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Setting standards to improve women's health

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LONG-TERM CONSEQUENCES OF POLYCYSTIC OVARY SYNDROME

This is the second edition of this guideline, which was previously published in May 2003 under the same title.

1. Purpose and scope

This guideline has been produced to provide information, based on clinical evidence, to assist clinicians with a special interest and for updating the generalist who manages women with polycystic ovary syndrome, to allow them to advise women about the long-term health consequences of the syndrome. This guideline does not cover infertility associated with polycystic ovary syndrome (PCOS), which has been extensively reviewed elsewhere.[1,2]

2. Introduction

PCOS is a common disorder, often complicated by chronic anovulatory infertility and hyperandrogenism with the clinical manifestation of oligomenorrhoea, hirsutism and acne.[3] Many women with this condition are obese and have a higher prevalence of impaired glucose tolerance, type 2 diabetes and sleep apnoea than is observed in the general population. They exhibit an adverse cardiovascular risk profile, characteristic of the cardiometabolic syndrome as suggested by a higher reported incidence of hypertension, dyslipidaemia, visceral obesity, insulin resistance and hyperinsulinaemia.[4] PCOS is frequently diagnosed by gynaecologists and it is therefore important that there is a good understanding of the long-term implications of the diagnosis in order to offer a holistic approach to the disorder.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews, DARE and EMBASE), TRIP, Medline and PubMed (electronic databases) were searched for relevant randomised controlled trials, systematic reviews and meta-analyses. The search was restricted to articles published between 1966 and October 2006. The databases were searched using the relevant MeSH terms including all subheadings and this was combined with a keyword search. MeSH heading search included 'polycystic ovary', 'metabolic', 'diabetes', 'cardiovascular' and 'glitazone' and the search limited to humans and the English language. The computer search was complemented by hand searching from original references and reviews.

The definitions of the types of evidence used in this guideline originate from the US Agency for Health Care Policy and Research. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'Good Practice Points'.

4. Prevalence of PCOS

Estimation of the 'true' prevalence has to be made with caution as many of the data available were collected prior to the new Rotterdam diagnostic criteria. Most clinical data suggests a prevalence of 6–7% of the population.[5–8] The present Rotterdam criteria are current best practice but it is recognised that PCOS encompasses a wide spectrum of disorder, overlapping with normality.

The prevalence of PCOS may differ according to ethnic background; for example, in women of South Asian origin, PCOS presents at a younger age, has more severe symptoms and a higher prevalence.[9,10]

5. Diagnosis

How is PCOS diagnosed?

Diagnosis of PCOS can only be made when other aetiologies have been excluded (thyroid dysfunction, congenital adrenal hyperplasia, hyperprolactinaemia, androgen-secreting tumours and Cushing syndrome). **B**

A consensus definition using precise diagnostic criteria should be used when diagnosing PCOS to facilitate effective patient care and robust clinical research. ✓

The National Institutes of Health (NIH) 1990 preliminary consensus definition has now been replaced by a more recent definition by the Rotterdam European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) PCOS Consensus Workshop Group.[11] This has suggested a broader definition for PCOS, with two of the three following criteria being diagnostic of the condition:

- polycystic ovaries (either 12 or more peripheral follicles or increased ovarian volume (greater than 10 cm^3)
- oligo- or anovulation
- clinical and/or biochemical signs of hyperandrogenism.

A raised luteinising hormone/follicle-stimulating hormone ratio is no longer a diagnostic criteria for PCOS owing to its inconsistency.[12] It should be noted that the diagnosis of PCOS can only be made when other aetiologies have been excluded. The recommended baseline screening tests are thyroid function tests, a serum prolactin and a free androgen index (total testosterone divided by sex hormone binding globulin (SHBG) x 100 to give a calculated free testosterone level). In cases of clinical evidence of hyperandrogenism and total testosterone greater than 5 nmol/l, 17-hydroxyprogesterone should be sampled and androgen-secreting tumours excluded. If there is a clinical suspicion of Cushing syndrome, this should be investigated according to local practice.

Evidence level IIb

These new diagnostic criteria have affected the value of a number of systematic reviews, as the majority of the reviews are based on the NIH 1990 criteria, which may not be entirely representative of those patients diagnosed by the new Rotterdam criteria in use today, in particular where ultrasound was used as the main diagnostic criterion.

6. Counselling

How should women be counselled?

Women diagnosed with PCOS should be informed of the possible long-term risks to health that are associated with their condition. They should be advised regarding weight control and exercise. **B**

7. Long-term consequences

7.1 Metabolic consequences of PCOS

What is the risk of developing type II diabetes in women with PCOS?

Women presenting with PCOS, particularly if they are obese (body mass index greater than 30), have a strong family history of type 2 diabetes or are over the age of 40 years, are at increased risk of type 2 diabetes and should be offered a glucose tolerance test. **B**

Insulin resistance in PCOS has been linked to later development of impaired glucose tolerance and type 2 diabetes.[13] Evidence from small long-term cohort studies, case–control studies and case series points to a risk of type 2 diabetes in middle age of 10–20%,[14–16] with a high rate of impaired glucose tolerance, suggesting that further cases of diabetes will develop later. Increased body mass, particularly truncal obesity, and a strong family history of diabetes (up to 83% in one study) increase the risk of developing type 2 diabetes in the presence of polycystic ovary phenotype.[16] However, the frequency of type 2 diabetes is also increased in women with PCOS who are not obese (body mass index less than 27 kg/m^2),[15,16] suggesting that PCOS is an independent risk factor for type 2 diabetes in middle age. A sensible approach to ensuring early detection of diabetes might be to offer screening to women with PCOS with measurement of fasting blood glucose, on a regular basis, perhaps annually. However, if the fasting blood glucose is 5.6 mmol/l or greater, body mass index is greater than 30 or a strong family history of diabetes, then an oral glucose tolerance test should be arranged. Although fasting glucose was poorly discriminatory for type 2 diabetes in studies to date, it is a more appropriate test for routine screening. Fasting insulin and HOMA-IR are not measured routinely in clinical practice in the UK and exhibit considerable variability that limits their usefulness only to population-based studies. These tests are not sensitive enough to be useful in individual cases and are not included in the diagnosis of the condition.

Evidence level IV

Guidance on the management of diabetes in pregnancy is available in the National Institute for Health and Clinical Excellence guideline, *Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period* (expected publication date March 2008).

7.2 PCOS and obstructive sleep apnoea

What is the risk of developing sleep apnoea in women with PCOS?

Women diagnosed with PCOS (or their partners) should be asked about snoring and daytime fatigue/somnolence and informed of the possible risk of sleep apnoea, and offered investigation and treatment when necessary. **B**

Sleep apnoea is an independent cardiovascular risk factor and has been found to be more common in PCOS. The difference in prevalence of sleep apnoea between PCOS and controls remained significant even when controlled for BMI.[17,18] It has been reported that the strongest predictors for sleep apnoea were fasting plasma insulin levels and glucose-to-insulin ratios.[19]

Evidence level III

7.3 PCOS and cardiovascular risk

What is the risk of developing cardiovascular disease in women with PCOS?

Clinicians need to be aware that conventional cardiovascular risk calculators have not been validated in women with PCOS. ✓

In clinical practice, hypertension should be treated but lipid-lowering treatment is not recommended routinely and should only be prescribed by a specialist. **B**

While it seems prudent to assess the cardiovascular risk factors of a woman with PCOS (including measurement of blood pressure, cholesterol, triglycerides and high-density lipoprotein cholesterol), it should be borne in mind that the conventional cardiovascular risk calculators have not been validated in this group.

It has been suggested that women with PCOS may have a higher cardiovascular risk than weight-matched controls with normal ovarian function.[20–22] They have increased cardiovascular risk factors such as obesity, hyperandrogenism, hyperlipidaemia and hyperinsulinaemia. Their abnormal lipid profiles mainly consist of raised triglycerides, total and low-density lipoprotein cholesterol.[23–25] The effect of PCOS on high-density lipoprotein cholesterol (HDL-C), however, is controversial, [23,24,26] and evidence on hypertension is also less consistent.[26] The elevation of risk factors in young women with PCOS may therefore put them at increased risk of developing accelerated atherosclerosis resulting in myocardial infarction.[14,24,25] In the Nurses' Health Study, menstrual cycle irregularity was associated with an increased risk of nonfatal and fatal coronary heart disease, although no data were available for confirmation of a diagnosis of PCOS.[27]

Despite the increase in cardiovascular risk factors, morbidity and mortality from coronary heart disease among women with PCOS has not been shown to be as high as predicted.[28] Studies to date are small in size and randomised controlled trials and prospective endpoint studies are lacking. Nevertheless, from a clinical perspective, clinicians should continue to identify cardiovascular risk factors in women with PCOS and treat these accordingly. In clinical practice, hypertension should be treated according to the Joint British Society Guidelines, which should be referred to.[29] These guidelines suggest that persistent blood pressures greater or equal to 140 mmHg systolic and or 90 mmHg diastolic, not responding to lifestyle measures, need to be considered for drug therapy (women with diabetes or other high risk factors with blood pressure greater than 130 mmHg systolic and or 80 mmHg diastolic may require drug therapy). Lipid-lowering treatment is not recommended routinely and should be prescribed by a specialist.

Evidence level III

8. PCOS and pregnancy

What are the implications of PCOS for pregnancy?

Women who have been diagnosed as having PCOS before pregnancy (such as those requiring ovulation induction for conception) should be screened for gestational diabetes before 20 weeks of gestation, with referral to a specialist obstetric diabetic service if abnormalities are detected **B**

Metformin is currently not licensed for use in pregnancy in the UK and is not recommended for use in pregnancy. **D**

There is a higher risk of gestational diabetes in women with PCOS.[30,31] The risk is believed to be greatest in obese women with PCOS who required ovulation induction in order to conceive. Such women should be screened for abnormal glucose tolerance in pregnancy and, if appropriate, referred for antenatal management by an obstetrician with special interest in diabetes in pregnancy. A recent meta-analysis concluded that women with PCOS have a significantly higher risk of pregnancy complications compared to controls.[32]

Metformin taken throughout pregnancy had been suggested to reduce the risk of miscarriage and gestational diabetes in women with PCOS.[33,34] Another meta-analysis provided reassurance that metformin is safe, with suggestive data that it may reduce incidence of miscarriage if taken in the first trimester of pregnancy.[35] However, the methodology of these studies was poor and metformin is currently not licensed for use in pregnancy in the UK. We do not recommend its use in pregnancy at present until further randomised prospective study results are available to provide adequate evidence of safety and efficacy of its use in this

context. A larger multicentre trial, the MiG trial, is due to report on the use of metformin in pregnancy soon. Nevertheless, being a class B drug, metformin has no reported evidence of animal or fetal toxicity or teratogenicity.

Comparing metformin-treated PCOS and control groups, no differences in height, weight and motor-social development in infants has been noted during the first 18 months of life.[36] Even though metformin is excreted in breast milk, it is at a very low level,[37–39] and there have been no concerns to date with its use.[36–38] There may still be unanticipated risks to the baby from the postnatal use of metformin by breastfeeding women.[40] Further studies are therefore needed before recommending the use of metformin in the puerperium.

Women who have been diagnosed in pregnancy with gestational diabetes have been found to have a high prevalence of PCOS on subsequent screening. This association is more common in women with raised body mass index.[41,42]

Evidence level IIb

9. Cancer and PCOS

What are the risks of cancer in women with PCOS?

Oligo- or amenorrhoea in women with PCOS may predispose to endometrial hyperplasia and later carcinoma. It is good practice to recommend treatment with progestogens to induce a withdrawal bleed at least every 3–4 months.

B

There does not appear to be an association with breast or ovarian cancer and no additional surveillance is required.

C

It has been known for many years that severe oligo- and amenorrhoea in the presence of premenopausal levels of estrogen can lead to endometrial hyperplasia and carcinoma.[43] In women with PCOS intervals between menstruation of more than 3 months may be associated with endometrial hyperplasia.[44] Regular induction of a withdrawal bleed with cyclical gestogens, such as progestogens for at least 12 days,[45,46] oral contraceptive pills or the Mirena® intrauterine system would be advisable in oligomenorrhoeic women with PCOS. Women who are oligomenorrhoeic and do not have normal withdrawal bleeds should be investigated and managed according to local protocols. This may include ultrasound scan, endometrial sampling and/or hysteroscopy.[47]

Evidence level IIa

Women with PCOS do not have any significant increase in risk of developing breast cancer compared with those without (RR 1.2; 95% CI 0.7–2.0).[48] A small number of studies have addressed the possibility of an association between PCOS and epithelial ovarian cancer risk, the results are conflicting but generally reassuring.[49] As there does not appear to be an association with breast or ovarian cancer, no additional surveillance is required beyond routine screening.

10. Strategies for reduction of risk

10.1 Exercise and weight control

How should women with PCOS be advised on lifestyle issues?

Women diagnosed with PCOS should be advised regarding weight loss through diet and exercise.

B

Lifestyle changes through diet and exercise remain the first line for treatment of obesity in PCOS. PCOS is often associated with obesity and abnormal fat distribution, especially of abdominal fat, even where the BMI is normal.[50] Obesity worsens insulin resistance that may exacerbate this dysfunction. Loss of significant weight has been reported to result in spontaneous resumption of ovulation,[51] improvement in fertility,[52] increased

SHBG and reduced basal level of insulin[53,54] accompanied by a normalisation in glucose metabolism.[55] Lifestyle alteration will reduce the likelihood of developing type 2 diabetes later in life. There is no clear evidence of an effect of diet and exercise on the long-term health of women with PCOS who have normal body habitus, although it seems prudent to advise such patients to maintain their body weight within the normal range.

While there is little long-term data on the effect of lifestyle intervention in women with PCOS, the diabetes prevention trial examined subjects with similar metabolic profiles and risk factors. This study found that lifestyle intervention reduced the risk of diabetes by 58%.[56] In the absence of any robust long-term follow-up data for lifestyle interventions, it would seem prudent to advise regular exercise (aiming for a mean 30 minutes sweat-inducing exercise daily) as the most important lifestyle measure, and to have a healthy, balanced diet of regular, hypocalorific meals through the day.

Evidence level Ib

10.2 Drug therapy

Is drug therapy appropriate for women with PCOS?

Insulin-sensitising agents have not been licensed in the UK for use in women who are not diabetic. Although a body of evidence has accumulated demonstrating the safety of these drugs, there is currently no evidence of a long-term benefit for the use of insulin-sensitising agents.

B

Use of weight-reduction drugs may be helpful in reducing insulin resistance through weight loss.

B

The demonstration of the potential long-term health consequences of PCOS have been accompanied by renewed interest in the use of insulin-sensitising agents such as metformin and the thiazolidinediones (troglitazone, rosiglitazone and pioglitazone) to reduce insulin resistance and thereby reduce risk of developing diabetes and other metabolic sequelae. Although a body of evidence as accumulated demonstrating the safety of these drugs, there is no evidence for a long-term benefit for use of sensitising agents. Both metformin[57–64] and troglitazone[65,66] have been shown to have beneficial short-term effects on insulin resistance in women with PCOS who are not diabetic. There is evidence that metformin may modestly reduce androgen levels by around 11% in women with PCOS compared with placebo and modest reductions in body weight have been reported by some, but not all studies. Women with a body mass index of more than 37 may not respond well to metformin therapy. It must be emphasised that both metformin and the thiazolidinediones are unlicensed for use in PCOS and patients should be counselled before initiating therapy. There is no current robust evidence to support the use of these drugs for the prevention of cardiovascular disease in PCOS and further research in this area is required. This is of particular importance with respect to a recent meta-analysis suggesting an increase in myocardial infarction and death in women with diabetes treated with rosiglitazone.[67] Inference from the diabetes prevention trial that examined a cohort of patients who had similar metabolic profiles to women with PCOS suggested that metformin is not superior to lifestyle intervention in improving cardiometabolic risk and progression to type 2 diabetes.[68]

Evidence level Ib

The use of metformin in induction of ovulation and fertility in women with PCOS will not be discussed here as it is beyond the remit of this guideline.

Orlistat[69] and sibutramine[70] have been shown to significantly reduce body weight and hyperandrogenism in women with PCOS. However, the use of sibutramine is not recommended in patients with systolic hypertension. There is currently no data on the use of rimonabant in women with PCOS but evidence suggests it may have benefit transferable to women with PCOS in weight reduction and improvement in the cardiometabolic profile.[71] Bariatric surgery may be indicated in selected women with morbid obesity.[72]

10.3 Surgery prognosis

What is the prognosis following surgery?

Ovarian electrocautery should be reserved for selected anovulatory women with a normal BMI. ✓

Anovulation associated with PCOS has long been known to be amenable to surgical treatment. A recent long-term cohort study up to 20 years after laparoscopic ovarian electrocautery has shown persistence of ovulation and normalisation of serum androgens and SHBG in over 60% of subjects, particularly if they have a normal BMI.[73]

Insulin resistance and serum lipids were not assessed. The long-term benefits of ovarian drilling, including alterations in the endocrine profile are supported by a second study.[74] However, no prospective studies have been powered to look at cardiovascular risk profiles and ovarian electrocautery should be reserved for selected anovulatory women with a normal body mass index or where a laparoscopy is required for other indications. It is also very important to highlight that ovarian surgery/drilling may affect the reproductive capacity of the ovaries in the future.

11. Image-related issues

How should women with hirsutism and acne be advised?

Women should be advised that there is insufficient evidence in favour of either metformin or the oral contraceptive pill in treating hirsutism or acne. ✓

Effects of hyperandrogenisation are among the most deleterious long-term consequences of PCOS when taken into consideration of its impact on a woman's self-image perception and the subsequent psychological effects. Hirsutism in the setting of PCOS is difficult to treat and there are currently no large randomised control trials on its treatment in this patient group. A recent Cochrane review to compare the use of insulin sensitising drugs versus combined oral contraceptive pills concluded that the limited data available demonstrated no evidence of difference in effect between metformin and the pill on hirsutism and acne.[75]

Licensed treatments for hirsutism include oral contraceptive pills, dianette (oestrogen and cyproterone acetate), cosmetic measures (such as laser, electrolysis, bleaching, waxing and shaving) and topical facial eflornithine (Vaniqa®, SkinMedica Inc.). However, there is a paucity of good-quality robust placebo controlled trials for hirsutism treatment, particularly for combination therapy. In practice, a combination of methods is often required to achieve an acceptable cosmetic result for the woman. Non-licensed treatments are available and their use will depend on individual practice and expertise. These agents include spironolactone, antiandrogens, such as flutamide, finasteride and high-dose cyproterone acetate. Adequate contraceptive measures are essential with these medications. Metformin as an insulin sensitiser has been shown to have a modest effect on hirsutism associated with a 11% reduction in testosterone levels.[76]

12. Auditable standards

1. Accurate diagnosis of PCOS defined and based on two of the three criteria from the Rotterdam consensus.
2. Blood pressure measurement and a fasting blood glucose should be taken.
3. Women with a body mass index greater than 30 or a strong family history of type 2 diabetes should have a glucose tolerance test, particularly if fertility is an issue.
4. All overweight PCOS women should be provided with dietary and lifestyle advice.
5. Amenorrhoeic or severely oligomenorrhoeic women with PCOS should have induced withdrawal bleeds at regular intervals to reduce the risk of developing endometrial hyperplasia.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website at www.rcog.org.uk/clingov1). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A	Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)
B	Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)
C	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group.

The Guidelines review process will commence in December 2010
unless otherwise indicated