Royal College of Obstetricians & Gynaecologists

Long-term Consequences of Polycystic Ovary Syndrome

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Long-term Consequences of Polycystic Ovary Syndrome

This is the third edition of this guideline, which was previously published under the same title in 2003 and 2007.

Executive summary of recommendations

Diagnosis

How is polycystic ovary syndrome (PCOS) diagnosed?

PCOS should be diagnosed according to the Rotterdam consensus criteria. D

Counselling

How should women with PCOS be counselled concerning the long-term implications of their condition and by whom?

Women diagnosed with PCOS should be informed of the possible long-term risks to health that are associated with their condition by their healthcare professional. ✓

Long-term consequences

Metabolic consequences of PCOS

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

Clinicians may consider offering screening for gestational diabetes to women who have been diagnosed as having PCOS before pregnancy. This should be performed at 24–28 weeks of gestation, with referral to a specialist obstetric diabetic service if abnormalities are detected. ✓

How should women with PCOS be screened for type II diabetes?

Women presenting with PCOS who are overweight (body mass index [BMI] ≥ 25 kg/m²) and women with PCOS who are not overweight (BMI < 25 kg/m²), but who have additional risk factors such as advanced age (> 40 years), personal history of gestational diabetes or family history of type II diabetes, should have a 2-hour post 75 g oral glucose tolerance test performed. B

In women with impaired fasting glucose (fasting plasma glucose level from 6.1 mmol/l to 6.9 mmol/l) or impaired glucose tolerance (plasma glucose of 7.8 mmol/l or more but less than 11.1 mmol/l after a 2-hour oral glucose tolerance test), an oral glucose tolerance test should be performed annually. B

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

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

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

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

All women with PCOS should be assessed for CVD risk by assessing individual CVD risk factors (obesity, lack of physical activity, cigarette smoking, family history of type II diabetes, dyslipidaemia, hypertension, impaired glucose tolerance, type II diabetes) at the time of initial diagnosis. C

In clinical practice, hypertension should be treated; however, lipid-lowering treatment is not recommended routinely and should only be prescribed by a specialist. D

What is the risk of having reduced health-related quality of life in women with PCOS?

Psychological issues should be considered in all women with PCOS. Depression and/or anxiety should be routinely screened for and, if present, assessed. If a woman with PCOS is positive on screening, further assessment and appropriate counselling and intervention should be offered by a qualified professional. A

Cancer and PCOS

What are the risks of cancer in women with PCOS and how should these women be screened?

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

Transvaginal ultrasound should be considered in the absence of withdrawal bleeds or abnormal uterine bleeding. In PCOS, an endometrial thickness of less than 7 mm is unlikely to be hyperplasia. C

A thickened endometrium or an endometrial polyp should prompt consideration of endometrial biopsy and/or hysteroscopy. ✓

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

Strategies for reduction of risk

Exercise and weight control

How should women with PCOS be advised on lifestyle issues?

It is recommended that lifestyle changes, including diet, exercise and weight loss, are initiated as the first line of treatment for women with PCOS for improvement of long-term outcomes and should precede and/or accompany pharmacological treatment. B

Is drug therapy appropriate for long-term management of women with PCOS?

Insulin-sensitising agents have not been licensed in the UK for use in patients without diabetes. Although a body of evidence has accumulated demonstrating the safety of these drugs, there is currently no evidence that the use of insulin-sensitising agents confers any long-term benefit. B

Use of weight reduction drugs may be helpful in reducing hyperandrogenaemia. C

Ovarian electrocautery

What is the prognosis following electrocautery?

Ovarian electrocautery should be considered for selected anovulatory patients, especially those with a normal BMI, as an alternative to ovulation induction. C

Bariatric surgery

What is the prognosis following bariatric surgery?

Bariatric surgery may be an option for morbidly obese women with PCOS (BMI of 40 kg/m² or more or 35 kg/m² or more with a high-risk obesity-related condition) if standard weight loss strategies have failed. C

1. Purpose and scope

This guideline aims to provide information, based on clinical evidence, to assist clinicians who manage women with polycystic ovary syndrome (PCOS) in advising these women about the long-term health consequences of the syndrome. The advice should be targeted to the individual and the presenting complaints. The delivery of the advice in this document to the patient will need to be done sensitively within the framework of the patient presentation that will differ for each individual. This guideline does not cover infertility associated with PCOS, which has been extensively reviewed elsewhere.[1,2]

2. Introduction and background epidemiology

PCOS is a common disorder, often complicated by chronic anovulatory infertility and hyperandrogenism with the clinical manifestations of oligomenorrhoea, hirsutism and acne.[3,4] Many women with this condition are obese and have a higher prevalence of impaired glucose tolerance, type II diabetes and sleep apnoea than is observed in the general population.[3] 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.[5,6] 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.

PCOS is one of the most common endocrine disorders in women of reproductive age.[7–9] Because of differences in the diagnostic criteria employed, prevalence estimates vary widely, ranging from 2.2% to as high as 26%.[9–14] The prevalence of PCOS when diagnosed by the Rotterdam criteria was over twice that found when the National Institutes of Health (NIH) criteria were used to diagnose PCOS.[14]

The prevalence of PCOS may be different according to ethnic background. For example, compared to Caucasians, a higher prevalence is noted among women of south Asian origin, where it presents at a younger age and has more severe symptoms.[15,16]

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. The Cochrane Library (including the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects [DARE]), EMBASE, TRIP, MEDLINE and PubMed were searched for relevant randomised controlled trials (RCTs), systematic reviews and meta-analyses. The search was restricted to articles published between 2006 and August 2012. The databases were searched using the relevant Medical Subject Headings (MeSH) terms including all subheadings and this was combined with a keyword search. The MeSH heading search included 'polycystic ovary syndrome', 'metabolic', 'diabetes', 'cardiovascular' and 'cancer'. The search was limited to humans and the English language. The computer search was complemented by hand searching from original references and reviews. 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. Diagnosis

4.1 How is PCOS diagnosed?

PCOS should be diagnosed according to the Rotterdam consensus criteria. D

The 1990 NIH preliminary consensus definition has now been replaced by a more recent definition by the Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM)-Sponsored PCOS Consensus Workshop Group.[17] Evidence level 4

The Rotterdam criteria[17] have suggested a broader definition for PCOS, with two out of three of the following criteria being diagnostic of the condition:

1. polycystic ovaries (either 12 or more follicles or increased ovarian volume [> 10 cm^3])

2. oligo-ovulation or anovulation
3. clinical and/or biochemical signs of hyperandrogenism.

It should be noted that the diagnosis of PCOS can only be made when other aetiologies for irregular cycles, such as thyroid dysfunction, acromegaly or hyperprolactinaemia, have been excluded if there is clinical suspicion. Women with non-Caucasian ethnicity might need different criteria to diagnose PCOS.[18]

Clinical features of hyperandrogenism include hirsutism characterised by excess facial and body hair and midline hair growth. Although free and total testosterone is used in the diagnosis of PCOS, the recommended baseline biochemical test for hyperandrogenism is free androgen index (total testosterone divided by sex hormone binding globulin [SHBG] x 100).[19] If there are signs of virilisation (e.g. deep voice, reduced breast size, increased muscle bulk, clitoral hypertrophy), rapidly progressing hirsutism (less than 1 year between hirsutism being noticed and seeking medical advice) or high total testosterone levels (greater than 5 nmol/l or more than twice the upper limit of normal reference range), androgen-secreting tumours and late-onset/nonclassical congenital adrenal hyperplasia (CAH) should be excluded. 17-hydroxyprogesterone should be measured in the follicular phase and will be raised in CAH. However, it is possible to have CAH without the testosterone being greater than 5 nmol/l, particularly if the woman is heterozygous for this condition. Hence measurement of 17-hydroxyprogesterone should be considered if there is a high index of suspicion, for example, specific groups such as Ashkenazi Jews or those with a family history of CAH, since the management of CAH is different than that of PCOS. If 17-hydroxyprogesterone is borderline, it will have to be confirmed by an ACTH stimulation test to diagnose CAH. If there is a clinical suspicion of Cushing's syndrome or acromegaly, this should be investigated as per local practice.[20] Reference ranges for different methods and different laboratories vary widely; clinical decisions should be guided by the reference ranges of the local laboratory and the androgens should preferably be measured using tandem mass spectrometry.[17,21,22]

Evidence level 2+

5. Counselling

5.1 How should women with PCOS be counselled concerning the long-term implications of their condition and by whom?

Women diagnosed with PCOS should be informed of the possible long-term risks to health that are associated with their condition by their healthcare professional. ✓

Women should be made aware of the long-term implications (as discussed in other sections) of their condition, including their cardiovascular risk, by their healthcare professional, in a way that is tailored to their individual circumstances. Women should be made aware of the positive effect of lifestyle modification, including weight loss, for improving their symptoms, especially those who are overweight or obese.[23]

Evidence level 1+

Women should be counselled that there is no strong evidence that PCOS by itself can cause weight gain or that having PCOS makes weight loss difficult or impossible. Many patients find great benefit from support groups (e.g. http://www.verity-pcos.org.uk) and details of these, and sources of information, should be provided.[24]

Evidence level 4

6. Long-term consequences

6.1 Metabolic consequences of PCOS

6.1.1 What is the risk of developing gestational diabetes in women with PCOS?

Clinicians may consider offering screening for gestational diabetes to women who have been diagnosed as having PCOS before pregnancy. This should be performed at 24–28 weeks of gestation, with referral to a specialist obstetric diabetic service if abnormalities are detected. ✓

The prevalence of gestational diabetes mellitus is twice as high among women with PCOS compared to control women.[25] Clinicians may consider offering a 2-hour post 75 g oral glucose tolerance test to all pregnant women with PCOS, similar as for screening in women with any other risk factors for gestational diabetes.The diagnosis and treatment of gestational diabetes is discussed in RCOG Scientific Impact Paper No. 23 in detail.[26]

Evidence level 4

6.1.2 How should women with PCOS be screened for type II diabetes?

Women presenting with PCOS who are overweight (body mass index [BMI] ≥ 25 kg/m²) and women with PCOS who are not overweight (BMI < 25 kg/m²), but who have additional risk factors such as advanced age (> 40 years), personal history of gestational diabetes or family history of type II diabetes, should have a 2-hour post 75 g oral glucose tolerance test performed.

B

In women with impaired fasting glucose (fasting plasma glucose level from 6.1 mmol/l to 6.9 mmol/l) or impaired glucose tolerance (plasma glucose of 7.8 mmol/l or more but less than 11.1 mmol/l after a 2-hour oral glucose tolerance test), an oral glucose tolerance test should be performed annually.

B

Insulin resistance is present in around 65–80% of women with PCOS, independent of obesity,[27] and is further exacerbated by excess weight.[28] Insulin resistance has been shown to worsen reproductive and metabolic features, type II diabetes and cardiovascular disease (CVD) risk in PCOS.[29] The highest incidence of metabolic abnormalities is seen in women with marked hyperandrogenism and anovulation.[6]

Evidence level 2+

There is an increased risk of impaired glucose tolerance and type II diabetes in PCOS independent of obesity.[30] Earlier onset hyperglycaemia and rapid progression to type II diabetes is also reported in PCOS.[31] PCOS is classified as a nonmodifiable risk factor for type II diabetes.[32] Furthermore, type II diabetes is a major CVD risk factor and lifestyle therapy has been shown to prevent or delay progression to type II diabetes. Hence early screening and identification in this high-risk group of women with PCOS is important. Women of non-Caucasian ethnicity (particularly south Asian women) should have an oral glucose tolerance test regardless of their BMI, in view of their propensity towards higher insulin resistance.[33]

Evidence level 2++

Fasting blood glucose level alone has been shown to be inaccurate and results in underdiagnosis of type II diabetes in PCOS.[34] Use of an HbA1c of 6.5% or greater has been proposed for diagnosis of diabetes. However, caution should be exercised as patients with type II diabetes may be missed[34] and the utilisation of HbA1c for the diagnosis of diabetes in PCOS warrants better definition. Hence an oral glucose tolerance test is considered to be appropriate for screening women with PCOS for diabetes. However, it would be reasonable to carry out HbA1c measurements where women are unwilling to have oral glucose tolerance tests or where the resources are not readily available.

Evidence level 2+

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

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

B

The prevalence of obstructive sleep apnoea is increased in obese women with PCOS. Androgen levels and insulin resistance are positively associated with obstructive sleep apnoea in PCOS.[35-38] Obstructive sleep apnoea contributes to insulin resistance in PCOS and continuous positive airway pressure (CPAP) therapy improves insulin sensitivity in affected women.[39]

Evidence level 2++

6.3 What is the risk of developing cardiovascular disease (CVD) in women with PCOS?

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

✓

All women with PCOS should be assessed for CVD risk by assessing individual CVD risk factors (obesity, lack of physical activity, cigarette smoking, family history of type II diabetes, dyslipidaemia, hypertension, impaired glucose tolerance, type II diabetes) at the time of initial diagnosis. C

In clinical practice, hypertension should be treated; however, lipid-lowering treatment is not recommended routinely and should only be prescribed by a specialist. D

CVD remains one of the leading causes of death in women. In women with PCOS, novel CVD risk factors[40–42] and early onset cardiovascular dysfunction (endothelial dysfunction, arterial stiffness, plaques and coronary artery calcification)[5,43] have been noted and are related to insulin resistance and obesity. High androgens and low SHBG have also been linked to increased CVD risk in both pre- and postmenopausal women.[44] A subset of the Women's Ischemia Syndrome Evaluation (WISE) study confirmed increased cardiovascular events and deaths in postmenopausal women with PCOS.[42]

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 acknowledged that the conventional cardiovascular risk calculators have not been validated in this group of women. Differences between PCOS and control women exist in several CVD risk factors that are more profound in obese women with PCOS.[45] Evidence level 2++

Since lifetime risk for CVD is higher in women with PCOS[40–42] and mostly preventable, all women with PCOS should be assessed for CVD risk by assessing individual CVD risk factors (obesity, lack of physical activity, cigarette smoking, family history of type II diabetes, dyslipidaemia, hypertension, impaired glucose tolerance, type II diabetes) at baseline and treated accordingly. At the time of initial diagnosis, women with PCOS should be assessed for obesity with BMI and waist circumference.

Blood pressure should be checked at the time of initial diagnosis and during oral contraceptive therapy. In clinical practice, hypertension should be treated according to the Joint British Societies' guidelines[46] which suggest that persistent blood pressures greater than or equal to 140 mmHg systolic and/or 90 mmHg diastolic, not responding to lifestyle measures, need to be considered for drug therapy (patients with diabetes or other high-risk factors with blood pressure greater than 130 mmHg systolic and/or 80 mmHg diastolic may require drug therapy). Women with hypertension who need to start oral contraceptive therapy should be counselled regarding its risks and benefits and should be monitored and treated as per the Joint British Societies' guidelines.[46] Evidence level 4

There is emerging evidence that statins improve hyperandrogenaemia and the metabolic profile in women with PCOS.[47,48] However, lipid-lowering treatment is not recommended for treating hyperandrogenaemia and should only be prescribed by a specialist. Evidence levels 1+ and 4

6.4 What is the risk of having reduced health-related quality of life in women with PCOS?

Psychological issues should be considered in all women with PCOS. Depression and/or anxiety should be routinely screened for and, if present, assessed. If a woman with PCOS is positive on screening, further assessment and appropriate counselling and intervention should be offered by a qualified professional. A

Women with PCOS are at an increased risk of psychological and behavioural disorders as well as reduced quality of life (QoL).[49–51] It has been shown that PCOS has a significant detrimental effect on QoL compared with controls and weight issues were most likely to affect QoL in women with PCOS.[41] Women with PCOS are at a higher risk of developing psychological difficulties (such as depression and/or anxiety), eating disorders and sexual and relationship dysfunction.[51] Evidence level 1+

Psychological issues, especially depression, should be screened for according to National Institute for Health and Care Excellence guidelines:[52,53] Evidence level 1–

Consider asking people who may have depression two questions specifically:

- During the last month, have you often been bothered by feeling down, depressed or hopeless?
- During the last month, have you often been bothered by having little interest or pleasure in doing things?

If a person answers 'yes' to either of the depression identification questions, but the practitioner is not competent to perform a mental health assessment, they should refer the person to an appropriate professional. If this professional is not the person's general practitioner (GP), inform the GP of the referral.

7. Cancer and PCOS

7.1 What are the risks of cancer in women with PCOS and how should these women be screened?

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

Transvaginal ultrasound should be considered in the absence of withdrawal bleeds or abnormal uterine bleeding. In PCOS, an endometrial thickness of less than 7 mm is unlikely to be hyperplasia. C

A thickened endometrium or an endometrial polyp should prompt consideration of endometrial biopsy and/or hysteroscopy. ✓

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 oligo- and amenorrhoea in the presence of premenopausal levels of estrogen can lead to endometrial hyperplasia and carcinoma.[54] There are moderate quality data to support the finding that women with PCOS have a 2.89-fold (95% CI 1.52–5.48) increased risk for endometrial cancer.[55] In women with PCOS, intervals between menstruation of more than 3 months (corresponding to fewer than four periods each year) may be associated with endometrial hyperplasia.[56] Regular induction of a withdrawal bleed with cyclical gestogens – gestogens for at least 12 days,[57,58] oral contraceptive pills or endometrial protection gained by exposure to gestogens by devices such as the Mirena® (Bayer plc, Newbury, Berks, UK) intrauterine system – would be advisable in oligomenorrhoeic women with PCOS[59] as part of good clinical practice, but the most effective regimen is unclear due to a lack of randomised clinical trials.[60] Evidence level 4

A prospective study of 56 consecutive amenorrhoeic women with PCOS who underwent transvaginal ultrasound to assess the endometrial thickness concluded that the endometrial thickness was positively correlated with endometrial hyperplasia; there were no cases of endometrial hyperplasia when the endometrial thickness was less than 7 mm.[56] McCormick et al. found that, compared with 7 mm, a higher cut-off of 9 mm in patients with PCOS had comparable sensitivity (100%), negative predictive value (100%) and positive predictive value (50%), but superior specificity (56%); for every 1 mm increase in endometrial thickness, the odds ratio of hyperplasia increased by 1.48 (95% CI 1.04–2.10).[61] Evidence level 2+

Women with PCOS do not have a significant increase in their risk of developing breast cancer compared to those without PCOS (RR 0.88, 95% CI 0.44–1.77).[62] 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.[63–65] As there does not appear to be an association with breast or ovarian cancer, no additional surveillance is required beyond routine screening.

8. Strategies for reduction of risk

8.1 Exercise and weight control

8.1.1 How should women with PCOS be advised on lifestyle issues?

It is recommended that lifestyle changes, including diet, exercise and weight loss, are initiated as the first line of treatment for women with PCOS for improvement of long-term outcomes and should precede and/or accompany pharmacological treatment.

B

Lifestyle management including diet, exercise and weight loss is recommended as the first line of treatment for women with PCOS;[23] these changes should precede and/or accompany pharmacological treatment. In women with PCOS and excess weight, a reduction of as little as 5% of total body weight has been shown to reduce insulin resistance and testosterone levels as well as improving body composition and cardiovascular risk markers.[45]

Evidence level 2++

In the general population, motivational interviewing and established behaviour techniques appear more effective than traditional advice giving for changes in weight, diet and/or exercise. Suggesting ways to access support to help with weight loss and exercise, establishing self-monitoring (including pedometer use), time management techniques, relapse prevention techniques, individual tailoring, engaging social support and setting goals have all been shown to be useful. Individual, group and mixed interventions have been shown to be effective.[23,66,67] Also, a wide range of providers (with appropriate training), including doctors, nurses, dietitians, nutritionists and exercise specialists, can deliver effective interventions for changing diet and/or exercise.[66–69] Use of behaviour change techniques and greater intensity, contact time and duration generate significantly more weight loss.[69]

Lifestyle management targeting weight loss (in women with a BMI of 25 kg/m^2 or more [overweight/obese]) and prevention of weight gain (in women with a BMI of 18.5–24.9 kg/m^2 [lean]) should include both reduced dietary energy (caloric) intake and exercise.This should be the first-line therapy for all women with PCOS for managing long-term consequences.[70] Prevention of weight gain should be targeted in all women with PCOS through monitored caloric intake and in the setting of healthy food choices, irrespective of diet composition. Behaviour change techniques should target prevention of weight gain in all women with PCOS.[71] Women who have failed to lose weight with lifestyle strategies and who have a BMI of 40 kg/m^2 or more or who have a BMI of 35 kg/m^2 or more together with a high-risk obesity-related condition (such as hypertension or type II diabetes) should be considered for bariatric surgery.[72]

Evidence level 2+

8.2 Is drug therapy appropriate for long-term management of women with PCOS?

Insulin-sensitising agents have not been licensed in the UK for use in patients without diabetes. Although a body of evidence has accumulated demonstrating the safety of these drugs, there is currently no evidence that the use of insulin-sensitising agents confers any long-term benefit.

B

Use of weight reduction drugs may be helpful in reducing hyperandrogenaemia.

C

The demonstration of the potential long-term health consequences of PCOS has been accompanied by the use of insulin-sensitising agents such as metformin and the thiazolidinediones to reduce insulin resistance and thereby reduce the risk of developing diabetes and other metabolic sequelae. However, there is no strong evidence regarding the long-term benefits for the use of sensitising agents in women with PCOS.[73–75] Metformin[76–79] has been shown to have beneficial short-term effects on insulin resistance and other cardiovascular risk markers in women with PCOS without type II diabetes.[80,81] There is evidence that metformin may modestly reduce androgen levels by around 11% in women with PCOS compared to placebo[82] and modest reductions in body weight have been reported by some, but not all, studies.[83] Women with a BMI of more than 37 kg/m^2 may not respond well to the standard dose of metformin therapy.[84] It must be emphasised that both metformin and the thiazolidinediones are unlicensed for use in PCOS and women should be counselled before initiating therapy so that they can make an informed choice.

Evidence level 2++

There is no current robust evidence to support the use of these drugs for the prevention of CVD in PCOS and further research in this area is required. Inference from the diabetes prevention trial that examined a cohort of patients who had similar metabolic profiles to women with PCOS suggested that lifestyle intervention was superior to metformin in improving cardiometabolic risk factors and progression to type II diabetes.[85]

Evidence level 2++

Metformin can be considered in women with PCOS who are already undergoing lifestyle treatment and do not have improvement in impaired glucose tolerance and in those women with impaired glucose tolerance.[68,77-79] The use of metformin in induction of ovulation in women with PCOS will not be discussed here as it is beyond the remit of this guideline.

Evidence level 2+

Incretin hormone-based therapies such as exenatide have been shown to reduce weight and improve insulin resistance in women with PCOS.[86] However, the clinical experience with these agents in PCOS is limited and significant side effects may occur; therefore, routine use of incretin-based therapies in PCOS is not recommended.

Evidence level 4

Orlistat induces a small weight reduction and improves biochemical hyperandrogenaemia but without changing glucose–insulin homeostasis or lipid patterns.[87]

Evidence level 2++

8.3 Ovarian electrocautery

8.3.1 What is the prognosis following electrocautery?

Ovarian electrocautery should be considered for selected anovulatory patients, especially those with a normal BMI, as an alternative to ovulation induction.

C

Anovulation associated with PCOS has long been known to be amenable to surgical treatment. A long-term cohort study has shown persistence of ovulation as well as normalisation of serum androgens and SHBG up to 20 years after laparoscopic ovarian electrocautery in over 60% of subjects, particularly if they have a normal BMI.[88]

Evidence level 2+

However, no prospective studies have been powered to look at cardiovascular risk profiles and ovarian electrocautery should be reserved for selected anovulatory patients with a normal BMI or where a laparoscopy is required for other indications. It is also important to highlight that ovarian surgery may adversely affect the reproductive capacity of the ovaries in the future.[89]

Evidence level 2–

8.4 Bariatric surgery

8.4.1 What is the prognosis following bariatric surgery?

Bariatric surgery may be an option for morbidly obese women with PCOS (BMI of 40 kg/m² or more or 35 kg/m² or more with a high-risk obesity-related condition) if standard weight loss strategies have failed.

C

Bariatric surgery may be indicated in selected women with PCOS and morbid obesity.[90] Bariatric surgery may induce a significant weight loss (up to 60% of excess weight) and improve diabetes, hypertension and dyslipidaemia, reducing mortality from CVD and cancer when compared with lifestyle modification.[91,92] Long-term weight loss of 14–25% may result.[92,93] In women with PCOS, bariatric surgery has been shown to be effective.[90,94] In 12 morbidly obese women with PCOS, an average postoperative weight loss of 41 kg in the first year improved hyperandrogenism, insulin resistance, dyslipidaemia and hypertension and reversed the PCOS diagnosis.[90]

Bariatric surgery may be an option for morbidly obese women with PCOS in whom long-term diet-based strategies have failed. However, surgically induced weight loss must be balanced against the risks of surgery. These risks include a 0.1–1.1% mortality rate, bowel obstruction, infection, oesophagitis and nutritional abnormalities[91] and hence bariatric surgery should be performed only after standard weight loss strategies have failed in women with PCOS with a BMI of 40 kg/m² or more or a BMI of 35 kg/m² or more together with a high-risk obesity-related condition.[72]

Evidence level 2+

9. Recommendations for future research

In view of the paucity of evidence in this area, the following research topics are recommended:

- large population-based studies on long-term consequences for non-Caucasian women
- prospective long-term study on the development of type II diabetes and cardiovascular outcomes
- elucidation of the long-term consequences for non-insulin resistant non-obese women with PCOS
- better evidence that non-pharmaceutical interventions for young women with PCOS alter long-term consequences
- better evidence that bariatric procedures for women with PCOS alter long-term consequences
- new, safe and effective pharmacological interventions to reduce cardiovascular outcomes, with long-term follow-up.

10. Auditable topics

Based on the above recommendations, the auditable standards are considered below:

1. 100% of women with PCOS should have an accurate diagnosis of PCOS as defined by at least two out of three Rotterdam criteria.
2. 100% of overweight (BMI greater than or equal to 25) women with PCOS and lean PCOS subjects with other risk factors such as advanced age (over 40 years old), personal history of gestational diabetes or family history of type II diabetes should have a 2-hour post 75 g oral glucose tolerance test performed.
3. 100% of women with PCOS should be assessed for CVD risk by assessing individual CVD risk factors (obesity, lack of physical activity, cigarette smoking, family history of type II diabetes, dyslipidaemia, hypertension, impaired glucose tolerance, type II diabetes) at baseline.
4. 100% of women with PCOS should be assessed for obesity with measurement of the BMI and waist circumference at every visit.
5. 100% of women with PCOS have their blood pressure checked routinely at every visit.
6. 100% of overweight women with PCOS should be provided with dietary and lifestyle advice.
7. Psychological issues should be considered and addressed in 100% of women with PCOS.

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Appendix I: Explanation of guidelines and evidence levels

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 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). 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

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Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

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

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2017, unless otherwise indicated.

