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Polycystic ovary syndrome

Can we make the diagnosis and management easier?

Polycystic ovary syndrome is a common endocrine disorder in women and has many different presentations, spanning adolescence through to the menopause. Initially placed into the gynaecological realm, it is now also widely accepted as a metabolic disease of uncertain origin and considered as treatable but not curable.

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Polycystic ovary syndrome (PCOS) affects about 10% of the female population worldwide, including approximately half a million women in Australia.[1] Victoria Beckham and Jules Oliver, the wife of the celebrity chef Jamie Oliver, both have spoken publicly about having PCOS. However, it is far from being a prerogative of celebrities, but rather a highly prevalent endocrine disorder, considered to be a leading cause of androgen excess and ovulation dysfunction.

PCOS has been viewed primarily as a gynaecological disorder in which treatment is targeted to restore regular menstrual pattern, achieve ovulation and facilitate pregnancy. The knowledge gained over the last decade has highlighted the fact that PCOS has a major effect throughout a woman's life, not only on her reproductive health, but also on her metabolic and cardiovascular health. Despite increased awareness of this disorder, the heterogeneity in presentation and

IN SUMMARY

- **Polycystic ovary syndrome (PCOS) is a common female endocrine disorder and the leading cause of excessive androgen production, impaired ovulation and infertility.**
- **Fundamental problems of PCOS including hyperandrogenism, hyperinsulinaemia, abnormal serum lipid levels and obesity have broad long-term health implications, including an increased risk of diabetes and cardiovascular disease.**
- **PCOS is a highly variable condition with a broad spectrum of symptoms, and the diagnosis can often be delayed.**
- **The aetiology of PCOS is still obscure but is most likely multifactorial with a strong genetic component.**
- **Effective lifestyle modifications improve pregnancy rates and metabolic profiles in most patients with PCOS without the need for medical intervention.**
- **GPs are well placed to make an early diagnosis of PCOS and provide education and management to help patients avoid the long-term consequences of this condition.**

Definitions of PCOS

National Institutes of Health criteria, 1990

This requires the presence of both the following criteria:

- signs of androgen excess (clinical or biochemical)
- oligomenorrhoea or anovulation.

Rotterdam criteria of the European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine, 2003[2]

This requires the presence of two out of three of the following criteria:

- signs of androgen excess (clinical or biochemical)
- oligomenorrhoea or anovulation
- polycystic ovaries (on ultrasound).

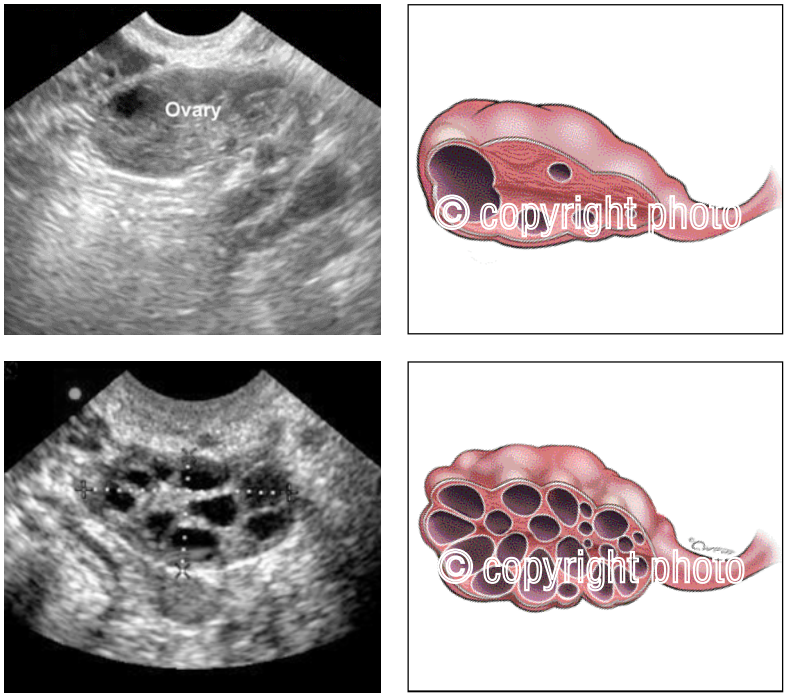
Criteria are defined as follows:

Hyperandrogenism: this is assessed by clinical features, biochemical indices or both. Clinical features include cutaneous manifestations (e.g. acne, oily skin, hirsutism, male-pattern alopecia) and voice deepening. Biochemical indices include measurements of androgen levels in the serum.

Oligomenorrhoea or anovulation: this is defined by ovulation that occurs less than once every 35 days, or is lacking, and manifests by menstrual irregularity.

Polycystic ovaries: this is defined by ultrasonograpic appearance of the ovaries characterised by peripheral cysts (10 or more) less than 10 mm in size in an enlarged ovary (see Figures 1a to d).

Syndromes with similar presenting features should be excluded prior to diagnosis.



Figures 1a to d. Ultrasound (a, top left) and illustration (b, top right) of a normal ovary. Ultrasound (c, bottom left) and illustration (d, bottom right) of a polycystic ovary.

lack of a clear-cut definition of PCOS can lead to a substantial delay in diagnosis in numerous patients. Unrecognised PCOS can often cause many physical and emotional manifestations and patients are usually seen for issues other than gynaecological ones. Early diagnosis, risk assessment and longitudinal care are of paramount importance to provide protection from long-term sequelae and to give patients with PCOS the tools and information they need to live healthier lives.

Definition

The precise definition of PCOS is still lacking. Currently, two definitions of PCOS from the National Institutes of Health (NIH) and Rotterdam criteria are in widespread use (see the box on this page).[2] Although both are widely accepted, their accuracy continues to be a topic of extensive debate. The Rotterdam criteria for PCOS is wider and includes many more patients, notably it can include those without androgen excess, whereas in the NIH definition androgen excess is a prerequisite. The different PCOS phenotypes are shown in Table 1.

Critics maintain that findings obtained from a study of patients with androgen excess cannot necessarily be extrapolated to patients without androgen excess. Patients without androgen excess demonstrate only some of the metabolic derangements and are considered to have the mildest expression of the PCOS spectrum, weakly associated with an increased risk of metabolic disease. It is also possible that the phenotypic differences of PCOS may indicate differences in aetiology.

continued

Table 1. Phenotypes of PCOS

Classic PCOS	Hyperandrogenism, oligomenorrhoea, with or without polycystic ovaries on ultrasound
Ovulatory PCOS	Hyperandrogenism, polycystic ovaries on ultrasound and normal periods
Mild PCOS	Oligomenorrhoea, polycystic ovaries on ultrasound and no hyperandrogenism

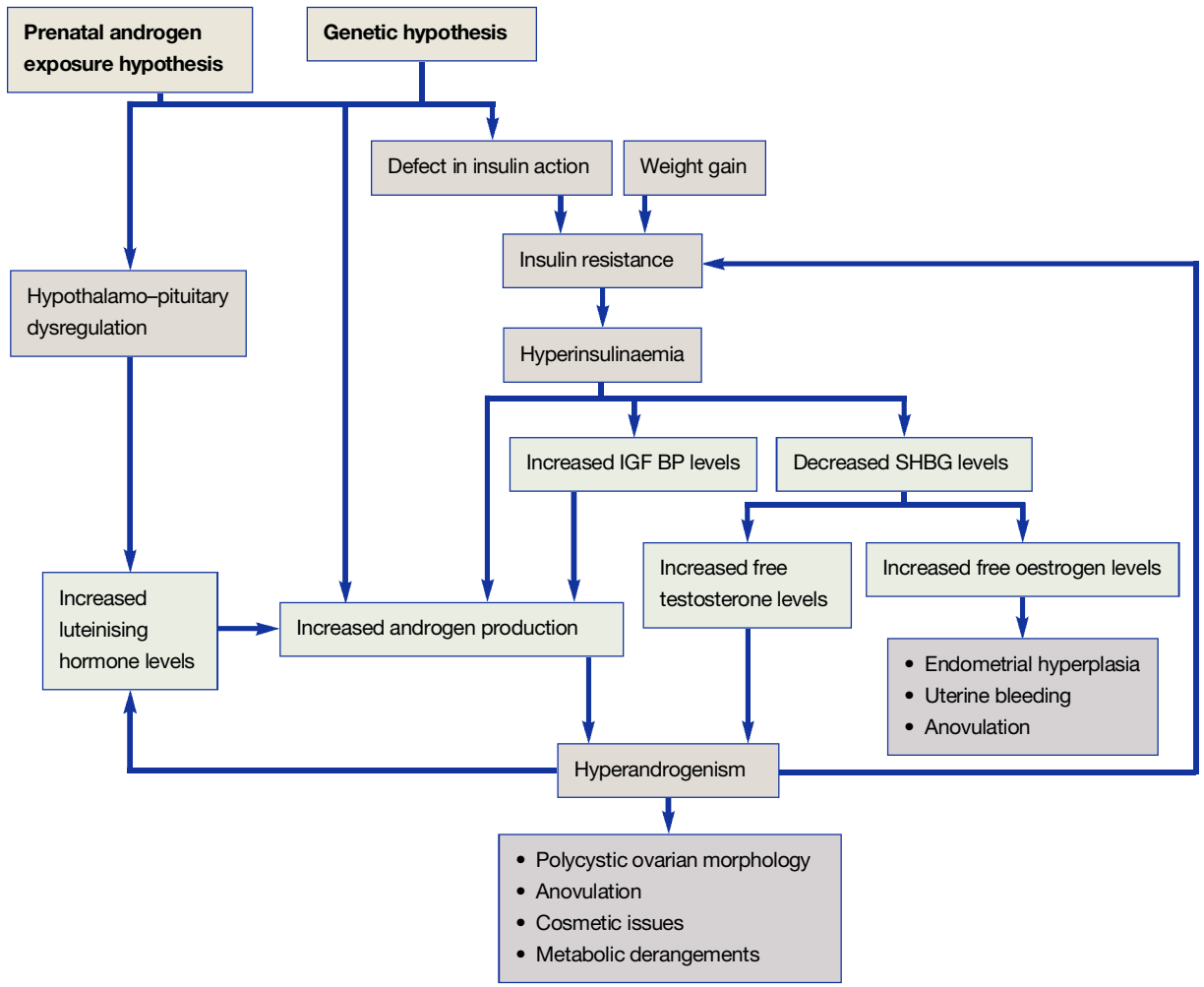
Aetiology

No single aetiological factor accounts for the spectrum of abnormalities seen in patients with PCOS; both genetic and environmental issues are implicated. The familial basis of PCOS was established by multiple family studies, demonstrating increased prevalence of hyperandrogenism, metabolic derangements and polycystic ovarian morphology in relatives of affected women.[3] Despite a large number of candidate gene associated studies, no one gene is universally accepted as being important in the pathogenesis, although fetal origins of the disease are likely.

Pathogenesis

Hyperandrogenism, ovarian dysfunction, abnormalities in the hypothalamic–pituitary axis and excess insulin activity represent an interactive system in the pathogenesis of PCOS (see the flowchart on this page); however, the mechanisms that account for all forms of PCOS are still poorly understood. Hyperandrogenism,

Underlying pathogenetic mechanisms in PCOS



ABBREVIATIONS: IGF BP = Insulin-like growth factor binding proteins; SHBG = sex hormone-binding globulin.

Figure 2. Polycystic ovary syndrome was first presented in 1935 by Stein and Leventhal who described masculinised obese women with amenorrhoea, sterility and enlarged ovaries containing multiple cysts.

predominantly of ovarian and to a lesser extent of adrenal origin, is considered to be a cardinal feature and significant contributor to the pathogenesis of PCOS. The theca cells, which envelop the follicles in the ovary and normally produce androgens as oestrogen precursors, are over-responsive in PCOS, are increased in size and overproduce androgens. It is still unclear whether the primary defect is insulin resistance, leading to hyperinsulinaemia and stimulation of ovarian androgen production, or if it is pre-existing hyperandrogenism that precipitates insulin resistance. It is likely that both phenomena occur. Paradoxically, in patients with PCOS the ovarian theca cells are hypersensitive to insulin, whereas other metabolic organs (e.g. muscle and liver) are insulin resistant in the same individuals.

Synergistic action of androgens, insulin and luteinising hormones (which may all be elevated due to excessive androgen action) on ovarian follicles leads to accelerated early follicular growth and later distortion of the dominant follicle selection, resulting in follicular arrest and disrupted ovulation. The lack of regular ovulation is accompanied by the relatively high and unchanging concentrations of oestrogen, which may further alter the control of production of luteinising hormone and cause endometrial hyperplasia.

Two hypotheses, which have been currently proposed and are outlined below, may explain the major features of PCOS.

- **Prenatal androgen exposure:** whereby exposure to excessive levels of androgens in a critical developmental period could play a role in the pathogenesis of PCOS, by affecting the activity of the adrenal gland, pancreas and hypothalamus.[4] However, the source for this exposure remains undetermined.
- **Genetic hypothesis:** which is based on the existence of a single or multiple genes affecting insulin and androgen function.

Table 2. Manifestations of PCOS

Common symptoms
Menstrual disorders (oligomenorrhoea or amenorrhoea)
Ovulation disorders (oligomenorrhoea or anovulation)
Infertility
Dysfunctional uterine bleeding
Clinical hyperandrogenism
Obesity
Insulin resistance
Long-term consequences
Impaired glucose tolerance/diabetes mellitus type 2
Dyslipidaemia
Hypertension
Cardiovascular disease
Pregnancy complications/miscarriage
Endometrial cancer
Others

Clinical manifestations

PCOS is a highly variable condition with a broad array of manifestations. Symptoms and severity of symptoms vary throughout life and between individuals. The combination of raised levels of androgens, oestrogen, insulin and luteinising hormone explain the classic PCOS presentation of hirsutism, anovulation, dysfunctional bleeding and derangements of glucose and lipid metabolism (Table 2).

Common symptoms

Common symptoms of PCOS are outlined below.

- **Oligomenorrhoea/amenorrhoea.** This is reported in up to 70% of affected women and reflects abnormalities in ovulation. These women present with irregular, few, or absent menstrual periods.
- **Infertility.** This generally results from chronic anovulation.
- **Dysfunctional uterine bleeding.** This is common in patients with PCOS because of the lack of ovulation and unopposed oestrogen action. The absence of regular menstruation induced by progesterone withdrawal may lead to endometrial hyperplasia and uncontrolled bleeding.
- **Hyperandrogenism.** This has been found in 60 to 80% of affected women and may manifest as at least one of the following:
  - hirsutism; excessive and increased body hair, typically in a male pattern, affecting predominantly the face, chest and abdomen (see Figures 2 and 3)
  - male-pattern alopecia; hair loss appearing as thinning hair on top of the head
  - acne, oily skin and/or seborrhoea.

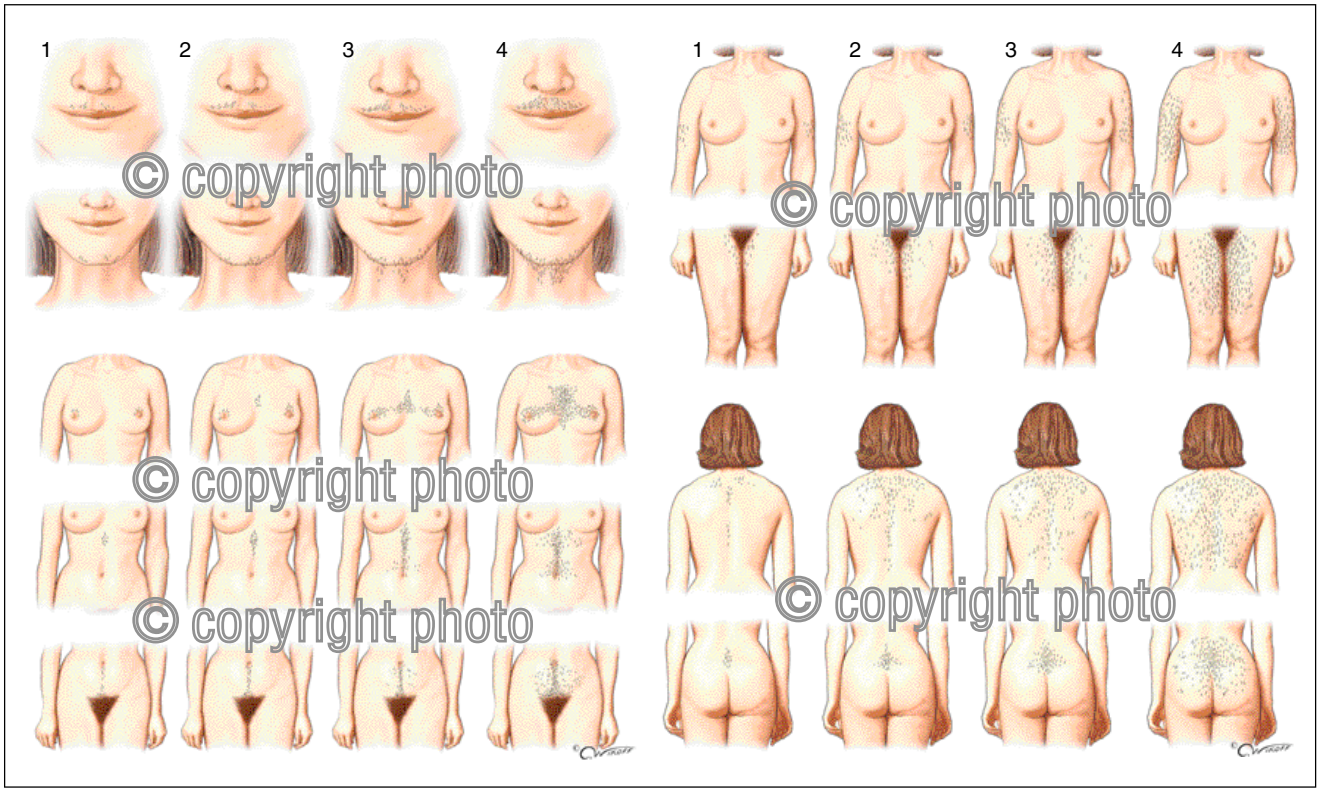


Figure 3. The modified Ferriman-Gallwey score, which is a method of evaluating and quantifying hirsutism in women. Hair growth is rated from 1 (few hairs) to 4 (complete and heavy cover) in nine locations, giving a maximum score of 36. Hirsutism is defined when the total score is above 7.

- **Obesity.** This presents in most patients with PCOS and has a varying incidence between countries and ethnic groups.[5] Obesity tends to be central (abdominal) in its distribution and even lean women with PCOS may have a fat distribution favouring central omental and visceral fat. Although obesity is not regarded as an intrinsic disturbance of the disorder, it has a substantial effect on the manifestation of PCOS by exacerbating metabolic and reproductive disorders as well as other features of the syndrome. Moreover, weight gain might promote the phenotype of PCOS in a susceptible population.[6]
- **Insulin resistance.** This presents in up to 70% of women with PCOS and is more prevalent in obese patients.

Long-term consequences

PCOS is associated with potential life-long health consequences. Women with this condition are at risk of the complications described below (see Table 2).

Metabolic issues

Some studies indicate a fourfold increase in the prevalence of the metabolic syndrome in women with PCOS compared with the general population, linking the hyperandrogenic state with unfavourable metabolic profiles. From an endocrine and metabolic standpoint, women with classic PCOS phenotypes present with higher androgen levels and more severe metabolic abnormalities than those with ovulatory PCOS phenotypes.[1] Moreover, the first-degree family members of women with PCOS show an increased rate of adverse metabolic profiles.

Impaired glucose tolerance and diabetes mellitus

Insulin resistance is a prominent feature of PCOS with patients often experiencing a more rapid rate of deterioration from normal glucose function to impaired glucose tolerance. Prevalence of type 2 diabetes is three- to seven-times higher in women with PCOS.[7,8] Compensatory hyperinsulinaemia initially allows women to maintain normal glucose tolerance, and thus fasting glucose and glucose challenge tests (oral glucose tolerance test 75 g glucose) are usually normal in young patients with PCOS.

Dyslipidaemia

Increased concentrations of triglycerides and low-density lipoprotein (LDL) cholesterol and decreased concentrations of high-density lipoprotein (HDL) cholesterol are common in women with PCOS, particularly if they are obese.

Table 3. Differential diagnoses of PCOS

Abnormal uterine bleeding	
Intrauterine pathology	
Other hormonal disturbances	
Pregnancy	
Anovulation	
Hyperprolactinaemia	
Hypothalamic disorders (e.g. stress, anorexia, excessive exercise)	
Thyroid dysfunction	
Hyperandrogenism	
Androgen-producing tumour	
Congenital adrenal hyperplasia	
Cushing's syndrome	
Idiopathic hirsutism	

Cardiovascular disease

The metabolic features of PCOS have led to widespread concern about the risk of cardiovascular disease, initially attributed to an increase in diabetes, dyslipidaemia and hypertension. Lately, PCOS-related androgen excess has also been suggested to be responsible for an adverse cardiac risk and accentuated as a potential 'health hazard'. A higher than expected prevalence of early asymptomatic coronary atherosclerosis, elevated homocysteine levels and lower nitrite/nitrate levels compared with controls have been demonstrated in young patients with PCOS.

A recent study evaluating the risk of cardiovascular events in postmenopausal women demonstrated that clinical features of PCOS are associated with higher rates of angiographic coronary artery disease and lower cardiovascular event-free survival.[9] Despite remaining controversy on the topic and the need for further investigation in prospective trials, evidence is equivocal that women with PCOS have an increased risk of cardiovascular disease.

Gynaecological issues

Pregnancy complications

Pregnancy complications (such as gestational diabetes and hypertensive disorders of pregnancy) and miscarriage rates are increased in women with PCOS; however, it remains controversial whether this risk is directly due to the syndrome or to the associated obesity.[10]

Endometrial cancer

Endometrial cancer has been estimated to be at least four times more common in women with PCOS than those without. It was initially thought to be related to prolonged stimulation of the endometrium by oestrogen in the absence of progesterone in anovulatory women. However, recent evidence suggests the contribution of other factors such as hyperandrogenism, obesity and insulin resistance.

Other issues

Women with PCOS have also been shown to have an increased incidence of sleep apnoea and depression, high levels of inflammatory markers and an increased risk of fatty liver disease. Fatty liver disease has been described predominantly in obese women with PCOS, suggesting the need for an evaluation for liver disease in this group of patients.

Presentation in adolescents

Excessive levels of androgens and insulin may lead to precocious (premature) puberty. Many adolescents with PCOS are obese. The presentation of PCOS in adolescents may be confusing because the symptoms of hyperandrogenism, such as acne or seborrhoea, are frequent in this age group and are often associated with irregular menstrual cycles. In most instances, these symptoms are transient and only reflect the immaturity of the hypothalamic–pituitary–ovarian axis during the first years following menarche. Conversely, the existence of these symptoms for more than two years after menarche warrants evaluation.

Diagnosis

To overcome the existing confusion in the classification of PCOS, we recommend adopting the Rotterdam criteria for diagnosis (see the box on page 29).

In many women the symptoms are easily recognisable; however, in others, because of sometimes vague presentations, it can take years to reach a diagnosis. Ethnicity can influence the extent of symptoms, especially hirsutism and obesity (both of which appear to be rare in Asian women). Differential diagnoses, diagnostic tests and the general diagnostic approach for PCOS are given in Tables 3 and 4 and the flowchart on page 38.[11,12]

Management

Currently, PCOS is a noncurable condition but its manifestations can be effectively managed. It is an entity with a long lifespan, requiring control of symptoms and preventive strategies.[13] Therapies change depending on the stage of life of a woman, presenting symptoms and desire for fertility (see the flowchart on page 40). Education on both the short- and long-term consequences of PCOS and regular follow up are extremely important for successful treatment and to help improve patient compliance.

Lifestyle changes

Diet, exercise and behavioural (stress reduction) management are first-line interventions in women with PCOS, especially in overweight patients.[14] Weight loss of as little as 5 to 10% of bodyweight, even if women still remain overweight, can reduce the severity of hirsutism and acne, restore menstrual regularity and ovulation, and protect against diabetes, dyslipidaemia and cardiovascular consequences. Weight reduction in women seeking to conceive increases motivation, improves chances for spontaneous or induced pregnancy and reduces pregnancy complications. Prevention of weight regain, including support from the physician and family, are more important than

Table 4. Diagnostic tests for diagnosis and evaluation of PCOS

Assessment/diagnostic tests	Evaluation of results/notes
History	
Frequency and regularity of menstrual cycles at puberty and current time Hormonal treatment, including the OCP History of risk factors for diabetes and cardiovascular disease, including family history	To elicit evidence of peripubertal menstrual dysfunction and hirsutism Menstrual abnormality may be masked by use of the OCP in young women and become evident only when they try to achieve pregnancy
Excessive hair growth on the face, chest and abdomen	Use of cosmetic treatments can alter the presentation
Examination	
Hirsutism	Hirsutism is assessed by the use of the modified Ferriman-Gallwey score, which assigns a score 1 to 4 for nine different body location areas (score 1 is for few hairs and score 4 is for total cover; see Figure 3). Hirsutism is defined when the total score is above 7
Blood pressure	Blood pressure of more than 130/85 mmHg warrants further monitoring and treatment
Waist to hip ratio	A ratio of more than 0.85 represents android (central) obesity. This ratio may be increased in patients with PCOS
BMI	BMI is calculated by weight/height^2 (kg/m^2). Women with a BMI of 25 to 29 are considered overweight. A BMI of over 30 indicates obesity
Gynaecological examination	To exclude other causes of bleeding and miscarriage
Pelvic ultrasound examination	Transvaginal ultrasound is the best imaging mode. Transabdominal ultrasound examination requires more expertise to obtain a good view, particularly in obese women
Ovarian morphology and size of ovaries	Presence of polycystic ovaries on gynaecological ultrasound is not a diagnostic essential but is important in some cases to make the diagnosis of PCOS. It also indicates endometrial thickness Polycystic ovaries alone are found in 16 to 25% of women with no evidence of menstrual dysfunction or hyperandrogenism[11] Polycystic ovaries may not be present in women with PCOS if they have used OCPs, insulin-sensitising agents or other forms of ovarian suppression
Laboratory evaluation **A. Hormone assays for differential diagnoses**	
17-hydroxyprogesterone (serum, in follicular phase of cycle)	To exclude late-onset congenital adrenal hyperplasia. If levels are >2 µg/L (6.1 nmol/L), a short adrenocorticotropic hormone-stimulating test should be performed for final diagnosis
Thyroid stimulating hormone (serum)	To exclude thyroid abnormality
Prolactin (serum)	To exclude hyperprolactinaemia
Cortisol (24-h urine)	To exclude Cushing's syndrome (only in patients with marked signs of androgen excess or other Cushing's features)
Total testosterone (serum)	To exclude an androgen-producing tumour (in such cases total testosterone levels usually exceed 7 nmol/L)
B. Assessment of hyperandrogenaemia*	
Total testosterone (serum)	Most important circulating androgen of ovarian origin. About 99% of total testosterone is bound to plasma proteins and is biologically inactive. In patients with PCOS, total testosterone levels are usually at the upper limit of normal or slightly elevated

continued

Table 4. Diagnostic tests for diagnosis and evaluation of PCOS – continued

Assessment/diagnostic tests	Evaluation of results/notes
SHBG (serum)	Most important plasma protein that binds (inactivates) up to 40% of testosterone
Free androgen index (calculated)	Calculation of bioavailable fraction of androgen (free and weakly bound to albumin) by total testosterone / SHBG x 100. This is a superior estimate of hyperandrogenism. Accuracy depends on reliable total testosterone and SHBG measurements
Free testosterone (by direct immunoassay)	Remains controversial. Bioavailable testosterone can be measured directly but most existent assays (predominantly immunoassays) are highly unreliable
Other androgens (dehydroepiandrosterone and androstenedione; serum)	Usually elevated in patients with PCOS, but their measurement is of little value in the average clinical setting and not recommended
C. Metabolic risk assessment†	
Glucose testing Fasting glucose OGTT Insulin testing	For diagnosis of diabetes and glucose intolerance Random and fasting glucose levels are usually normal in women with PCOS If fasting glucose is abnormal (>5.6 mmol/L) or in obese women, OGTT (with 75 g glucose) should be performed every one to two years OGTT targets: fasting glucose 5.6 to 6.9 mmol/L or/and post two hours 7.8 to 11 mmol/L = glucose intolerance. Fasting glucose ⩾7 mmol/L or/and post two hours ⩾11.1 mmol/L = diabetes OGTT with insulin measurement is inaccurate, expensive and difficult OGTT with both glucose and insulin measurement is the most informative screening test in obese patients with PCOS Peak insulin 80 to 100 µIU = hyperinsulinaemia (post one or two hours)[12]
Lipid status Total cholesterol HDL cholesterol Triglycerides	To access metabolic features and to help in planning and follow up of recommended dietary modifications to reduce obesity and cardiovascular risk
D. Assessment of ovarian function	
LH FSH Progesterone Oestradiol	Little role in the diagnosis of PCOS. Justified when infertility is an issue. Ovulation problems are usually manifested by menstrual abnormalities and no other tests are usually needed. LH:FSH ratio is sometimes more than 2:1 in one-third of women with PCOS and may be helpful diagnostically. Is not routinely necessary if the clinical picture is otherwise clear
Other investigations	
Liver involvement Transaminases (serum) Ultrasound of upper abdomen	For evaluation of fatty liver disease. Recommended predominantly in obese patients with PCOS
Endometrial biopsy Hysteroscopy	May be used to investigate unexplained vaginal bleeding or abnormal uterine lining appearance on gynaecological ultrasound
Laparoscopy of the pelvis Computed tomography Magnetic resonance imaging	Not justifiable for suspected PCOS alone

* Serum analyses fail to measure hyperandrogenism in 20 to 40% of patients because of relative inaccuracy of assay methods. Most commercial assessments are not designed for detection in women, have broad normal ranges and lack age-appropriate norms. † Metabolic risk assessments are justified in all patients with PCOS, independently of bodyweight.

ABBREVIATIONS: BMI = body mass index; FSH = follicle stimulating hormone; HDL = high-density lipoprotein; LH = luteinising hormone; OCP = oral contraceptive pill; OGTT = oral glucose tolerance testing; PCOS = polycystic ovary syndrome; SHBG; sex hormone-binding globulin.

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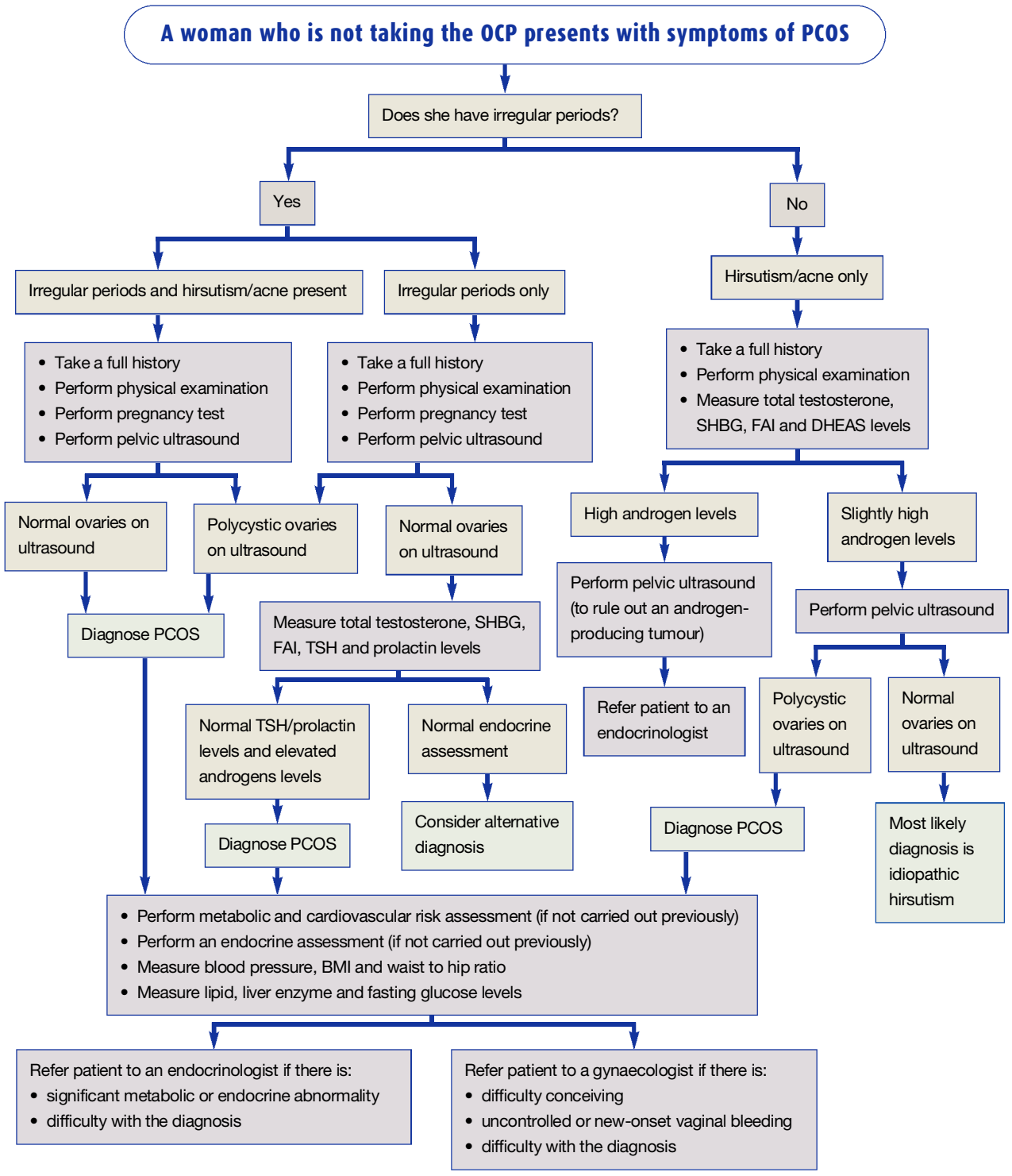
Diagnostic approach for women with PCOS



ABBREVIATIONS: BMI = body mass index; DHEAS = dehydroepiandrosterone sulfate; FAI = free androgen index (calculated); PCOS = polycystic ovary syndrome; OCP = oral contraceptive pill; SHBG = sex hormone-binding globulin; TSH = thyroid-stimulating hormone.

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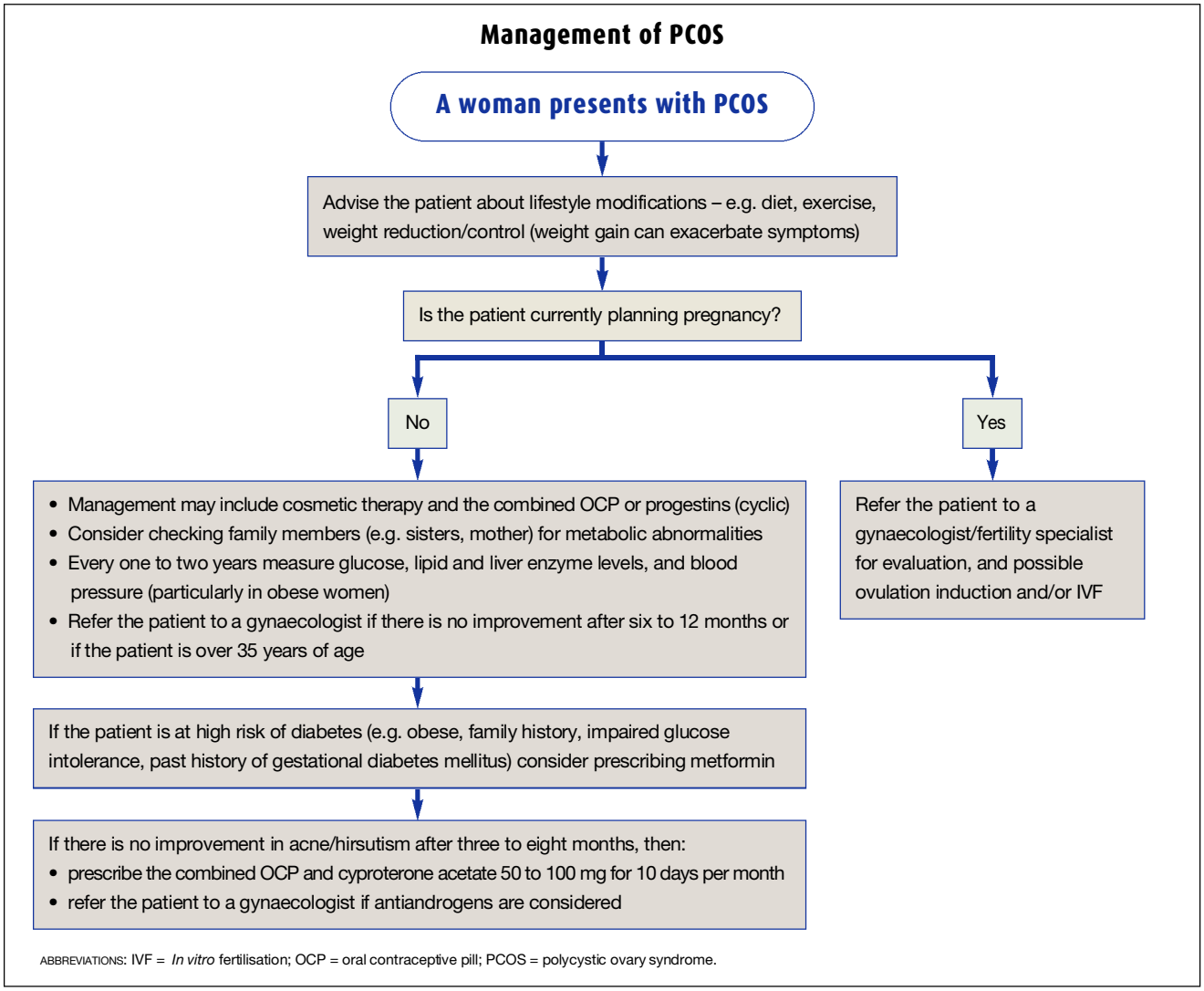

dietary composition. A moderate energy-reduced diet with reduction to an intake of 500 to 1000 kcal/day, achievement of up to 10% of bodyweight loss within six to 12 months, followed by moderate fat or carbohydrate restriction for weight maintenance has been shown to be efficient in the long term. Physical activity should be gradually increased to at least three and a half hours per week of moderate exercise (e.g. swimming and walking).

Medications are mainly used to suppress androgen and insulin levels and to restore regular menstrual pattern to prevent endometrial hyperplasia.

Treatment of acne and hirsutism

Acne and/or hirsutism are improved with weight reduction combined with cosmetic approaches. Hair removal by shaving, depilation or laser therapy is proven to be an effective initial strategy and improves the psychological state of affected women. If the above mentioned strategies are ineffective or unaffordable, the combined oral contraceptive pill (OCP) is a widely prescribed effective treatment for hirsutism and acne, which also regulates menstrual cycles and provides contraception. Women should be advised that it might take between three and eight months of taking the OCP to achieve improvement.

In cases of persistent acne and hirsutism, the combination of antiandrogen therapy and the combined OCP can prove to be efficient. If antiandrogen therapy is considered, referral of the patient to a specialist in reproductive endocrinology may be appropriate. The most commonly used antiandrogens are cyproterone acetate and spironolactone. Cyproterone acetate is a progestogen that blocks androgen receptors, suppresses 5α-reductase and increases sex hormone binding globulin (SHBG) concentrations. It is used on the first 10 days of a woman's menstrual

cycle and its dose may be substantially increased every two to three months from 10 to 100 mg/day. Cyproterone acetate might lead to reduced libido, weight gain, mood changes and rarely liver function changes. Spironolactone is an aldosterone antagonist that competitively blocks androgen receptors. It is well tolerated in doses up to 200 mg/day (the usual dose is 75 to 200 mg/day), but it is associated with side effects such as uterine bleeding (it should be used with the OCP), breast pain, thrombocytopenia, leucopenia, agranulocytosis, lethargy, headache, ataxia, fever and pruritus. Women treated with spironolactone should be checked annually for measurement of electrolyte levels and liver and renal functions.

The androgen-receptor antagonist flutamide is effective but is associated with frequent adverse effects and low patient compliance. The topical antiandrogen cream eflornithine, an ornithine decarboxylase inhibitor, has shown promising results with long-term use; however, its use is restricted by high costs and reversed hair growth after cessation of treatment.

Metformin, an insulin-sensitising agent, might be useful in the treatment of cosmetic issues associated with PCOS with comparable efficacy to the combined OCP, but its use for this indication alone is not justified.

Oral contraceptives for menstrual dysfunction

The combined OCP is very efficient in reducing androgen levels and controlling menstrual cycles. The oestrogen component of the combined OCP stimulates hepatic production of SHBG, which reduces bioavailable androgen. The progestin component of the combined OCP provides competitive antagonism to androgen at its receptors, reducing the action of testosterone at the target organ. Nearly every combination of OCP is effective in managing PCOS; the choice of OCP is based on the progestin component, since oestrogen is similar in the different pills, and present data show similar efficacy for standard available oestrogen doses (20 to 35 μg). Pills containing drosperinone (an analog of spironolactone) and cyproterone acetate are considered to be of more benefit in patients with hyperandrogenic symptoms; other progestins have weaker antiandrogen potency but might still be effective.

Despite ovulation problems, women with PCOS are not protected from spontaneous conception and contraception should be offered to every woman of a reproductive age who does not seek pregnancy. Prevention of endometrial hyperplasia is an additional benefit of taking the combined OCP. There is ongoing unresolved debate about whether or not the OCP increases insulin resistance.

To control menstrual cycles only and to prevent irregular, occasionally excessive uterine bleeding in women who do not tolerate or do not wish to use the OCP, progesterone-only medications are advisable. They should be given regularly (10 days every one to three months) to mimic progesterone release from the ovulating ovary.

Treatment of metabolic and cardiovascular derangements

Insulin resistance is one of the key factors in PCOS development, therefore suppression of insulin levels may be assumed useful in ameliorating clinical presentations and in preventing long-term consequences of PCOS.

Metformin effectively reduces insulin resistance by inhibiting hepatic glucose production and increasing glucose uptake in peripheral tissues. Its use in women with PCOS became widespread due to numerous reports (mostly from nonrandomised trials) on benefits in clinical measures. Moderate cost and good tolerability made it even more attractive; however, with regards to current evidence, the use of metformin should be more judicious.[15] Metformin appears to be beneficial in improving androgen levels, lipid profile and hirsutism, and in the restoration of menstrual cycles; however, according to data from recent Cochrane analyses, these effects are modest, based on small numbers of women and are comparable to other treatments. Existing data are therefore insufficient to acknowledge that metformin reduces the risk of diabetes and cardiovascular disease in women with PCOS.[12,16]

Metformin is associated with gastrointestinal disturbances and decreased vitamin B_{12} absorbance, and is contraindicated even in patients with mild renal impairment. It is better tolerated if started at 500 mg and increased within a week to 1500 mg/day. No literature exists as to the safety of the long-term use of metformin in young women. Metformin can be considered for patients at high risk of diabetes (e.g. obese, family history, insulin resistance). It should be used in addition to lifestyle improvements or if other treatments are nonapplicable. It should not be considered as a 'weight-loss drug'.

The OCPs have variable effects on metabolic and vascular derangements in patients with PCOS. Glucose intolerance can be managed by metformin and its combination with the combined OCP might be more effective. Inflammatory and atherosclerotic markers have been shown to be improved with these treatments, but there are insufficient data to support the efficacy of metformin and/or the combined OCP in preventing cardiovascular disease or diabetes. Likewise, limited evidence exists on the effectiveness of antiandrogenic treatment on long-term consequences of PCOS, and their use for prevention of these complications in asymptomatic young women is not justified.[16]

According to the American Association of Clinical Endocrinologists' position statement 'women with PCOS should undergo comprehensive evaluation for recognized cardiovascular risk factors and receive appropriate treatment based on findings'.[15]

Treatment of infertility

Lack of ovulation seems to be a major problem for women with PCOS who are trying to achieve pregnancy. Nonetheless, other problems can arise and thorough investigations of couples should be carried out before initiation of treatment despite the apparent ovulation problem. Lifestyle modifications are the treatment of first choice in overweight anovulatory women, and even small weight losses can lead to restoration of ovulation. Clomiphene is currently the first-line oral medication to induce ovulation; 70 to 85% of women with PCOS respond to clomiphene, with a cumulative pregnancy rate of 70 to 75% over six to nine cycles of treatment.[17,18] In ovulation induction cycles, metformin alone is less effective than clomiphene; the combination of both results in higher ovulation rates, but this has mainly been found in clomiphene-resistant patients. There are no clear data to suggest that metformin improves pregnancy outcomes, but pregnancies achieved in patients taking metformin carry less risk of multiple gestation and ovarian hyperstimulation syndrome.

Induction of ovulation with gonadotropins is more effective and is the next step if clomiphene and metformin fail. Because the ovaries of women with PCOS are uniquely sensitive to these agents, the risks of multiple gestation and ovarian hyperstimulation are significantly higher. A low-dose regimen and close monitoring of ovarian response by trained personnel is strongly recommended in these patients. *In vitro* fertilisation is considered as an option if ovulation induction steps are not successful or if additional infertility factors are present.

Ovarian diathermy or laser drilling has been used with results comparable to those of clomiphene and gonadotropins. The short-term complication rate is minimal; however, as an invasive procedure it may produce pelvic adhesions, damage to adjusting organs, pelvic infection and bleeding. Surgery to the ovary should be performed only after extensive discussion with the patient.

Suggestions for rural GPs

Irregular menstrual periods and the presence of acne or excessive hair growth in patients should raise suspicion for PCOS. Most women with PCOS can be diagnosed clinically without the need for laboratory investigation. However, laboratory tests are essential for exclusion of other syndromes that mimic PCOS; therefore screening for hyperandrogenaemia and a metabolic risk assessment may be needed.

Internet resources for patients

Polycystic Ovarian Syndrome Association of Australia
www.posaa.asn.au

USA Polycystic Ovarian Syndrome Association
www.pcosupport.org

The Jean Hailes Foundation for women's health
www.jeanhailes.org.au

Australian PCOS website produced by The Jean Hailes Foundation
www.managingPCOS.org.au

As polycystic ovarian morphology is not critical for a diagnosis of PCOS, gynaecological ultrasound may be postponed if the diagnosis is clear. However, it is of value for baseline evaluation and further follow up of endometrial thickness in women with oligomenorrhoea for the early detection of endometrial hyperplasia. Gynaecological examination and exclusion of pregnancy are important in patients with abnormal uterine bleeding or new-onset amenorrhoea.

Hormonal investigation of ovarian function is justified in patients with PCOS if infertility is an issue but has no value in the general management of PCOS.

Referral

The diagnosis of PCOS may prove difficult in a few patients, and referral of these women to a medical or reproductive endocrinologist may be valuable. Excessive or frequent vaginal bleeding, uncontrolled dermatological or endocrine problems, high metabolic risk, early-onset diabetes or infertility justify specialist referral of patients.

Most gynaecologists have experience in using clomiphene in women who have problems conceiving, but patients who require gonadotropins should be referred to an infertility expert. Referral of patients with PCOS to a dietitian and/or psychologist is advisable for those who face difficulty in implementing lifestyle changes.

Conclusion

Most patients with PCOS can be diagnosed and managed in general practice. PCOS is a lifetime condition of variable presentations with hyperandrogenism as a predominant feature and significant metabolic sequelae. Mood disorders are common and should be recognised and treated to improve quality of life and facilitate better outcomes. Initial assessment of androgenic status, metabolic risks, long-term follow up, lifestyle modifications and psychological support are the cornerstones of managing PCOS in every patient.

Women with PCOS should be well informed on the progressive features of the syndrome to better solicit their involvement and motivation (see the box on this page listing some useful websites on PCOS for patients). Given the genetic origins of the syndrome, screening of family members for metabolic derangements can be considered. MT

References

A list of references is available on request to the editorial office.

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Polycystic ovary syndrome

Can we make the diagnosis and management easier?

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