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Diagnosis and Management of Polycystic Ovary Syndrome

A Practical Guide

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Contents

Abstract

Polycystic ovary syndrome (PCOS) is a syndrome, which can be defined as a group of recognisable patterns of symptoms or abnormalities that indicate a particular medical situation. The current definition of PCOS requires the presence of two of the following three conditions: (i) oligo- and/or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenism; and (iii) polycystic ovaries – and the exclusion of other aetiologies. It is generally accepted that the prevalence of PCOS is approximately 5–10%, and that of polycystic ovaries alone is 21–23%. Other features of PCOS are obesity, insulin resistance, impaired glucose tolerance

and type 2 diabetes mellitus, dyslipidaemia, cardiovascular disease, obstructive sleep apnoea and infertility.

An approach to a patient with possible PCOS should be directed towards making a diagnosis and screening for associated endocrine abnormalities. Therapeutic interventions are directed towards addressing the needs of the patient at present and towards preventing long-term complications of the syndrome. Body mass index, which is a primary mediator in the relationship between PCOS and health-related quality of life in obese PCOS adolescents, may play a similar role in other PCOS patients. Any intervention directed at reducing central obesity will not only improve quality of life but also correct hyperinsulinism and improve fertility and lipid and androgen profiles. It is also the only currently available intervention that can have a lifelong impact on reducing possible long-term complications of the syndrome.

Lifestyle modification is the cardinal intervention. Pharmacological treatments are available for specific indications. Infertility can be treated with clomifene (clomiphene citrate), metformin, gonadotropins or surgery to the ovaries. Cyproterone (alone or in combination with ethinylestradiol) and spironolactone are the main drugs used in the treatment of hirsutism. Other drugs that can be considered include flutamide, ketoconazole and finasteride.

Women with PCOS require ongoing surveillance to detect impaired glucose tolerance, hyperlipidaemia, endometrial hyperplasia and consequent complications. Obese women, in particular, require regular glucose tolerance testing because of the potential for rapid progression from normal to impaired glucose tolerance and diabetes.

The focus of this article is the epidemiology, diagnosis and management of this common endocrine disorder. Diagnostic and co-morbid features are discussed separately to facilitate understanding of PCOS. Symptom-directed strategies, as well as short- and long-term goals of treatment, are outlined.

1. Epidemiology

Polycystic ovary syndrome (PCOS) is difficult to define. First, it is a syndrome, i.e. a group or recognisable patterns of symptoms or abnormalities that indicate a particular medical situation. One of the implications is that a single finding does not in itself permit the diagnosis to be formed. Secondly, the definition has been evolving. Initially described two centuries ago as a case of a bearded woman with diabetes mellitus, Stein and Leventhal[1] provided other descriptions last century. We have now arrived at a current 21st-century definition, which was developed at The Rotterdam European Society of Human Reproduction/American Society for Reproductive Medicine (ESHRE/ASRM)-Sponsored PCOS Consensus Workshop Group in 2003.[2]

Bearing in mind those limitations, it is generally accepted that the prevalence of PCOS is in the region of 5–10% and that of polycystic ovaries alone is 21–23%.[3]

The 2003 definition of PCOS requires the presence of two of the following three symptoms: (i) oligo- and/or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenism; (iii) polycystic ovaries; and the exclusion of other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumours or Cushing's syndrome).[2]

As there can be different interpretations of the above-mentioned terms, the most commonly accepted definitions need to be considered.

1.1 Oligo- and/or Anovulation

Oligo- and/or anovulation commonly manifests as oligomenorrhoea (fewer than nine menses per year) or dysfunctional uterine bleeding (which is irregular or unpredictable). It is also accepted that any cycle lasting <24 days or >35 days is abnormal.[4]

1.2 Clinical and/or Biochemical Signs of Hyperandrogenism

One of the cardinal clinical presentations of hyperandrogenism is hirsutism (excessive growth of coarse dark and thick hair in a male pattern distribution). This may not be obvious, as hirsutism is often treated well before the patient is ever evaluated endocrinologically. It may be significantly less prevalent in women of East Asian origin or in adolescence.[2] Normative data in large populations are still lacking and few clinicians use standardised methods (for instance the Ferriman-Gallwey score) for objective scoring.[3] The sole presence of acne, but possibly not alopecia, is also a potential marker for hyperandrogenism.

Biochemical signs of hyperandrogenism rely on measurements of free testosterone or the free androgen index (FAI) [testosterone multiplied by 100 divided by sex hormone-binding globulin levels]. Recommended methods for the assessment of free testosterone include equilibrium dialysis, calculation of free testosterone from the measurement of sex hormone-binding globulin and total testosterone, or ammonium sulfate precipitation. From a clinical perspective, it would be useful to inquire as to the particular method used in the local laboratory. Problems with androgen assays include lack of well established normative ranges, wide variability in the normal population, and lack of data for adolescents, older women and the different body mass index (BMI) ranges.[3] Hormonal treatment prior to measurement may also affect the readings. For instance, the oral contraceptive pill will lower the values.

1.3 Polycystic Ovaries

This ultrasound-based diagnosis often causes a lot of confusion for both the patient and clinician. The currently accepted definition is the presence of ≥12 follicles in each ovary measuring 2–9mm in diameter, and/or increased ovarian volume (>10mL). Follicle distribution should be omitted, as well as the increase in stromal echogenicity and volume.

This definition does not apply to women on the oral contraceptive pill. Only one ovary fitting the description is required to make a diagnosis. It is best to perform a transvaginal scan in the early follicular phase (between days 3–5) of the menstrual cycle, as ovarian morphology changes throughout the menstrual cycle. Ovarian volume should be measured using the formula 0.5 × length × width × thickness and follicle number by estimating in both longitudinal and anteroposterior cross-sections of the ovaries. Women with irregular cycles can be scanned at random or after progesterone-induced bleeding.[2]

1.4 Exclusion of Other Aetiologies

As part of a diagnostic process, non-classical congenital adrenal hyperplasia, hyperprolactinaemia, Cushing's syndrome, acromegaly and adrenal/ovarian androgen-producing tumours need to be excluded. In most patients, this can be done on clinical grounds after history and examination. If required, measurements of morning 17-hydroxyprogesterone (17OHP), prolactin, urine 24-hour cortisol levels, insulin-like growth factor 1 and plasma androgen levels may help to clarify the issue.[5]

1.5 Other Features of Polycystic Ovary Syndrome: Not Included in Diagnostic Criteria but Part of a Syndrome

1.5.1 Obesity

The incidence of obesity in women with PCOS varies between countries and ethnic groups. In the US, >50% of women with PCOS are overweight or obese, but this prevalence differs little from that in the general community. In other countries, PCOS appears to be associated with obesity but at a lower

rate than in the US. 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.[6]

1.5.2 Insulin Resistance

This is independently related to PCOS, with women of normal weight with PCOS showing a degree of hyperinsulinaemia and impaired glucose disposal after meals and during glucose tolerance tests (oral or intravenous).

1.5.3 Impaired Glucose Tolerance and Type 2 Diabetes Mellitus

These are major complications in overweight women with PCOS. Although fasting glucose level is usually normal, insulin release after a glucose load is increased and glucose disposal is impaired. An epidemiological study in the UK that followed up women with a histological diagnosis of PCOS after wedge resection of the ovaries found clear evidence of an increase in the rate of diabetes mellitus.[7] This confirmed the results of many other studies from the US and Europe. In obese women with PCOS, progression from normal glucose function to impaired glucose tolerance or diabetes is more rapid than in women without PCOS.[3]

1.5.4 Dyslipidaemia

Hypertriglyceridaemia, increased concentrations of 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. Levels of plasminogen activator inhibitor-1 may also be raised, suggesting a chronic underlying inflammatory-like process.[8]

1.5.5 Cardiovascular Disease

A higher than expected prevalence of PCOS has been reported among young women with angiographically proven narrowing of the coronary vessels. Women with PCOS were also more likely to have sonographic evidence of premature obstruction of other large vessels. However, a UK study of medical records and death certificates of women with a histological diagnosis of PCOS revealed no evidence for an increase in myocardial infarction or other types of heart disease.[9] Other limited epidemiological studies to date have not shown an increased incidence of coronary heart disease events. The association is still under investigation.

1.5.6 Obstructive Sleep Apnoea

This condition is more common in PCOS and cannot be explained by obesity alone. Insulin resistance seems to be a better predictor of sleep-disordered breathing than is age, BMI or circulating testosterone levels.[10,11]

1.5.7 Infertility

Women with PCOS seeking to become pregnant may have difficulties because of anovulation, and later may be concerned about the impact of being overweight and hirsute. It is unclear whether miscarriage is increased in PCOS, or whether pregnancy loss is a result of excess bodyweight.

2. Diagnosis

An approach to a patient with a possible PCOS should be 2-fold, directed towards making a diagnosis as well as screening for associated endocrine abnormalities.

It is necessary to have a high level of suspicion, especially with a patient who presents with a history of intrauterine growth retardation or post-term birth. Other features that can alert clinicians include premature pubarche, peripubertal onset, and methods used in the past to deal with hirsutism, including previous use of the contraceptive pill. Specific enquiry should be directed towards symptoms suggestive of thyroid dysfunction, hyperprolactinaemia and excessive daytime sleepiness.

On clinical examination, measurement of BMI, waist circumference, Ferrimen-Gallwey score, blood pressure and exclusion of other causes of vaginal bleeding will help to narrow the diagnosis. It is important to look for Cushing's stigmata in this group of patients. The authors advocate selective use of biochemistry. Testosterone (total or adjusted for sex hormone-binding globulin, e.g. FAI) is helpful to show hyperandrogenaemia and to rule out an androgen-secreting tumour, and 17OHP to exclude congenital adrenal hyperplasia. Other androgens,

such as dehydroepiandrosterone sulfate (DHEA-S) and androstenedione, are not particularly useful. Transvaginal ultrasound is the ideal tool to assess ovarian morphology and to measure endometrial thickness.

In view of its prevalence, it is essential to exclude glucose intolerance by oral glucose testing. It is doubtful whether insulin measurement is indicated, as interpretation is clouded by obesity. Because random and fasting glucose levels are usually normal in women with PCOS, the standard recommendations for diagnosing diabetes by measuring these levels are not applicable, and glucose tolerance testing is recommended. We recommend assessment of lipid status (total and HDL cholesterol and triglyceride levels).

In our opinion, laparoscopy of the pelvis, computed tomography and magnetic resonance imaging are never justifiable for suspected PCOS alone. Endometrial biopsy and hysteroscopy may be used to investigate unexplained vaginal bleeding.

3. Management

Therapeutic interventions are directed towards addressing the needs of the patient at present and at preventing long-term complications of the syndrome. Studies in obese PCOS adolescents, for instance, have shown that BMI is a primary mediator in the relationship between PCOS and health-related quality-of-life reduction.[12] We can speculate that a similar relationship may exist in other PCOS patients as well.

Any intervention directed at reducing central obesity will not only improve quality of life, but also correct hyperinsulinism and improve fertility and lipid and androgen profiles. It is also the only currently available intervention that can have a lifelong impact on reducing possible long-term complications of the syndrome. This global solution is known as 'lifestyle modifications'. It is the only treatment without significant adverse effects.

Several studies have shown that weight loss can lead to resumption of ovulation within weeks. Even a 5% reduction in body mass restores ovulation and fertility. Rapid changes in body composition and fat mass can be shown during lifestyle change. High-protein diets seem to be as effective as low-carbohydrate diets, provided that fat and total calories are comparable. Although lifestyle changes are difficult to maintain, women seeking to become pregnant are highly motivated, making this a first-line intervention in overweight women with PCOS. Glucose intolerance can also be managed by diet, exercise and weight control.

Experience indicates that group therapy, combining exercise, information sessions and dietary advice, works best. This can be organised both at general practitioner and hospital level, utilising resources available in the community. However, without ongoing support, longer-term changes in weight are more difficult to maintain.

Aside from lifestyle modifications, there are several pharmaceutical interventions that are available for specific indications.

3.1 Infertility

The cause of infertility in patients with PCOS is generally lack of ovulation because of a failure of the follicles to develop beyond 10mm. Most cycles are anovulatory and induction of ovulation is essential.

Clomifene (clomiphene citrate) is an oral estrogen antagonist that raises circulating levels of follicle-stimulating hormone (FSH) and induces follicular growth in most women with PCOS and anovulation. The initial regimen is 25–50 mg/day for 5 days. Therapy can be monitored by estrogen levels, follicular ultrasound examination and luteal progesterone level (>20 nmol/L). It is imperative that this full monitoring is employed at least until the appropriate dose/response is established, because of the risk of multiple pregnancies and ovarian hyperstimulation syndrome. As with any drugs, patients should be fully informed about those important adverse effects.[4]

Failure of response is associated with high BMI and high androgen levels. Dosages up to 200 mg/day can be used before failure of response is established.

Use of the insulin-sensitising drug metformin at dosages of 500–2500 mg/day is controversial, but

appears valuable in a number of areas. Metformin is effective in achieving ovulation in women with PCOS with an odds ratio (OR) of 3.88 (95% CI 2.25, 6.69) for metformin versus placebo and 4.41 (95% CI 2.37, 8.22) for metformin and clomifene versus clomifene alone. An analysis of pregnancy rates suggests a significant treatment effect for metformin and clomifene (OR 4.40, 95% CI 1.96, 9.85).[13] It has been widely used for this purpose, and no specific neonatal complications have been described, despite it being classed as 'category C' in Australia (drugs that have caused or may be suspected of causing harmful effects on the human fetus).

Metformin has been promoted in recent years as a first-line treatment for anovular PCOS patients.[14] Further data are required to confirm this. Metformin increases menstrual cyclicity (OR 12.88, p = 0.01, 95% CI 1.85, 89.61) and also has a significant effect in reducing fasting insulin levels (weighted mean difference [WMD] −5.37, 95% CI −8.11, −2.63), blood pressure and LDL cholesterol.[13] It also appears to have other beneficial effects, including improvements in androgen levels and hirsutism, and a reduction in various parameters of the metabolic syndrome. However, the effects are modest and these findings are based on small numbers of women. There is inadequate evidence at present to suggest its use in pregnancy to prevent gestational diabetes or recurrent miscarriage.

There is no evidence of the effect of metformin on BMI or waist : hip ratio. Important adverse effects include higher incidence of nausea, vomiting and other gastrointestinal disturbance. When starting metformin therapy, a gradual increase of the dose may help to alleviate those adverse effects. Metformin therapy does not seem to cause serious adverse effects.[13]

The new insulin-sensitising agents, the 'glitazones' – troglitazone (now discontinued), rosiglitazone and pioglitazone – have been used in Saudi Arabia, Bulgaria, Turkey, Finland and the US, and have been shown to be very effective for ovulation induction, but are not approved by the Australian Pharmaceutical Benefits Scheme for PCOS. Approved indications should be checked by practitioners before prescribing in their respective countries. There is greater concern about the effects on the fetus of these drugs compared with metformin and they should not be used by women who are trying to become pregnant.

Ovulation induction with gonadotrophins such as FSH has proved successful for at least 3 decades, but demands skill and experience to avoid multiple pregnancies and ovarian hyperstimulation syndrome. Patients start on low-dose recombinant FSH administered subcutaneously. Monitoring of ovarian response involves ultrasound examination, often with estradiol measurement. Human chorionic gonadotropin is given when one follicle reaches 16–20mm in size. Any more than two follicles of an appropriate size increases the risk of multiple pregnancies. Multiple gonadotrophin cycles may be required to achieve pregnancy, but this approach is preferable before more invasive procedures such as *in vitro* fertilisation.[4]

Ovarian diathermy or laser drilling has been used in recent years with apparently good results. A recent systematic review comparing drilling with clomifene and gonadotropins proved equivalence in the studies examined.[15] However, as with wedge resection, this surgery may produce pelvic adhesions. Destructive surgery to the ovary should be used only after extensive discussion with the patient and not because the ovaries are found to be polycystic incidentally during routine laparoscopy.

3.2 Menstrual Dysfunction and Endometrial Hyperplasia

Menstrual dysfunction, including irregular periods, in women with PCOS can be managed by administration of progestins (e.g. medroxyprogesterone or norethisterone) or the oral contraceptive pill.

If adverse effects are acceptable to the patient (generally gastrointestinal), metformin can be used to improve cyclicity. However, the drug is not approved for this indication in Australia. The prescriber should check relevant drug information applicable to his/her country.

Endometrial hyperplasia should be assessed by ultrasound examination, endometrial biopsy or hysteroscopy, and can be treated by hormonal therapy such as the oral contraceptive pill or progestins.[4]

3.3 Hirsutism

Several treatment options for hirsutism are available. Because of its mode of action, as discussed in section 3.1, metformin should be considered as part of a long-term strategy to deal with hirsutism.

Cyproterone is an anti-androgen with potent progestational action and, in combination with ethinylestradiol, it inhibits 5α-reductase activity in the skin of hirsute women, increases sex hormone-binding globulin levels and has a significant anti-gonadotrophin effect.

The use of cyproterone was the subject of a recent Cochrane analysis. Van der Spuy and le Roux[16] investigated the effectiveness of cyproterone alone or in combination with ethinylestradiol in reducing hair growth in women with hirsutism secondary to ovarian hyperandrogenism. Using standard Cochrane methodology, they identified 11 studies, 9 of which were included in the final analysis. Most of the studies were small, with only one having >100 participants. No study was identified that compared the use of cyproterone with placebo or cyproterone alone to cyproterone used concurrently with ethinylestradiol to treat hirsutism.

There was a subjective improvement in hirsutism (OR 45.0, 95% CI 2.01, 1006.80) when cyproterone combined with ethinylestradiol was used compared with placebo. No objective clinical assessment was performed. This was based on one small study of 20 participants where cyproterone in a dose of 2mg incorporated into an oral contraceptive (Diane-35) was compared with placebo. Adverse effects may include weight gain, depression, fatigue, breast symptoms and sexual dysfunction.

Currently used therapeutic regimens are the oral contraceptive pill (e.g. ethinylestradiol 35μg plus cyproterone 2mg daily for 21 of 28 days). Estrogen increases sex hormone-binding globulin levels and provides contraceptive efficiency. In addition, oral estrogen and cyproterone (estradiol valerate 2mg daily and cyproterone 50mg for 14 days a month) can be used.

Spironolactone is the other main drug used in the treatment of hirsutism.[16] Its mode of action is by inhibition of steroidogenesis, blockage of the androgen receptor and inhibition of 5α-reductase. It reduces androgens to a similar level to cyproterone, with an OR of reduction Ferriman-Gallwey score of −7.2 (95% CI; −10.9, −3.2). The usual dose is 75–200 mg/day. To reduce the chance of adverse effects, especially abnormal uterine bleeding, it is started in divided doses up to three times daily. Other adverse effects may include benign breast neoplasm, breast pain, agranulocytosis, thrombocytopenia, leukopenia, drowsiness, lethargy, headache, confusion, rash, pruritus, fever and ataxia. It may cause hypertrichosis and interact with ACE inhibitors, NSAIDs, digoxin and other diuretics. Women undergoing treatment with spironolactone should have their urea and electrolytes, or renal and liver function tests checked annually.

Flutamide (a androgen-receptor blocker) is the next most effective drug after spironolactone. In a single study, it showed a trend of being better than cyproterone.[17] Administration does not change the levels of circulating androgens but does stop the clinical manifestations. The usual dosage is 250–500 mg/day. Flutamide may interact with warfarin and other hepatically metabolised drugs such as paracetamol, NSAIDs and opioid analgesics. It may also cause hepatic and endocrine disturbances. It is not safe in early pregnancy.[16]

Ketoconazole is not usually used for hirsutism.[16] It is an enzyme inhibitor that blocks the cytochrome P450 enzyme system and reduces steroid hormone production. When used in PCOS patients, it lowers androgen levels to a greater extent than cyproterone. It is contraindicated in pregnancy, and a dosage of 400 mg/day is generally well tolerated, with nausea and vomiting being the most common adverse effects.

Finasteride is a 5α-reductase inhibitor (it blocks conversion of testosterone to dihydrotestosterone in the tissues). It reduces androgen levels to a lesser degree than cyproterone, and is contraindicated in

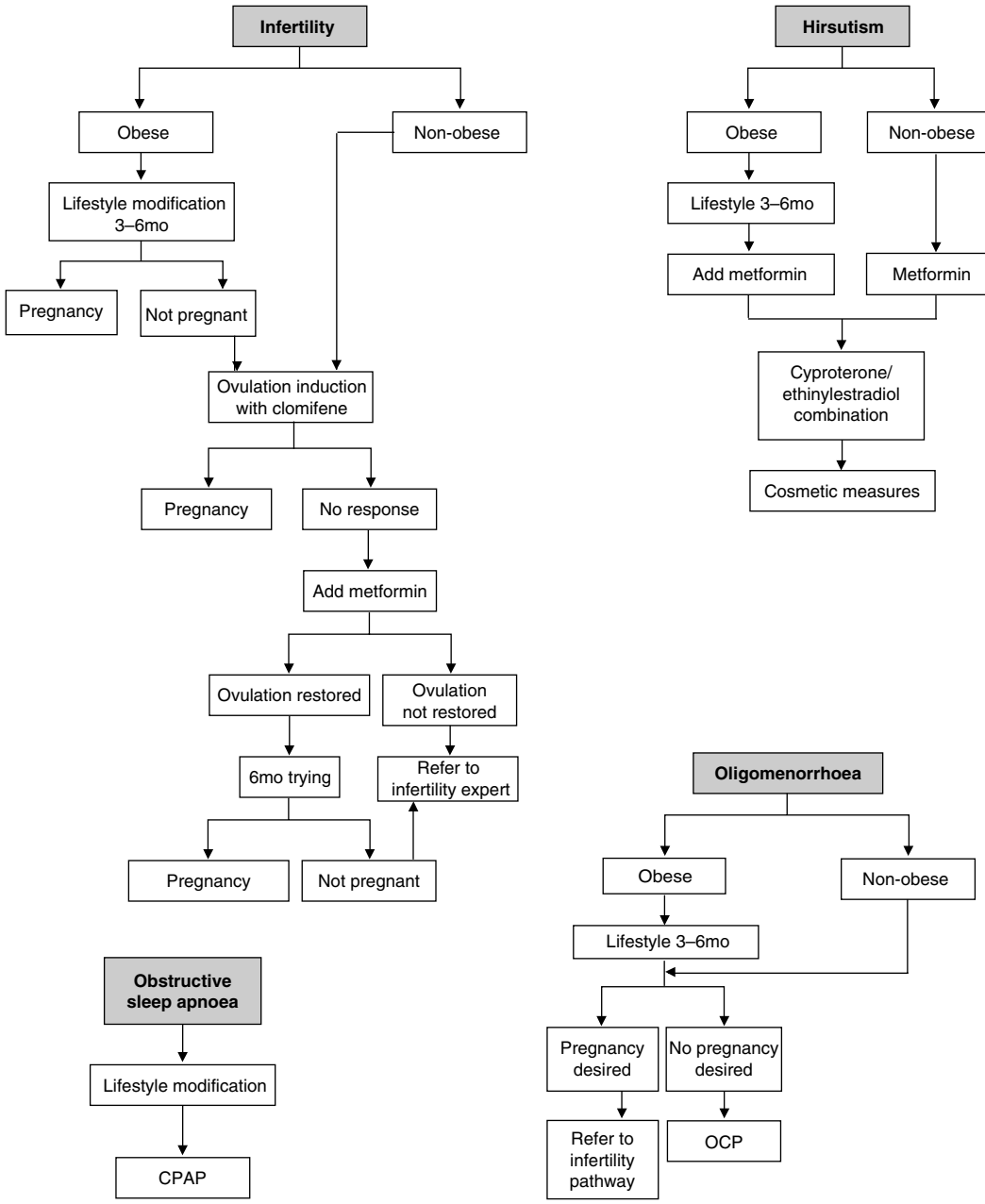

Fig. 1. Problem-based management flow chart for women with polycystic ovary syndrome (PCOS). Management is based on diagnosis and identification of the main presenting problem. **CPAP** = continuous positive airway pressure; **OCP** = oral contraceptive pill.

pregnancy or potential pregnancy. At the usual dosage of 5 mg/day, it can cause breast tenderness.[16]

When choosing between cyproterone and other drug modalities (ketoconazole, spironolactone, flutamide or finasteride), we can expect similar clinical outcomes in terms of their impact on hirsutism. Therefore, it is sensible to base therapy on the adverse effect profile, patient's acceptability and affordability. Cyproterone combined with ethinylestradiol seems to be the preferred first choice. No matter what we do, patients need to be counselled that response times for drugs can be up to 3–6 months, because of the hair follicle life-cycle. In the meantime, cosmetic measures (e.g. laser electrolysis, bleaching, waxing or shaving) can be used.

Eflornithine 13.9% is an irreversible ornithine decarboxylase inhibitor that can be used topically to slow the facial hair growth. Used as a cream twice a day, the first effects are seen within 2–8 weeks, with the maximum effect seen within 24 weeks. It is contraindicated in pregnancy and breastfeeding, and the hair pattern reverts to pretreatment levels within 8 weeks of stopping the treatment. Adverse effects tend to be limited to the skin, with burning and tingling being the most common.[18]

3.4 Long-Term Management

Women with PCOS require ongoing surveillance to detect impaired glucose tolerance, hyperlipidaemia, endometrial hyperplasia and consequent complications.[3] Obese women, in particular, require regular (possibly annual) glucose tolerance testing because of the potential for rapid progression from normal to impaired glucose tolerance and diabetes.

3.5 Referral

The diagnosis of PCOS may prove difficult in a few women, and referral to a medical or reproductive endocrinologist may be valuable. Most gynaecologists have experience of using clomifene, but referral to an infertility expert is best when gonadotropins are needed.

3.6 Proposed Problem-Based Management Flow Chart

Figure 1 provides a proposed management flow chart based on whether the primary presenting problem is infertility, oligomenorrhoea, hirsutism or obstructive sleep apnoea. For all patients, the diagnosis is based on current criteria and after investigation for co-morbidity. It is essential to maintain surveillance for diabetes and lipid changes for all these women.

4. Conclusion

PCOS is a global endocrinological condition that requires a global approach. Once diagnosed, it lends itself to both pharmacological and non-pharmacological measures. It is diagnosed when two of the following three conditions are present: (i) oligo- and/or anovulation; (ii) clinical and/or biochemical signs of hyperandrogenism; and (iii) polycystic ovaries. Congenital adrenal hyperplasia, androgen-secreting tumours and Cushing's syndrome have to be excluded on a clinical basis or with the help of appropriate biochemical tests.

When approaching a patient with PCOS, treatment should be directed towards addressing her immediate needs and preventing long-term consequences, in particular development of insulin resistance, impaired glucose tolerance and type 2 diabetes, dyslipidaemia and infertility. Although the cardinal intervention (lifestyle modifications) is the only one that can minimise those risks, there are several pharmacological interventions available that can help the patient to manage her symptoms and achieve long-term goals. Infertility can be managed in general practice with clomifene with the addition of metformin. When pregnancy is not desired, the oral contraceptive pill will correct menstrual irregularities. Hirsutism will improve with the use of laser, cyproterone or spironolactone, and in the long term with lifestyle changes facilitated by metformin use.

When lifestyle changes are supported appropriately by pharmacological interventions, with ongoing surveillance for long-term complications, patients with PCOS can lead a productive life.

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