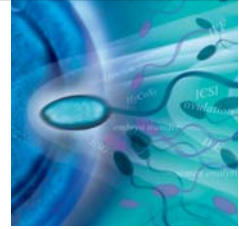




Polycystic ovary syndrome

A management update



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BACKGROUND Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women and is associated with both reproductive and metabolic disorders.

OBJECTIVE This article discusses the health risks, clinical assessment and investigations consistent with the new internationally agreed definition of PCOS, available treatments, and the long term monitoring of women with PCOS.

DISCUSSION Women with PCOS have an increased risk of endometrial carcinoma, type 2 diabetes mellitus, and possibly cardiovascular disease. Polycystic ovary syndrome is a diagnosis of exclusion of other causes of hyperandrogenism. Screening for diabetes is important. Treatment is directed at the presenting symptom as the primary cause is unknown. Long term medical treatment may include the oral contraceptive pill or metformin. Long term surveillance is recommended for the early detection and treatment of potential metabolic complications.

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder affecting 4–7% of reproductive aged women. It is characterised by chronic anovulation and hyperandrogenism,^{1–3} and is the most common endocrinopathy in women.⁴ Consequently, it is the most common cause of anovulatory infertility, oligo-amenorrhoea, amenorrhoea, and hirsutism.⁵ It has recently also become clear that PCOS is linked to a number of metabolic disturbances including type 2 (noninsulin dependent) diabetes mellitus (T2DM) and possibly cardiovascular disease (CVD) (*Table 1*).^{6–8}

Pathogenesis

The exact pathophysiological mechanism leading to the characteristic PCOS phenotype remains unknown. Some investigators explain it as primarily an intrinsic ovarian problem (excess ovarian production of androgens), others as adrenal (excess adrenal production of androgens), and again others as hypothalamic-pituitary dysfunction (exaggerated gonadotropin releasing hormone pulsatility resulting in hypersecretion of luteinising hormone). Perhaps the most widely accepted explanation is metabolic, with the aetiologic factor being insulin resistance (IR) (defined as a reduced glucose response to a given amount of insulin) and consequent compensatory hyperinsulinaemia.

Evidence of decreased insulin sensitivity is seen in both lean (30%) and obese (75%) women with PCOS;^{9,10} but IR, accompanied by compensatory hyperinsulinaemia, is most marked when there is an interaction between obesity and PCOS.¹¹ Hyperinsulinaemia stimulates both ovarian and adrenal androgen secretion directly and suppresses sex hormone binding globulin (SHBG) synthesis from the liver resulting in an increase in free, biologically active

androgens. This excess in local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation. *Figure 1* illustrates this commonly proposed hypothesis attempting to explain some of the underlying mechanisms leading to the wide spectrum of clinical manifestations of PCOS including both reproductive and metabolic morbidities.

Genetics

The literature to date provides a strong basis for arguing that PCOS clusters in families, supporting an underlying

genetic cause of the disorder. The risk of developing PCOS appears to be governed to a large degree by family history, as about 35% of mothers and 40% of sisters of PCOS patients are affected by the disorder.¹² However, the mode of inheritance of PCOS is still uncertain, although the majority of studies are consistent with an autosomal dominant pattern, modified perhaps by environmental factors. Although a number of candidate genes involved in the androgen biosynthetic pathway or metabolic pathways involved in insulin action have been proposed, the putative PCOS gene(s) has yet to be identified. This is not surprising considering the diversity of the syndrome and the controversial diagnosis to date.¹³

Diagnosis

Since its first description in 1935 by Stein and Leventhal,¹⁴ a range of histologic, biochemical, sonographic, and clinical characteristics has been associated with PCOS. Until recently, there had been no general agreement about its definition. These discrepancies in past definitions have recently been resolved by an international consensus workshop group (The Rotterdam Consensus Group 2003) who recommend that all clinicians and investigators now use the internationally agreed definition of PCOS to ensure uniformity in routine clinical management and research studies (*Table 2*).¹⁵

Polycystic ovaries but not PCOS

Polycystic ovaries (PCO) are seen in about 20% of the general female population and the natural history and health risks of these normal, healthy asymptomatic women is poorly understood.¹⁶ The presence of a single polycystic ovary is sufficient to provide the diagnosis (*Table 2*). The distribution of follicles and a description of the stroma are not required in the diagnosis. Polycystic ovaries are seen in 67–86% of women with PCOS.

A subgroup of women with ‘asymptomatic’ PCO (up to 30%) may have subtle abnormalities resembling PCOS; suggesting that important yet silent abnormalities may exist in otherwise healthy women with PCO. Expression of the syndrome over time in women with PCO may be precipitated by various factors, most predominately increase in body weight as a gain in weight is associated with a worsening of symptoms.⁵ The Rotterdam Consensus Group recommend that a woman having ‘asymptomatic’ PCO (ie. absence of ovulatory disorder or hyperandrogenism) should not be considered as having PCOS until more is known about this situation.¹⁵

Women with ‘asymptomatic’ PCO appear to have

Table 1. Clinical features that may be observed in women with PCOS

Reproductive

- menstrual cycle disturbances resulting from anovulation (oligomenorrhea, amenorrhea, dysfunctional uterine bleeding)
- obesity
- infertility
- hyperandrogenisation (hirsutism or acne or androgen dependent alopecia)
- miscarriage
- endometrial hyperplasia or cancer

Metabolic

- impaired glucose intolerance
- type 2 diabetes mellitus
- gestational diabetes
- dyslipidaemia
- cardiovascular disease

Table 2. The Rotterdam Consensus Group criteria for the definition of PCOS¹⁵

The diagnosis of PCOS requires that at least two of the following three criteria are met:

1. Oligo-ovulation and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism. Clinical hyperandrogenism includes hirsutism, acne, or androgenic alopecia. Biochemical hyperandrogenism (or hyperandrogenaemia) includes a raised level of circulating androgens such as total testosterone, free testosterone or free androgen index (FAI), or dehydroepiandrosteronesulphate (DHEAS)
3. Polycystic ovaries on ultrasound (defined as the presence of 12 or more follicles in either ovary measuring 2–9 mm in diameter, and/or increased ovarian volume greater than 10 mL). If a follicle >10 mm in diameter is present, the scan should be repeated at a time of ovarian quiescence in order to calculate the ovarian volume

Other causes for hyperandrogenism that mimic PCOS (eg. congenital adrenal hyperplasia, Cushing syndrome, androgen secreting tumours) should be excluded

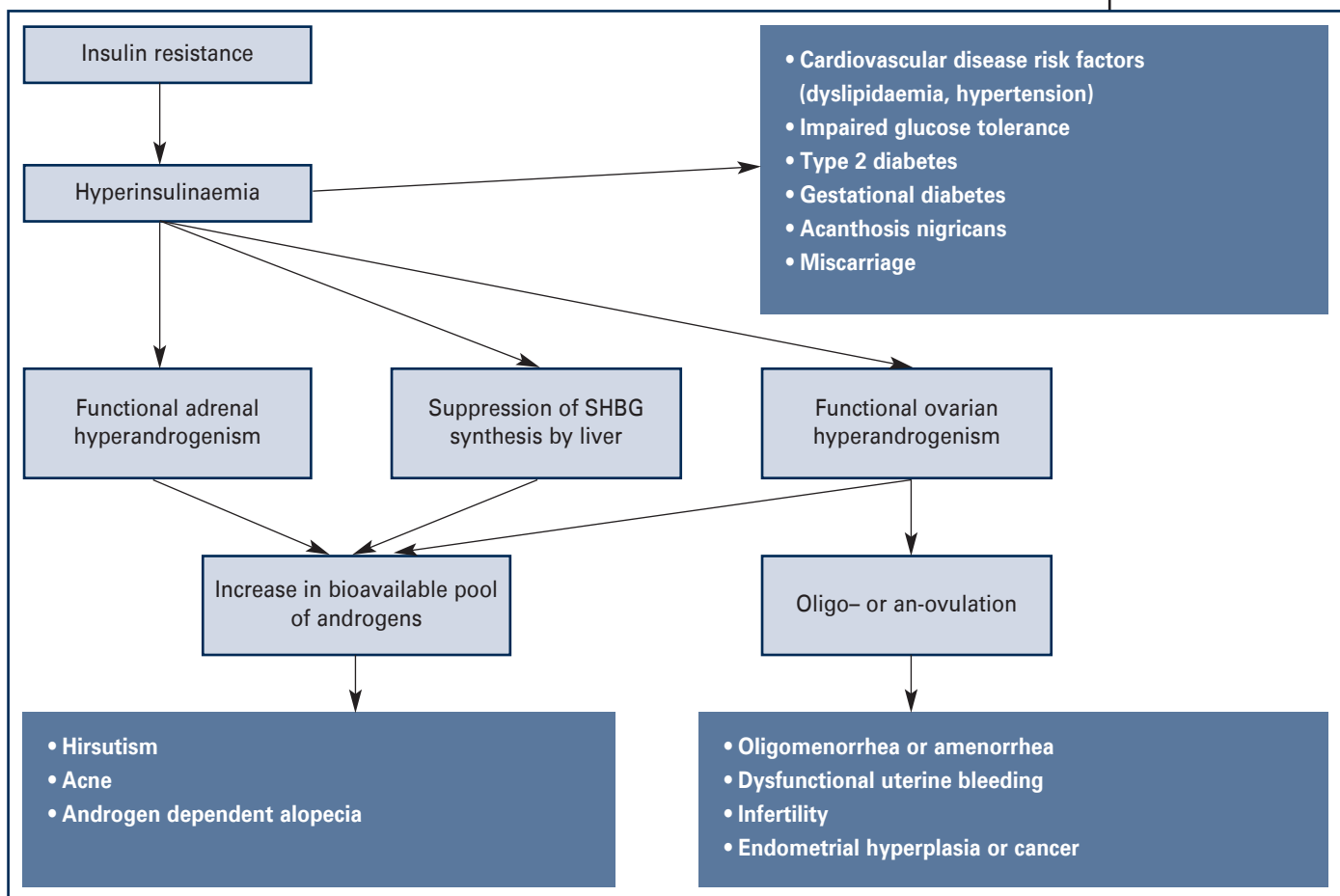


Figure 1. Potential central role of insulin resistance in the promotion of both reproductive and metabolic sequelae of PCOS

similar fecundity and fertility to women with normal appearing ovaries.¹⁷ There are implications of ‘asymptomatic’ PCO if fertility treatment is required for an associated condition such as male factor, as these women have a higher sensitivity to follicle stimulating hormone (FSH) injections resulting in an increased risk of ovarian hyperstimulation syndrome. Interestingly, women with ‘asymptomatic’ PCO have a higher pregnancy rate from in vitro fertilisation compared to women with normal ovaries.¹⁸

Long term health risks

Reproductive

Women with PCOS are thought to be at increased risk for endometrial cancer (the degree of risk has not been clearly defined) through chronic anovulation with consequent unopposed oestrogen exposure (ie. unopposed by progesterone) of the endometrium. However, epidemiological evidence to support this hypothesis is limited as such studies often incorporate patients with chronic anovulation (PCOS is the commonest cause of anovulation), and these results cannot necessarily be

extrapolated to all women with PCOS.¹⁹ An association between PCOS and ovarian cancer appears unlikely. A link between PCOS and breast cancer seems probable on theoretical grounds (obesity, hyperandrogenism and infertility occur frequently in PCOS, and are all risk factors associated with the development of breast cancer) but epidemiological studies are inconclusive.²⁰

Approximately 30–50% of pregnancies in women with PCOS end with spontaneous miscarriage during the first trimester, representing a threefold increase compared to healthy women.^{21,22} However, three large prospective studies could not demonstrate an association between PCOS and miscarriage.^{23–25} The higher risk of spontaneous abortion observed in women with PCOS is likely to be confounded by their high prevalence of obesity, an independent risk factor for miscarriage.²⁵ Women with PCOS are also at increased risk of developing gestational diabetes mellitus.^{26,27}

Metabolic

Women with PCOS have multiple risk factors for T2DM (obesity, family history of type 2 diabetes, IR, reduced

beta cell dysfunction) and clear evidence now exists that women with PCOS, regardless of ethnicity, have a 5–10 fold increased risk of developing T2DM, compared to age and weight matched women.⁶ Polycystic ovary syndrome is also associated with an increased risk of impaired glucose intolerance (IGT). There is a 31–35% prevalence of IGT and a 7.5–10.0% prevalence of T2DM in PCOS.⁶ Family history of diabetes and obesity are important predictors for the development of T2DM. Preliminary data indicates that between 10 and 30% of women with a normal or impaired oral glucose tolerance test (OGTT) will develop T2DM over 2–3 years of follow up.⁶

The prevalence of risk factors for CVD is increased in PCOS (ie. obesity, diabetes, IR, hypertension, dyslipidaemia, increased serum plasminogen activator inhibitor levels, increased carotid artery intima-media thickness on ultrasound) suggesting that women with PCOS are also at increased risk of developing CVD. However, limited epidemiological studies to date have shown no direct evidence of an increased incidence of coronary heart disease events in middle aged women with a history of PCOS.⁷

Diagnostic approach

History

History is specifically aimed at elucidating clinical reproductive symptoms such as: menstrual disturbance (oligo-amenorrhea or amenorrhea, anovulatory dysfunctional uterine bleeding), androgen excess (hirsutism, acne, androgenic alopecia), infertility, and recurrent miscarriages. Body weight changes, lifestyle factors (eating and exercise habits), and family history (PCOS, T2DM, obesity) are also important to enquire about. Virilisation (ie. cliteromegally, deep voice, breast atrophy, significant hirsutism, muscularity, male body habitus, increased libido) is rarely seen in PCOS and is suspicious of an androgen secreting tumour.

Examination

Measurement of the patient's height and weight is performed to calculate the body mass index (BMI) in order to determine if the patient is overweight (BMI 26–29 kg/m²) or obese (BMI \geq 30 kg/m²). Measurement of blood pressure is important. Hirsutism can be assessed semi-qualitatively using the Ferriman-Gallwey score.²⁸ Gynaecological examination is usually unhelpful and only necessary to exclude other causes of bleeding and miscarriage. Acanthosis nigricans – a hyperpigmented hyperplasia of the skin typically seen in the axillae, skin flexures, under the breasts, and nape of the neck – is a marker associated with IR.

Investigations

Table 3 outlines the author's approach to standard investigations. Which tests to perform in order to help confirm the diagnosis of PCOS and exclude other hyperandrogenic disorders (congenital adrenal hyperplasia, Cushing syndrome and androgen secreting tumours) that mimic the PCOS phenotype remains a matter of debate.

Which screening test to perform for IGT and T2DM is also controversial. *Table 4* summarises current recommendations by the American Diabetes Association (ADA), Australian National Health and Medical Research Council (NHMRC), and the Rotterdam Consensus Group.^{15,29,30} I follow the Rotterdam Consensus Group guidelines and perform a 2 hour 75 g OGTT in obese (BMI \geq 28 kg/m²) women with PCOS, as fasting plasma glucose (FPG) appears to be a poor predictor of both IGT and T2DM compared to an OGTT.^{15,31}

The Rotterdam Consensus Group also recommends against screening for IR in PCOS, as IR testing is not necessary either to make the diagnosis of PCOS or

Table 3. Suggested routine testing for PCOS

- Pelvic ultrasound (preferably transvaginal for best imaging)
 - endometrial thickness (to exclude endometrial pathology including endometrial hyperplasia)
 - ovaries (presence of polycystic ovaries, exclude ovarian androgen producing tumours)
- Hormone assays (time for days 2–5 of cycle if oligomenorrhea)
 - β CG if amenorrhea (exclude pregnancy, the commonest cause of 2^o amenorrhea)
 - FSH, LH, E2 (raised LH in up to 50% of patients, exclude other causes of anovulation such as hypogonadotropic hypogonadism or premature ovarian failure)
 - thyroid function tests (exclude hypothyroidism, another cause of anovulation)
 - prolactin (exclude hyperprolactinaemia, another cause of anovulation, with the caveat that some PCOS patients may have prolactin levels slightly above normal)
 - 17 hydroxyprogesterone (exclude congenital adrenal hyperplasia)
 - androgens (DHEAS,^a total testosterone, SHBG,^b FAI^c to possibly help confirm PCOS and exclude androgen producing tumours)
- Metabolic screening
 - 2 hour 75 g OGTT if BMI \geq 28 kg/m² (exclude IGT and type 2 diabetes mellitus)
 - fasting lipids (exclude dyslipidaemia such as \uparrow total cholesterol, \uparrow LDL cholesterol, \uparrow triglycerides, \downarrow HDL cholesterol)

a = dehydroepiandrosterone sulphate, b = sex hormone binding globulin, c = free androgen index

Table 4. Current guidelines for screening for IGT and T2DM in PCOS

Expert group	Screening test	PCOS women requiring screening
American Diabetes Association ²⁹	Fasting plasma glucose	All
Australian National Health and Medical Research Council ³⁰	Fasting plasma glucose	Obese (BMI \geq 30 kg/m ²)
Rotterdam Consensus Group ¹⁵	75 g oral glucose tolerance test	Obese (BMI \geq 28 kg/m ²)

select treatments in routine clinical practice. In addition, there is no validated clinical test for detecting IR.¹⁵

Treatment of PCOS

Most patients with PCOS can be diagnosed and treated in general practice. When to refer will generally depend on the individual general practitioner's interest and expertise in managing the particular morbidities associated with PCOS (*Table 5*). Treatment is largely directed at the immediate presenting complaint as the primary cause of PCOS is currently unknown. However, symptom orientated treatment does not correct the underlying pathophysiologic defect.

Overweight and obesity

The first line intervention in PCOS women who are overweight (BMI 25–29 kg/m²) or obese (BMI \geq 30 kg/m²) is weight loss via lifestyle changes such as dietary modification (low calorie diet) and exercise. High protein diets and low glycaemic index diets may help in weight loss, but their impact on metabolic parameters (IR, lipids) is inconclusive based on the limited evidence to date. There is little evidence that the use of metformin leads to weight loss, despite its gastrointestinal side effects. Anti-obesity drugs are of little value; gastric stapling or banding may have some value in the very overweight.^{32,33}

Short term weight loss (often as little as 5% body weight) has been consistently successful in reducing IR and restoring ovulation, regular cycles, and fertility.³⁴ Weight gain worsens the signs and symptoms induced by hyperinsulinaemia, while weight loss improves IR and is capable of reversing the endocrine and metabolic profile and symptomatology of PCOS.³⁵

Infertility

Treatment options (after weight loss if overweight or obese) include ovulation induction with clomiphene citrate, metformin, metformin combined with clomiphene citrate, FSH injections, and possibly laparoscopic ovarian diathermy. If ovulation induction has been unsuccessful or there is an additional infertility factor to anovulation (ie. male factor), then in vitro fertilisation may be required.

Metformin monotherapy improves ovulation but has not been shown to improve pregnancy rates. However, metformin as co-treatment with clomiphene citrate is superior to clomiphene citrate alone in restoring ovulation and achieving pregnancy. The use of metformin, as opposed to clomiphene citrate, as first line medical ovulation induction treatment for anovulatory PCOS is presently speculative, and will remain so until randomised trials directly comparing these two therapies are performed.^{33,36}

Other menstrual and androgenisation symptoms

Treatments may include:

- the combined oral contraceptive pill (OCP) for contraception, endometrial protection, regularisation and lightening of menses, improvement of hirsutism/acne
- cyclical progestogens for endometrial protection, regularisation and lightening of menses
- anti-androgens such as spironolactone or cyproterone acetate in combination with the OCP (improvement of hirsutism/acne), or
- the insulin sensitising agent metformin (see below).

The choice of treatment depends on the presenting symptom(s) and side effect profiles.

Impaired glucose tolerance

If a woman with PCOS has IGT, lifestyle interventions including weight management, regular physical activity and dietary modification should be implemented. Glucose intolerance can also be managed with metformin, which has been demonstrated to reduce the risk of progression to T2DM in general population women with IGT, but diet and exercise is more effective.³⁷

Chronic treatment of PCOS

OCPs and metformin

Oral contraceptive pills have been the traditional therapy for the long term treatment of PCOS and exert a number of beneficial effects as described above. Concern has been raised by limited and contradictory evidence that OCPs may reduce insulin sensitivity and glucose tolerance in women with PCOS.³⁸

Table 5. Indications for specialist consultation

- Abnormal unexplained per vaginal bleeding or very heavy bleeding
- Anovulatory dysfunctional uterine bleeding not responding to pharmacological treatment
- Infertility management, especially if there are other infertility factors involved such as a poor semen analysis
- High suspicion of other hyperandrogenic disorders needing exclusion or advice on the exclusion of such disorders
- Diagnosis of T2DM
- Severe hypercholesterolaemia
- Recurrent miscarriage
- Patient not tolerant of usual treatments
- Treatment failures

The recognition that IR plays a major role in the pathophysiology of PCOS has led to the novel use of the insulin sensitising drug metformin as a treatment option. Metformin has theoretical benefits including reduction of IR, prevention of T2DM and CVD prevention. Metformin restores regular menses in approximately 62% of predominately obese PCOS women with oligomenorrhea or amenorrhea.³⁶

A limited number of observational studies have demonstrated that continuing metformin therapy during pregnancy is associated with a reduction in miscarriage rates in women with PCOS.^{21,39} However, these findings would need to be confirmed in a properly designed randomised double blind placebo controlled trial before routine use of metformin in early pregnancy in PCOS could be recommended.

A single observational study has reported that PCOS patients who took metformin throughout their pregnancy had a tenfold reduction in the risk of developing gestational diabetes (31–3%).³⁹ Again, these findings would require confirmation from randomised controlled trials before such general use is advocated.

Metformin has been shown to reduce the risk of T2DM in women with IGT (not specifically PCOS women), but intense lifestyle intervention consisting of diet and exercise is more effective.³⁷ Metformin has also been shown to decrease cardiovascular events in overweight T2DM women.⁴⁰ No studies have evaluated the effect of OCPs or metformin on the development of T2DM or CVD in PCOS.³⁸ Long term clinical trials directly comparing the efficacy and safety of the OCP and metformin are required in order to help clarify the speculation that metformin may have theoretical metabolic benefits over OCPs in long term treatment.

Conclusion

Although many questions remain to be answered by good quality clinical research, lifestyle changes should be strongly encouraged in an attempt to reduce the risk of both T2DM and CVD in women with PCOS. Expert opinion recommends long term surveillance for the early detection and treatment of potential metabolic complications, and as such have recommended periodic testing for IGT or T2DM, dyslipidaemia and possibly IR, with no consensus on the interval of testing but ranging from annually to every 5 years. Long term screening for T2DM using a fasting plasma glucose test is recommended for all women with PCOS at least every 3 years, or if obese (BMI ≥ 30 kg/m²) every 3 years, according to the current ADA and Australian NHMRC guidelines respectively.^{29,30} Women with IGT should be tested annually.³⁰

Summary of important points

- PCOS affects 4–7% of reproductive aged women and is characterised by chronic anovulation and hyperandrogenism.
- The underlying pathogenesis in PCOS is unknown, but insulin resistance is proposed to play a major role.
- The Rotterdam Consensus Group recommend that PCOS be defined when at least two of the following features are present (after exclusion of other aetiologies): oligo- or an-ovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovaries.
- Women with PCOS are at increased risk of developing impaired glucose tolerance, type 2 diabetes mellitus and possibly CVD.
- Lifestyle intervention with attention to diet and exercise is first line treatment in overweight or glucose intolerant women with PCOS.
- Long term surveillance is recommended for the early detection and treatment of potential metabolic complications of PCOS.

Conflict of interest: none declared.

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