrogenism is established in this patient by the presence of hirsutism, acne and androgenic alopecia. Insulin resistance signs are also present manifesting as acanthosis nigricans.

- Hirsutism. Hirsutism is defined as excessive growth of terminal dark hair characterised by a male distribution pattern in women (e.g., facial hair above the upper lip, on the chin, cheeks and sideburns; midline chest/abdomen/lower back hair; hair on the inner thighs [male escutcheon]). Clinicians should distinguish hirsutism from hypertrichosis in women. The latter is not caused by excess androgens, although hyperandrogenaemia may aggravate its clinical presentation. Hair growth in hypertrichosis is typically not restricted to androgen-sensitive areas, but is rather diffuse and consists mainly of vellus or lanugo-type hair (short [<0.5 cm), fine, unpigmented hair]. Hypertrichosis can be hereditary/congenital or acquired due to various medical conditions (e.g., anorexia nervosa, cancer) or medications (e.g., phenytoin, diazoxide, minoxidil). The modified Ferriman-Gallwey scoring system is often used to diagnose and quantify hirsutism (hirsutism: score >7; mild hirsutism: score 8–15; severe hirsutism: score >15). However, this scoring system has limitations (e.g., lack of normative data for ethnic populations) and does not assess the impact of hirsutism on the psychological well-being and quality of life. Furthermore, it is often not practical to utilise such scores in clinical practise because patients frequently apply cosmetic hair removal methods before an initial assessment. Regardless of scoring methods, a thorough medical history with details about the onset and progression of excessive growth of terminal hair and about any previous treatments is essential to provide diagnostic clues and guide laboratory testing in hirsute women. Clinicians should further look for other signs of hyperandrogenism (e.g., acne, seborrhoea, male pattern hair loss, virilization) and insulin resistance, such as skin tags and acanthosis nigricans. Accordingly, testing for elevated androgen levels is suggested: (1) in women with moderate or severe hirsutism and (2) in

women with hirsutism of any degree when it is characterised by sudden onset and/or rapid progression, or when it is associated with any of the following: menstrual irregularity or infertility; clitoromegaly; central obesity; acanthosis nigricans.

- Oligomenorrhea. Oligomenorrhea is defined as ≤8 menstrual periods per year (or cycle length of >35 days) and typically reflects anovulatory cycles (chronic oligo-ovulation or anovulation). A thorough menstrual history must be obtained with details about menarche, menstrual cyclicity, the last menstrual period date, and previous treatments, pregnancies, abortions, miscarriages and infertility problems. Clinicians should further ask about premenstrual symptoms (e.g., fluid retention, cramps, breast swelling and tenderness) which could indicate ovulation. It is usually normal for a woman to experience menstrual irregularity and anovulatory cycles for up to 2 years after menarche and for several years before menopause. However, predictable and regular cycles should be expected during the rest of the reproductive years (normal cycle range: 25–35 days).

What are the differential diagnoses?

In the context of the above symptoms and signs, there is high clinical suspicion of PCOS in our case patient which is the most frequent cause of androgen excess in women of reproductive age (70–75 %). Common disorders that are also associated with symptoms/signs of androgen excess in reproductive-age women and should be considered in the differential diagnosis of PCOS are listed in Table 13.1. According to the current clinical practise guidelines for PCOS diagnosis by the Endocrine Society, hyperprolactinaemia, thyroid disease (particularly hypothyroidism), and nonclassic congenital adrenal hyperplasia (primarily 21-hydroxylase deficiency) must be ruled out in all women presenting with suspected PCOS.

- Hyperprolactinaemia. Measurement of early morning prolactin levels is essential to exclude hyperprolactinaemia. Clinicians should also look for symptoms/signs indicating a prolactinoma (e.g. galactorrhoea).
- Primary hypothyroidism. Measurement of thyroid-stimulating hormone (TSH) plasma levels is usually sufficient to exclude hypothyroidism.
- Nonclassic congenital adrenal hyperplasia (NC-CAH; 21-hydroxylase deficiency). Early morning plasma levels of 17-hydroxyprogesterone (17-OHP) should be measured to rule out NC-CAH due to 21-hydroxylase deficiency. NC-CAH can be detected in approximately 1.5–6.8 % of women presenting with androgen excess. Its clinical presentation may not differ from that of PCOS and heightened clinical suspicion is required in women with a positive family history or in those of high-risk ethnic group (e.g., Ashkenazi Jewish ancestry). Early morning 17-OHP levels in the range of 200–400 ng/dL are considered abnormal (this applies to the early follicular phase of a normal menstrual cycle, because 17-OHP levels increase with ovulation, and also depends on the assay). However, if the early morning 17-OHP levels are at the lower end of this range, an ACTH stimulation test should be used for diagnosis (stimulated increase to 17-OHP levels of >1,000 ng/dL 60 min after the intravenous injection of ACTH).
- Androgen-secreting tumours. Androgen-secreting tumours are present in about 0.2 % of women with androgen excess (more frequently are ovarian; >50 % are malignant). Markedly increased testosterone levels that exceed two to three times the upper limit of the laboratory reference range suggest an androgen-secreting tumour (testosterone reference ranges vary depending on the lab/method). Significantly raised testosterone levels with acute onset and rapid progression of clinical hyperandrogenism should be evaluated as an androgen-secreting tumour until proven otherwise. Virilization can develop in less than a few months with marked androgen excess, while a longer period might be required in the presence of persistent modest hyperandrogenaemia. Rapid progression of

Table 13.1 Common disorders to consider in the differential diagnosis of the polycystic ovary syndrome (PCOS)

Differential diagnoses	Hirsutism and/or hyperandrogenaemia	Oligomenorrhea or amenorrhea	Distinctive characteristics	
			Clinical features	Laboratory tests
Hyperprolactinaemia; prolactinoma	Mild or absent	Present	Galactorrhoea; macroprolactinomas may cause visual disturbances headache, cranial nerve palsies and hypopituitarism symptoms	Increased plasma levels of prolactin
Primary hypothyroidism	Mild or absent	Potentially present	Slow relaxing tendon reflexes; periorbital oedema; bradycardia; hypothermia; dry-coarse skin; deep voice-hoarseness; potentially thyroid goitre	Increased plasma levels of TSH; decreased T4 levels; potentially increased prolactin levels (in secondary hypothyroidism TSH levels can be low or normal)
Nonclassic (late-onset; adult onset) congenital adrenal hyperplasia (21-hydroxylase deficiency)	Present	Not often present	Common in women of Ashkenazi Jewish, Hispanic, Slavic and central European ancestry; family history of hirsutism and/or infertility	Increased levels of 17-hydroxyprogesterone at 8 am or after stimulation (60 min after intravenous ACTH)
Androgen-secreting adrenal or ovarian tumours	Markedly present	Present	Virilization with severe manifestations (e.g., clitoral enlargement, male pattern alopecia, deepening of voice, decreased breast size, increased muscle mass); usually recent/sudden onset and rapid progression of symptoms	Markedly increased levels of testosterone (>2–3 upper normal range) and androstenedione; markedly increased DHEAS levels suggest an adrenal tumour and should prompt imaging of the adrenals (CT or MRI)
Cushing's syndrome	Present	Present	Facial plethora; cervical, thoracic, and/or central obesity; violaceous/red striae >1 cm wide; easy bruising; progressive proximal muscle weakness; thin skin especially in young patients	24-h urinary free cortisol levels and midnight salivary cortisol levels are increased; failure to suppress morning plasma cortisol by an overnight dexamethasone suppression test
Acromegaly	Mild or absent	Often present	Prognathism; tooth separation; gradual acral enlargement (e.g., increased shoe/glove size); coarsening of facial features (e.g., lower lip and nose); hypertension; potentially compressive effects from a macroadenoma	Increased plasma levels of insulin-like growth factor-1 and failure to suppress GH levels or paradoxical rise in GH levels after an oral glucose tolerance test
Premature ovarian failure	Absent	Present	Estrogen deficiency symptoms (e.g., hot flashes, urogenital atrophy); potential presence of other autoimmune endocrinopathies (e.g., autoimmune thyroiditis, autoimmune adrenal failure)	Increased plasma levels of FSH with normal or decreased estradiol levels
Simple obesity	Often present	Not often present	Diagnosis of exclusion	Absent

(continued)

Table 13.1 (continued)

Differential diagnoses	Hirsutism and/or hyperandrogenaemia	Oligomenorrhea or amenorrhea	Distinctive characteristics	
			Clinical features	Laboratory tests
Idiopathic hirsutism (hirsutism with regular menstrual cycles and without increased circulating androgens)	Present	Absent	Diagnosis of exclusion; usually mild hirsutism (Ferriman-Gallwey hirsutism score: 8–15); more common in women of Mediterranean heritage	Absent
Drug-induced androgen excess (e.g., anabolic or androgenic steroids, danazol, valproic acid)	Often present	Potentially present	Detailed history to rule out exogenous androgen use and drug-induced androgen excess	Absent

Routinely assess: (1) Prolactin early in the morning; (2) Thyroid-stimulating hormone (TSH) (3) 17-hydroxyprogesterone early in the morning (before 8 am; follicular phase; 17-hydroxyprogesterone levels 60 min after stimulation with intravenous ACTH might be additionally required)

Testosterone measurement based on clinical features: Total testosterone early in the morning (in regularly cycling women best assess on day 4–10 of the menstrual cycle) with sex hormone binding globulin (SHBG) levels for calculation of the Free Androgen Index (FAI: 100 × total testosterone/SHBG); or free testosterone depending on the available lab/method

Further laboratory tests based on clinical features: (1) Cortisol in the morning (8 am) after 1 mg dexamethasone at midnight; (2) Androstenedione; (3) Dehydroepiandrosterone sulfate (DHEAS); (4) Follicle stimulating hormone (FSH) and luteinizing hormone (LH) in the morning (8 am)

Human Chorionic Gonadotropin (hCG): Pregnancy should also be excluded first by urine or serum hCG in all women of reproductive age that present with amenorrhea or an irregular uterine bleeding pattern (irregular uterine bleeding is frequently caused by complications of pregnancy such as threatened or incomplete miscarriage and ectopic pregnancy)

clinical hyperandrogenism and virilization are rarely seen in PCOS. In PCOS the ovarian secretion of both androstenedione and testosterone is increased, while the adrenal synthesis of dehydroepiandrosterone sulfate (DHEAS) may also be enhanced. DHEAS is secreted almost exclusively from the adrenals and should be measured if there is clinical suspicion of an androgen-secreting tumour. Markedly increased plasma DHEAS levels must prompt imaging studies of the adrenals.

What laboratory tests would help in confirming the diagnosis?

Clinicians must first exclude (1) pregnancy by a urine or serum test for human chorionic gonadotropin (hCG); and (2) exogenous androgen use and drug-induced androgen excess by asking the patient to list all prescribed and over the counter medications, including any herbal supplements and injections. Our case patient listed only a multivitamin tablet and denied any other medications or supplements. Furthermore, her urine hCG test was negative. Thus, a set of biochemical and hormonal assessments, including a standard 2 h oral glucose tolerance test (OGTT), was requested for this patient and was subsequently done early in the morning (8 am) after overnight fasting.

- Biochemical hyperandrogenism. Testosterone is found in the circulation in three fractions: (1) tightly bound to sex hormone binding globulin (SHBG; 65–68 % of the total testosterone); (2) weakly bound to albumin (30–33 %); and (3) free testosterone (1–2 %). The latter two fractions constitute the bioavailable testosterone (non SHBG-bound) which can be readily diffused into target tissues where it is converted to dihydrotestosterone by the enzyme 5α-reductase. Thus, SHBG is a crucial regulator of the bioavailable testosterone levels. SHBG is synthesised primarily in the liver and high levels of testosterone and insulin suppress its production, whereas thyroxine and estrogen enhance it. Accordingly, circulating SHBG levels are decreased in hyperandrogenaemia and hyperinsulinaemia, leading to increased free/bioavailable testosterone levels. In PCOS this creates a feed-forward vicious cycle between androgen excess, hyperinsulinaemia and low SHBG levels. Measurement of circulating androgens may not be necessary for PCOS diagnosis in cases of clinical hyperandrogenism without any signs of virilization, since either clinical or biochemical hyperandrogenism satisfy the PCOS diagnostic criteria. Establishing biochemical hyperandrogenism for the diagnosis of PCOS has limitations because there is no diagnostic level of circulating testosterone, while the existing normative data in women are not clearly defined. Furthermore, the different assays for testosterone measurement in women are not standardised across laboratories. Particularly measurement of free testosterone with direct tracer immunoassays can be problematic compared to the gold standard methods (e.g., equilibrium dialysis). If a reliable measurement of free testosterone cannot be obtained, the free androgen index (FAI) can be calculated based on total testosterone and SHBG levels (FAI: 100 × total testosterone/SHBG; levels in nmol/L). FAI has been shown to correlate well with the free testosterone levels measured by equilibrium dialysis.
- Gonadotropins. Luteinizing hormone (LH) and follicle stimulating hormone (FSH) are not necessarily required for the diagnosis of PCOS, since neither their ratio nor their absolute circulating levels are included in PCOS diagnostic criteria. Raised LH levels with low-normal FSH levels and an increased LH/FSH ratio (>2) are more frequently noted in lean PCOS women. These findings are less common in overweight/obese PCOS women, presumably due to effects of hyperinsulinaemia on LH secretion. Thus, a high LH/FSH ratio supports the diagnosis of PCOS but the absence of such findings has no diagnostic value.
- Glucose tolerance. The current PCOS clinical practice guidelines by the Endocrine Society recommend an initial assessment of glucose tolerance by a standard OGTT in PCOS patients. Measurement of fasting glucose levels may not be sufficient to detect impaired

Table 13.2 Definitions and proposed criteria for establishing the diagnosis of the polycystic ovary syndrome (PCOS)

NIH [6]	Rotterdam ESHRE [9]	AE-PCOS society [1]
(**A**) **BOTH of the following:**	(**A**) **At least TWO of the following:**	**(A) BOTH of the following:**
Hyperandrogenism: clinical and/or biochemical (not specified)	**Hyperandrogenism:** clinical (hirsutism) and/or biochemical (free testosterone or FAI)	**Hyperandrogenism:** clinical (hirsutism) and/or biochemical (free testosterone by sensitive assays)
Ovarian dysfunction: Chronic anovulation or oligo-ovulation (≤6 menses per year)	**Ovarian dysfunction:** oligo- or anovulation	**Ovarian dysfunction:** oligo- or anovulation **and/or** polycystic ovary morphology on ultrasound
	Polycystic ovary morphology on ultrasound: at least one ovary with ≥12 follicles of 2–9 mm and/or ovarian volume >10 ml in the absence of a dominant follicle >10 mm	
(**B**) **Plus exclusion of other androgen excess or related disorders** (e.g., hyperprolactinaemia, hypothyroidism and nonclassic congenital adrenal hyperplasia must be excluded in all cases)		

Clinical hyperandrogenism: hirsutism (excessive terminal hair with a male distribution pattern); acne; male pattern alopecia

Biochemical hyperandrogenism: typically increased total or free testosterone. FAI: Free androgen index (100 × total testosterone/SHBG)

Anovulation: may manifest with menstrual bleeding at intervals of >35 days or <21 days. For women with menstrual bleeding within the normal interval range (25–35 days) ovulation can be verified by a luteal phase day 7 (midluteal) progesterone level [>5 ng/mL – luteal phase day 7 (midluteal) corresponds to cycle day 21 for 28-day intervals and cycle day 28 for 35-day intervals]

Polycystic ovary morphology on ultrasound: ≥12 follicles of 2–9 mm and/or ovarian volume >10 ml. Only one ovary fitting these criteria is sufficient. These ultrasound criteria do not apply to women on oral contraceptive treatment, because it can affect ovarian morphology. If there is evidence of a dominant follicle (>10 mm) or a corpus luteum the ultrasound scanning should be repeated during the next cycle

Abbreviations: *NIH* National Institutes of Health, *ESHRE* European Society of Human Reproduction and Embryology, *AE-PCOS* Androgen Excess-Polycystic Ovary Syndrome Society

glucose tolerance (IGT) in PCOS women. In patients that are unable or unwilling to complete an OGTT, measurement of haemoglobin A1c (HbA1c) is recommended instead, although it appears less sensitive for detecting IGT.

In our case patient, testosterone levels were 2.5 nmol/L (local laboratory normal reference: <1.8 nmol/L) with normal levels of prolactin, TSH, 17-OHP, DHEAS, androstenedione, LH and FSH. SHBG levels were at the lower limit of the laboratory reference range. Normal complete blood count, liver enzymes, and fasting lipid panel were also noted. Based on the OGTT results, plasma glucose increased from fasting levels of 5 mmol/L (90 mg/dL) to 8.6 mmol/L (155 mg/dL) after 2 h. Finally, pelvic ultrasonography revealed: (1) left ovary of 24×20×22 mm with 12 follicles of 2–9 mm; and (2) right ovary of 18×16×18 mm with 4 follicles of 2–9 mm (with absence of a dominant follicle >10 mm; and without any visible endometrial or adrenal pathology).

How would you interpret these results and what is the final diagnosis?

To date, there are three definitions that can be used to establish the diagnosis of PCOS (Table 13.2). PCOS remains a diagnosis of exclusion, hence all definitions require the exclusion of other disorders which are associated with symptoms/signs of androgen excess in women (see Tables 13.1 and 13.2). According to current guidelines by the Endocrine Society, early morning plasma levels of prolactin, TSH and 17-OHP should be routinely measured in the diagnostic evaluation of PCOS in order to exclude hyperprolactinaemia, thyroid disease (particularly hypothyroidism), and NC-CAH (primarily 21-hydroxylase

deficiency), respectively. Depending on the clinical suspicion and presenting symptoms/signs, further laboratory tests may be required in selected patients to exclude other relevant disorders (see Table 13.1).

In our case patient early morning plasma levels of prolactin, TSH and 17-OHP were normal. Furthermore, the assessment of biochemical hyperandrogenism revealed marginally increased levels of total testosterone and normal levels of androstenedione/DHEAS. Based on this, together with the relatively gradual progression of the presenting symptoms/signs, the absence of significant virilization and the results from pelvic ultrasonography further testing to pursue the diagnosis of an androgen-secreting adrenal or ovarian tumour was not considered necessary. In addition, the clinical presentation of our case patient did not prompt investigations for Cushing's syndrome or acromegaly (see Table 13.1).

Finally, PCO morphology was noted on ultrasound in our case patient that satisfied the ultrasound criteria incorporated in the two most recent PCOS definitions (see Table 13.2). In clinical practice, ultrasound scanning of the ovaries is not necessary for the diagnosis of PCOS if the patient already meets the criteria of hyperandrogenism (clinical and/or biochemical) and oligo- or anovulation. Clinicians should recognise that ovarian morphology is affected by age and that PCO morphology can be detected in approximately 20 % of normal women of reproductive age and in 40–50 % of normal adolescents (multifollicular ovaries are a feature of normal puberty that over time subsides with regular menstrual cycling). Furthermore, transvaginal ultrasounds may raise ethical and practical issues in some patients, while the accuracy of transabdominal ultrasound scanning is limited in severely obese patients.

In the context of the above results, the diagnosis of PCOS can be established in our case patient based on any of the three existing PCOS definitions. In addition, the results of the standard OGTT revealed IGT, but not impaired fasting glucose (IFG), based on the current criteria by the American Diabetes Association (ADA) [IFG: fasting glucose of 100–125 mg/dL (5.6–6.9 mmol/L); IGT: 2-h glucose in the OGTT of 140–199 mg/dL (7.8–11.0 mmol/L)].

What are the treatment options in this patient?

Aims of treatment are to ameliorate symptoms of hyperandrogenism, restore menstrual cyclicity, address anovulation and infertility, and prevent/treat complications. Patients should be advised that long-term management will be required because the treatment will not be curative. Accordingly, the treatment plan in PCOS women of reproductive age can include one or more of the following options:

Oral Contraceptives

Monotherapy with oral contraceptives is recommended as first-line treatment for hirsutism/acne in reproductive-age PCOS women who do not desire pregnancy. The use of oral contraceptives in these patients additionally provides adequate contraception and regulates the menstrual bleeding pattern reducing the risk of endometrial hyperplasia. Combined oral contraceptive pills (COCP) contain a potent, synthetic estrogen (ethinyl estradiol) and a progestin component. COCP decrease hyperandrogenism mainly by (1) stimulating hepatic SHBG synthesis and, thus, decreasing the bioavailable levels of androgens; and (2) suppressing pituitary LH secretion and, thus, decreasing ovarian androgen synthesis. COCP formulations have different progestin components with various degrees of androgenicity. Progestins derived from testosterone have mild androgenic activity, while progestins that are not structurally related to testosterone act as androgen receptor antagonists (e.g., norgestimate and desogestrel belong to third generation progestins and are considered non-androgenic). Cyproterone acetate (CPA) is a synthetic antiandrogen progestin (COCP with a daily dose of 2 mg CPA and 35 μg ethinyl estradiol). Furthermore, the progestin drospirenone is a spironolactone analogue that has antiandrogenic (weak antiandrogen; 3 mg used in COCP are approximately equivalent to 1 mg CPA and

25 mg spironolactone) and anti-mineralocorticoid activity (potassium monitoring is required). The existing clinical evidence is not sufficient to suggest one COCP formulation over another or over other hormonal contraceptives (i.e., patch and vaginal ring) in PCOS. Both the efficacy and safety (metabolic and thromboembolic risk) profile of different formulations should be considered in each patient before prescribing a COCP regimen. Screening for contraindications to hormonal contraceptives is also essential; absolute contraindications to COCP include: smoking ≥15 cigarettes per day in women ≥35 years old, blood pressure ≥160/100 mmHg; diabetes with vascular disease or neuropathy/retinopathy; multiple CVD risk factors including evidence of vascular disease or history of ischemic heart disease; history of or acute venous/arterial thrombosis or pulmonary embolism; known thrombogenic mutation; systemic lupus erythematosus with antiphospholipid antibodies; acute active liver disease; and migraine headaches with aura. Currently there are insufficient data to support a recommendation regarding the optimal duration of oral contraceptive treatment in PCOS women, hence patients can potentially continue on their regimen until pregnancy is desired or a contraindication becomes evident.

Antiandrogens

Antiandrogens (i.e., androgen receptor blockers and 5α-reductase inhibitors) are used in combination with COCP for the treatment of moderate/severe hirsutism in PCOS. Monotherapy with antiandrogens may be also used for hirsutism when hormonal contraceptives are contraindicated, but this is not recommended unless another reliable contraception method (e.g., intrauterine device) is ensured due to the risk of fetal male pseudohermaphroditism [in utero feminisation of a 46,XY (male) fetus]. Spironolactone, CPA and finasteride can be prescribed with relatively similar efficacy in PCOS, while the use of flutamide is not recommended because of its potential severe hepatotoxicity.

Spironolactone acts as an androgen antagonist and significantly inhibits the 5α-reductase activity. Spironolactone doses of 100 mg per day (divided to twice daily) are usually effective for hirsutism treatment, but higher doses (e.g., 200 mg per day) may be required. Spironolactone-related hyperkalaemia is rare in patients with normal renal function, but an initial transient diuretic effect is usually noted and may cause postural hypotension and dizziness. Careful monitoring of electrolytes, renal function and blood pressure is required within the first fortnight of treatment at initiation and at each dose increment.

Cyproterone acetate (CPA; not available in the US) acts as an antiandrogen mainly by inhibiting the androgen receptor via competition with testosterone and dihydrotestosterone for receptor binding. In addition, CPA may less potently inhibit the 5α-reductase activity, while it also suppresses circulating gonadotropin and androgen levels. Due to its slow metabolism and long half-life, CPA is administered in the early phase of the treatment cycle in a reverse sequential regimen. Thus, ethinyl estradiol (doses of 20–50 μg daily) is given for 3 weeks (day 5–25) to ensure normal menstrual cycling, and CPA (doses of 50–100 mg daily) is administered for the first 10 days of the cycle (day 5–15). Once the maximal treatment effect is achieved, lower doses of CPA (e.g. 5 mg daily) can be prescribed for maintenance, while a COCP with a daily dose of 2 mg CPA and 35 μg ethinyl estradiol is also available. CPA is usually well tolerated, but can exhibit dose-dependent metabolic effects similar to those of high-dose COCP.

Finasteride acts as an antiandrogen by inhibiting the type 2 5α-reductase. Because clinical manifestations of hyperandrogenism appear to depend on the combined activity of type 1 and type 2 5α-reductase, finasteride is considered partially effective. Despite its partial inhibitory effect, prolonged treatment with finasteride at doses of 2.5–5 mg daily is shown to have practically equal efficacy to other antiandrogens. Significant improvement of hirsutism is usually noted after 6 months of treatment with a finasteride dose of 5 mg daily which is the most frequently used dose in clinical practise. A potential advantage of finasteride is its benign safety profile with no major side/adverse effects and good tolerance by patients.

Flutamide is a pure antiandrogen that acts by inhibiting the androgen receptor in a

dose-response manner. Flutamide doses of 250 top 500 mg daily have similar efficacy to other antiandrogens, but flutamide treatment is not recommended because of its potential severe hepatotoxicity. If flutamide is prescribed the lowest effective dose should be used and the patient must be closely monitored.

Topical antiandrogen creams (e.g., 5 % canrenone [the active metabolite of spironolactone] and 0.25–0.5 % finasteride) appear to have limited efficacy for hirsutism with inconsistent results from clinical trials.

Direct Hair Removal/Reduction Methods

Removal of excessive terminal hair by direct methods can be used for hirsutism in PCOS, usually in combination with pharmacotherapy. While the latter restricts hair regrowth, existing terminal hair should be removed by direct methods once androgen suppression is achieved. Among direct methods, photoepilation therapy with laser or intense pulsed light treatments is currently suggested.

Temporary Methods of Direct Hair Removal

Epilation methods involve the removal of the intact hair with its root (e.g., plucking, tweezing, waxing) and can be used in addition to pharmacotherapy in the first months of hirsutism treatment until the drug effects become clinically apparent. These methods are inexpensive and relatively safe, usually causing only transient discomfort. Depilation methods (e.g., shaving) remove the hair shaft from the skin surface and the effect usually lasts only for a few days. Patients should be assured that shaving does not increase the growth (rate and/or duration of the anagen phase) or thickness (diameter) of hair, which is a common misconception. Chemical depilatory products are also often used to separate the hair from its follicle and dissolve it. Irritant contact dermatitis and folliculitis may occur with such agents.

Permanent Methods of Hair Reduction

Electrolysis and photoepilation therapy with laser or intense pulsed light are used for "permanent" hair reduction which is defined as >30 % reduction in the number of terminal hairs after a treatment regimen that is stable for a period longer than the complete growth cycle of hair follicles (4–12 months depending on body area).

Electrolysis treats each hair individually since this technique requires the insertion of a fine needle into the hair follicle. Galvanic electrolysis and thermolysis are available, causing destruction of the hair follicle by inducing a chemical reaction or heat, respectively. Electrolysis can be used on any hair/skin colour and is usually applied for localised small areas as a cost-effective option. Electrolysis requires an experienced operator and can be time-consuming and relatively painful. Topical lidocaine/prilocaine anaesthetic creams may be used to reduce pain. Potential local side effects, especially by inexperienced operators, include erythema, post-inflammatory pigment changes and even scarring due to tissue destruction.

Photoepilation (light-assisted hair reduction) methods include laser and intense pulsed light (IPL) therapy which achieve hair removal by selective photothermolysis, using light wavelengths that are absorbed by the melanin of the hair and pulse durations that selectively destroy the hair without damaging the adjacent tissue. Thus, hair follicles are destroyed, but vellus (light-coloured/unpigmented) hair may remain. Of note, the choice of the photoepilation method/device should be made according to the skin and hair colour of the patient. Ideal candidates for laser hair reduction therapy are women with light skin and dark hair. Relatively short wavelength devices (e.g., ruby and alexandrite lasers) are optimal for these women, whereas longer wavelength lasers (e.g., neodymium:yttrium-aluminum-garnet, Nd:YAG, lasers) or IPL appear appropriate for women with dark skin and dark hair. For patients with white/light coloured hair IPL combined with radiofrequency (electromagnetic waves delivered together with the light pulse on the same machine) may be effective. Potential local side effects include dyspigmentation and scarring. Other limitations to photoepilation methods are the need for multiple treatments and the cost of therapy which varies depending mainly on the size of the treated area.

Topical Eflornithine Treatment

A 13.9 % eflornithine hydrochloride cream (Vaniqa) is licensed and is an irreversible inhibitor of the enzyme L-ornithine decarboxylase, which catalyses the conversion of ornithine to putrescine. The latter plays a key role in the regulation of cell growth and differentiation within the hair follicle. Thus, topical eflornithine treatment reduces the hair growth rate locally, but is not a hair removal method. Continuous topical application of eflornithine cream (typically twice daily; at least 8 hours apart) is shown to reversibly slow facial hair growth with clinically significant improvement of facial hirsutism and quality of life. These results are usually noted after 6–8 weeks of treatment, while once the topical administration is discontinued facial hair growth returns to pre-treatment levels after approximately 8 weeks. Topical eflornithine treatment for facial hirsutism in PCOS is usually used in combination with other interventions, such as pharmacotherapy, to achieve a more rapid initial response. Systemic absorption of eflornithine with topical treatment for facial hirsutism is extremely low. Local side effects include itching and dry skin. Patients should be advised that this cream is not licensed for treatment of hirsutism in areas other than the face.

Lifestyle Modification: Weight Loss

Weight loss is recommended in overweight/obese PCOS women. A weight-centric management plan is crucial for these patients in clinical practice to achieve sustained weight loss and prevent T2DM and other manifestations of the metabolic syndrome. Weight management in PCOS should typically follow the clinical guidelines for obesity treatment in the general population, including lifestyle interventions, pharmacotherapy (e.g., Orlistat) and bariatric surgery, based on the BMI and existing comorbidities of each patient.

Metformin

Metformin is increasingly prescribed in PCOS women, even without coexisting T2DM, because it may improve metabolic and reproductive outcomes in selected patients. Metformin therapy for symptomatic treatment of PCOS should be initiated under specialist care. Based on the current clinical practise guidelines by the Endocrine Society metformin is recommended in PCOS women with T2DM or IGT who are failing lifestyle modification, whereas it should not be first-line treatment for hirsutism/acne, weight loss, or prevention of pregnancy complications in PCOS. The optimum use of metformin in PCOS treatment is currently under debate and there are differences among various national guidelines which reflect the need for larger and better designed clinical trials with metformin in different PCOS patient populations (e.g., in ethnic populations and adolescents).

In the treatment of overweight/obese PCOS women, metformin may be used as adjuvant to lifestyle interventions to ameliorate the adverse effects of insulin resistance. Metformin reduces hepatic glucose production, decreases glucose absorption and increases glucose uptake into skeletal muscle. Thus, metformin therapy decreases the overall insulin requirements and may contribute to interrupt the vicious cycle between compensatory hyperinsulinaemia and hyperandrogenism in PCOS. A growing body of evidence indicates that metformin treatment in PCOS may induce significant improvements in glucose and insulin plasma levels, surrogate measures of insulin resistance (e.g., SHBG), lipid profile, blood pressure, as well as slight reduction in BMI and WHR. However, there is inconsistency concerning the reported metabolic outcomes of metformin therapy in PCOS, since other studies, including placebo-controlled randomised clinical trials (RCTs), have failed to reproduce these metabolic effects. A recent systematic review of RCTs reported that metformin has limited effects on weight loss, insulin and lipid profiles in obese PCOS women. This inconsistent and heterogeneous response to metformin therapy may be attributed, at least in part, to the variability in the phenotypic expression of PCOS that is allowed by the different PCOS definitions. Metformin appears to be more effective in PCOS patients at the more severe end of this spectrum. In addition, metformin therapy may have reproductive benefits in

PCOS women by reducing hyperandrogenism and restoring menstrual regularity, ovulation and fertility. Indeed, a significant clinical outcome of metformin therapy in PCOS is improved menstrual cyclicity, although it appears to be less effective than oral contraceptives. Existing data from RCTs also indicate that metformin is associated with improved clinical pregnancy rates in PCOS, but there is no evidence that it improves live birth rates.

Infertility Treatment

PCOS women with chronic oligo/anovulation who desire pregnancy are candidates for medical induction of ovulation. Current guidelines recommend clomiphene citrate (initial dose of 50 mg/day orally; starting on day 3 of the cycle and lasting for 5 days [days 3–7 of the cycle]) as first-line infertility treatment in PCOS women with anovulatory infertility and without other infertility factors. Increasing data also support the role of aromatase inhibitors (e.g., letrozole) as an alternative first-line oral pharmacological treatment for anovulatory infertility in PCOS. If pregnancy is not achieved with these first-line oral treatments, due to either anovulation (resistance to induction of ovulation) or failure to conceive despite induced ovulation, patients should be referred to a specialist infertility clinic for further evaluation and treatment. Failure to conceive despite achieving induced ovulation should prompt a thorough fertility work-up in both partners of the couple, including semen analysis and evaluation of the uterine and tubal anatomy, in order to explore additional infertility factors which might not be related to PCOS. Finally, metformin appears to have an adjuvant role to first-line treatments in induction of ovulation in obese PCOS women and is helpful to prevent the ovarian hyperstimulation syndrome (OHSS) in patients receiving gonadotropin treatment for in vitro fertilisation (IVF).

Do women with PCOS require screening/management of comorbidities long term?

Type 2 Diabetes Mellitus (T2DM) and Cardiovascular Disease (CVD) Risk

PCOS is associated with manifestations of the metabolic syndrome, particularly central obesity, insulin resistance, T2DM, dyslipidaemia and hypertension. PCOS patients typically have higher prediabetes/T2DM prevalence and more CVD risk factors than age- and weight-matched women without PCOS. Thus, PCOS may lead to increased CVD morbidity and mortality later in life, although the documented CVD morbidity and mortality in middle-aged PCOS women is not as increased as would be expected. In clinical practice, it is required to screen all PCOS patients for CVD risk factors by assessing BMI, waist circumference, blood pressure, fasting lipids, glucose tolerance, smoking status and family history of premature CVD (<55 and <65 years of age in male and female relatives, respectively).

Non-alcoholic Fatty Liver Disease (NAFLD) – Non-alcoholic Steatohepatitis (NASH)

NASH corresponds to the most severe histologic form of NAFLD, characterised by steatosis and various degrees of inflammation, hepatocyte injury and fibrosis. NASH may gradually lead to cirrhosis, liver failure and hepatocellular carcinoma. In clinical practice, awareness of the high risk of NAFLD in PCOS women is suggested, particularly if central obesity and insulin resistance is present. However, universal routine screening by serum markers of liver dysfunction (e.g. aminotransferases) and ultrasound scanning of the liver in obese PCOS patients is not currently recommended, because there is no simple screening test for NAFLD with high sensitivity and specificity.

Depression, Anxiety and Eating Disorders

Common psychological disorders are more prevalent in PCOS. Indeed, PCOS women exhibit significantly higher rates of depression (28–64 %) and anxiety (34–57 %) compared to women in the general population (8 and 18 %, respectively). In addition, there are data suggesting an increased

risk of psychosexual dysfunction (e.g., loss of feminine identity, reduced sexual satisfaction) and negative body image perception (e.g., feeling less physically attractive or healthy) in PCOS women. Finally, eating disorders (e.g., binge-eating disorder) appear more frequent in PCOS, with reports showing that the prevalence of any eating disorder may reach 21 % in PCOS women. Based on this evidence, the current guidelines by the Endocrine Society and the PCOS Australian Alliance suggest screening of PCOS women for depression, anxiety and eating disorders.

Obstructive Sleep Apnea (OSA)

Overweight/obese PCOS women exhibit increased prevalence of OSA and sleep-disordered breathing, potentially attributed to hyperandrogenism and obesity (particularly central). Clinical studies have shown that PCOS patients, after controlling for BMI, have 30 times the risk of sleep-disordered breathing compared to control women and that OSA is more frequent in obese PCOS women than in weight-matched controls. Thus, it appears that obesity alone is not sufficient to account for the high OSA prevalence in PCOS. OSA may have significant deleterious cardiometabolic effects in PCOS patients, since chronic intermittent hypoxia and disruption of normal sleep patterns increase the sympathetic nervous system activity and oxidative stress and, hence, can progressively induce further weight gain, insulin resistance and hypertension.

Initial screening for OSA is suggested in all overweight/obese PCOS women in order to identify suggestive symptoms (e.g. excessive daytime somnolence, snoring, choking/apnea episodes during sleep). OSA screening can also be performed through validated questionnaires (e.g., Epworth Sleepiness Scale, Berlin Questionnaire) and patients that are positive on this screening should be referred to a specialist in sleep medicine for diagnostic evaluation by polysomnography.

Endometrial Cancer

Current evidence suggests that PCOS women are three times more likely to develop endometrial cancer. Overall, PCOS women with amenorrhea appear to be at a greater risk of endometrial hyperplasia and cancer which may be higher still in the presence of obesity and/or T2DM. The current guidelines by the Endocrine Society recommend heightened awareness of the increased risk of endometrial cancer in PCOS, particularly in the presence of dysfunctional uterine bleeding, prolonged amenorrhea, obesity or T2DM. However, these guidelines suggest against routine ultrasound screening for endometrial thickness in all PCOS women.

Importantly, in PCOS women with chronic anovulation exposure of the endometrium to unopposed non-fluctuating levels of estradiol in the absence of progesterone increases the risk of endometrial hyperplasia/cancer. In order to decrease this risk, clinicians should offer long-term treatment with a COCP regimen or cyclical progestogen to induce periodic withdrawal bleeding. Regular withdrawal bleeding at least every 3 months is considered to significantly reduce the risk of endometrial hyperplasia and cancer in PCOS.

Pregnancy Complications

PCOS women have higher rates of GDM, pregnancy-induced hypertension, pre-eclampsia and pre-term birth; whilst the infant is also at higher risk of neonatal complications (e.g. small for gestational age infant, increased neonatal ICU admission and mortality rates). Finally, PCOS women have been shown to exhibit higher rates of spontaneous miscarriage after assisted reproduction compared to women without PCOS. This is considered related to the high obesity incidence in PCOS and the type of infertility treatment that PCOS women may receive, because it has been reported that after adjustment for these factors the increase in the risk of spontaneous miscarriage in PCOS women was not significant.

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