Abstract

Polycystic Ovarian Syndrome (PCOS) is a common disorder with clinical manifestations of anovulatory infertility and hyperandrogenism with oligomenorrhea/amenorrhoea, hirsuitism and acne. There is a higher prevalence of obesity, impaired glucose tolerance, type 2 diabetes, hyperinsulinaemia and adverse cardiovascular profile in these patients. The complicated interplay between genetic factors, abdominal obesity and insulin resistance play a key role in pathophysiology. Management should be tailored to individual needs. The understanding of the principles of management of long term implications aids to offer holistic approach to this disorder. Many different therapies may be offered to regulate menstrual cycle, induce ovulation and improve signs of hyperandrogenism. Lifestyle improvement and weight reduction are the most important predictors of long term health.

This article is aimed to guide general practice especially emphasising the long term management, evidence for use of various therapies and points of referral to specialist.

Keywords
Polycystic ovaries, hyperinsulinaemia, anovulatory infertility, metformin, obesity

Introduction

Polycystic ovarian syndrome (PCOS) is a common, heterogeneous endocrine disorder. It affects 6–7% of the female population of reproductive age. The prevalence of PCOS may increase with increasing obesity in the population. It also varies according to ethnic background; south asian women present at a younger age, with more severe symptoms. PCOS presents as a wide spectrum of symptoms, overlapping with normality. It presents with chronic anovulation, irregular periods, hyperandrogenism leading to hirsuitism and acne. These women are at risk of developing type II diabetes mellitus, hypertension, cardiovascular disease, endometrial hyperplasia and endometrial cancer. The challenge for a general practitioner is to diagnose the problem, be aware of the long term consequences, tailor the treatment to individual needs, and formulate a management protocol and follow up programme to prevent long term problems.

Diagnosis

PCOS is defined by the Rotterdam European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM). This consensus definition should be used to facilitate effective patient care and robust research. PCOS is defined as the presence of two of the following three criteria listed in Box 1.

Criteria for diagnosis of PCOS
- Polycystic ovaries (>12 peripheral follicles or increase in ovarian volume >10 cc)
- Oligomenorrhoea and/or anovulation
- Clinical and/or biochemical characteristics of hyperandrogenism

Box 1: Criteria for diagnosis

The raised luteinising hormone (LH) to follicle stimulating hormone (FSH) ratio is no longer considered a diagnostic criteria.

The diagnosis of PCOS can only be made only after excluding other conditions listed in Box 2.

Differential diagnosis of PCOS
- Thyroid dysfunction
-Raised prolactin levels
- Congenital Adrenal Hyperplasia
- Androgen-secreting tumours
- Cushing’s syndrome

Box 2: Differential diagnosis of PCOS

The recommended baseline investigations are thyroid function tests, serum prolactin and free androgen index [total testosterone/ sex hormone binding globulin (SHBG) x 100]. The signs of hyperandrogenism can be due to either increased total testosterone or reduced SHBG leading to increased free testosterone level despite normal...
total testosterone. In cases of clinical evidence of hyperandrogenism and total testosterone >5 nmol/l, androgen secreting tumours should be excluded by doing 17-hydroxyprogesterone levels.

Pathophysiology

PCOS results from a combination of hereditary factors leading to ovarian dysfunction, and external factors in the form of hypothalamo-pituitary-ovarian dysfunction and hyperinsulinemia. A number of genetic abnormalities appear to cause symptoms of PCOS, whereas environmental influences like nutrition and lifestyle also influence expression of the syndrome3.

Clinical presentation

PCOS presents with a wide spectrum of signs and symptoms. The range of symptoms differs from patient to patient.

Menstrual irregularity

Oligomenorrhoea and amenorrhoea are the most common presentations in PCOS. However 15-30% patients may have ‘normal’ periods. This is due to chronic anovulation and may lead to endometrial hyperplasia at a later stage.

Hirsuitism and acne

A high level of insulin lowers secretion of SHBG, which increases bioavailability of free androgen. This stimulates peripheral androgen receptors, increasing the 5 alpha reductase activity, which stimulates the conversion of testosterone to more potent metabolite, dihydrotestosterone.

Hirsuitism is a common symptom in PCOS, 25% of patients suffer with acne and male pattern alopecia. Virilisation is not a feature of PCOS, other causes should be ruled out in its presence. Late onset congenital adrenal hyperplasia should considered in such patients and should be ruled out by 17-hydroxyprogesterone levels4.

Obesity

Obesity is present in 10-65% of patients with PCOS. There is higher truncal distribution of fat manifested as increased waist to hip ratio. Obesity is not the cause of PCOS, but it is associated with increased severity of symptoms and metabolic disturbances. It may also reduce the effect of therapy.

Infertility

Anovulatory infertility affects 30-75% of the patients with PCOS, whereas anovulation is the cause of infertility in 20% of all the couples suffering from infertility. The exact pathophysiology is unexplained but may be related to insulin resistance.

PCOS and Pregnancy

The prevalence of polycystic ovaries is higher in women who have a history of recurrent miscarriage (41%) compared to general population (22%). However presence of polycystic ovaries itself does not predict increased pregnancy loss in ovulatory women who conceive spontaneously. A definite link between PCOS and miscarriage has not been clearly demonstrated in the studies to date. The current focus is to explore the role of insulin resistance in ovulatory women with PCOS, and a history of recurrent miscarriage.

The risk of gestational diabetes is higher in women with PCOS. The risk is believed to be increased further in obese women and in those who required ovulation induction for management of infertility. These women should be screened for gestational diabetes before 20 weeks of gestation and should be referred to specialist obstetric diabetic clinic if abnormalities are detected.

Metformin is currently not licensed for use in pregnancy. Some studies have suggested that metformin reduces the risk of miscarriage and gestational diabetes in women with PCOS, the evidence however is not reliable as the study design was poor5,6. Metformin has no reported animal or fetal toxicity or teratogenicity. Further research is needed before recommending routine use of metformin in pregnant women with PCOS.

Long-Term Health Consequences

Type II diabetes

Insulin resistance is the hallmark of pathophysiology of PCOS. It is associated with latter development of impaired glucose tolerance and type II diabetes. Evidence from literature suggests risk of developing type II diabetes in middle age in women with PCOS is 10-20%. This risk is further increased in women with body mass index(BMI) of >30, strong family history of type II diabetes and age >40 years2. RCOG recommends that all women with PCOS with added risk factors should be offered a glucose tolerance test. It also recommends screening all women with PCOS and offering fasting blood glucose levels annually, to ensure early detection of type II diabetes. Fasting glucose test is poorly discriminatory for type II
Polycystic Ovarian Syndrome: What you need to know and do as a GP

diabetes and there is no strong evidence to recommend its use.

**Cardiovascular risk**

Women with PCOS have a higher cardiovascular risk compared to weight matched controls with normal ovarian function. The risk factors for cardiovascular disease such as obesity, hyperandrogenism, hyperlipidaemia and hyperinsulinaemia are also higher in PCOS patients. Despite increased cardiovascular risk, morbidity and mortality among women with PCOS in long term studies have not proved as high as predicted. It seems logical to assess cardiovascular risk in women with PCOS including blood pressure measurement and lipid profile. There are no current recommendations to guide frequency of assessment.

In general practice, hypertension should be treated according to Joint British Society guidelines but use of lipid lowering drugs is not recommended routinely and should only be prescribed by a specialist. Conventional cardiovascular risk calculators have not been validated for use in women with PCOS.

**Sleep apnoea**

The risk of sleep apnoea is significantly higher in women with PCOS even when controlled for BMI. Sleep apnoea is also an independent cardiovascular risk factor. Clinicians should be aware of this association and should elicit a history of snoring and day time fatigue. Investigations and treatment should be offered when necessary.

**Cancer**

The risk of endometrial hyperplasia and endometrial cancer is higher in women with PCOS. Oligomenorrhoea and amenorrhoea with premenopausal levels of oestrogen can lead to endometrial hyperplasia and cancer. Hypertension and type 2 diabetes have a known association with endometrial cancer and these conditions are now known to be associated with PCOS. Withdrawal bleeding every 3-4 months to prevent this risk is recommended.

Obesity, infertility and hyperandrogenism are features of PCOS and are known to be linked to breast cancer. However studies have not shown any significantly increased risk of breast cancer in women with PCOS and no additional surveillance is needed.

The risk of ovarian cancer in women with PCOS has been addressed in few studies. The chronic anovulation in PCOS theoretically seems to be protective, but multiple ovulation inductions in the infertile patients may increase the risk. The results from the studies are conflicting but generally reassuring. Hence no additional screening should be offered to these patients.

**Management**

The treatment should be tailored to the needs of an individual patient. It is very important to define the goals of treatment in the beginning, which may include weight reduction, fertility treatment, management of hirsuitism and acne, regularising menstrual pattern and prevention of long term consequences of PCOS. It should be remembered that specific goals of therapy will differ from time to time at different stages of life.

**Weight management**

Weight reduction with diet and lifestyle changes is the cornerstone of management of PCOS. Weight loss has been reported to be associated with spontaneous resumption of ovulation, improved conception rates, increased SHBG, reduced insulin resistance and improvement in glucose metabolism. Lifestyle changes reduce the risk of developing type 2 diabetes later in life by 58%. The evidence of benefit of diet, exercise and lifestyle changes is not so robust in women with PCOS, who have normal weight. Nevertheless, they should be advised to maintain their body weight within normal limits.

Metformin and other insulin sensitising agents are not licensed for use in non diabetic women. Effect of metformin on reducing weight has been reported by some, but not all studies. The diabetes prevention trial reported that metformin is not superior to lifestyle intervention to prevent long term consequences of PCOS.

Weight reduction drugs may help in reducing weight and hence insulin resistance. Studies have shown significant decrease in body weight and hyperandrogenism with orlistat and sibutramine. Sibutramine is contraindicated in patients with raised systolic blood pressure.

**Regularising menstrual pattern**

Combined oral contraceptive pills (COCP) can be used in women who do not wish to conceive. This will result in regular shedding of endometrium, hence reduces the risk of endometrial hyperplasia. Dianette containing cyproterone acetate and Yasmin containing drospirenone can be used to control hirsuitism and acne, while regularising the menstrual cycle at the same time. It is believed that COCP may also be advantageous in reducing LH levels by negative feedback. Raised LH levels in PCOS are believed to play a central part in pathophysiology of metabolic dysfunction.

An alternative is to induce withdrawal bleeding with progestogens every one to three months. This regime is especially useful in cases where COCP is contraindicated. The association of obesity with PCOS contraindicates the use of COCP in many patients, obesity being an independent risk factor for thromboembolism.

Levonorgestrel intrauterine system (Mirena) can be used to counter the unopposed endometrial proliferation. The compliance is better with this product compared to oral tablets.
Hirsuitism

A baseline assessment should be carried out using a standardised scoring system, like the Ferriman and Gallwey score, which may help to monitor the effects of therapy. Multiple modes of management including systemic drugs, local therapy, physical therapy, weight reduction and counselling should be used to achieve optimum results. Hair growth occurs in cycles, so at any given time, only the active follicles are targeted. Patients should be informed that at least 16 weeks of therapy is required before noticing any difference.

Patients should be informed about cosmetic options including laser, electrolysis, bleaching, waxing and shaving. Re-growth is a problem with all these measures. Laser and electrolysis may achieve permanent effect after repeated treatments over a period of six to nine months.

Metformin has a moderate effect on hirsuitism, as has been shown to reduce testosterone levels by 11%². COCPs may be used in mild to moderate hirsuitism, believed to act by increasing SHBG, those preparations containing anti androgenic progesterone components such as Diane (containing cyproterone acetate) and Yasmin (containing drospirenone, a derivative of spironolactone) may be helpful.

Anti-androgens like cyproterone acetate, spironolactone, flutamide, finasteride and ketoconazole have been shown to be effective. Adequate contraception is required in patients using anti androgens, as transplacental passage may affect the development of a male fetus³.

Efollinithine (vaniqua) may be used for facial hirsuitism.

Fertility treatment

The importance of weight loss cannot be over-emphasised, it improves the prospect of both spontaneous and drug induced ovulation. Weight loss of about 5% can restore spontaneous ovulation. If lifestyle change and weight loss do not restore spontaneous ovulation, referral to a specialist clinic is needed. Baseline infertility investigations should be done to rule out other causes of infertility.

Anovulatory infertility is treated by clomiphene citrate (anti oestrogen) 50-100mg. It is usually the first line treatment in non obese women. It induces ovulation in 60-85% with conception rate of 30-50%. Clomiphene is associated with a multiple pregnancy rate of 8-10% and there is an increased risk of ovarian cancer after prolonged use (more than 12 months)². It is recommended that clomiphene should be started only if facilities for follow up with ultrasound follicular tracking are available at least in the first cycle to monitor the effect of medication.

Metformin was in initial studies shown to restore ovulation. The advantages are mono-ovulation, no need of ultrasound monitoring and no risk of ovarian cancer. However in a recent study, the ovulation rate, rate of ongoing pregnancy and abortion rate was not significantly different in clomiphene plus metformin group compared with clomiphene plus placebo. Additionally a significant proportion of women discontinued treatment due to side effects in the metformin group. In the light of this evidence, there is no advantage of adding metformin with clomiphene for treatment of ovulatory dysfunction. 1 Metformin may be used in obese women with an abnormal glucose tolerance test. It can also be used to initiate weight loss with calorie control and exercise.

The option for women resistant to anti oestrogens is injectable gonadotrophins. The reported live birth rate is 54% at 6 months and 62% at 12 months⁴. There is an increased risk of ovarian hyperstimulation (OHSS) and multiple pregnancy (up to 20%). The risk of OHSS is higher in PCOS patients compared to a normal population.

Laparoscopic ovarian diathermy also has a role in resistant cases. It seems to be as effective as gonadotrophins with no added risk of multiple pregnancy or OHSS. There is a risk of peri ovarian adhesions which can be reduced by limiting the number of burns per ovary⁴ and by ovarian cooling. Some studies have reported a lower miscarriage rate compared with medical management of anovulation⁸.

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Box 3: Key summary points for long term management
**Reference List**


**Self Assessment**

**Further Reading Suggestions**


2. www.stratog.net.uk