



Drug treatments in polycystic ovary syndrome

Beres Joyner, General Practitioner, Senior Lecturer, Rural Clinical Division, School of Medicine, University of Queensland, Rockhampton, Queensland

Summary

The recognition that insulin resistance has a central role in polycystic ovary syndrome has led to new approaches to treatment. While clinical presentations may still be managed symptomatically, there is increasing interest in insulin sensitisers including metformin. Drug treatments do not displace the management of behavioural risk factors to achieve weight loss in women who are overweight or obese. Weight loss leads to improvement in symptoms, and other long-term health benefits.

Key words: metformin, ethinylloestradiol, cyproterone, spironolactone.

(*Aust Prescr* 2004;27:129–31)

Introduction

Polycystic ovary syndrome is a heterogeneous condition characterised by hyperandrogenism and anovulation. It presents during a woman's reproductive years as menstrual disturbance, infertility, hirsutism, or acne. Insulin resistance is very common in women with polycystic ovary syndrome. It is also common in women who have a body mass index greater than 30 kg/m². In polycystic ovary syndrome obesity therefore adds to insulin resistance. These women have an increased prevalence of cardiovascular risk factors and many have the metabolic syndrome. Follow-up studies have shown an earlier onset of type 2 diabetes mellitus. These women are not oestrogen deficient and they may develop endometrial hyperplasia which confers an increased risk of endometrial cancer.

Polycystic ovary syndrome can be diagnosed clinically. However, it should be considered a diagnosis of exclusion and other endocrine disorders should be considered. These include congenital adrenal hyperplasia, androgen secreting tumours of the ovaries or adrenal glands, Cushing's syndrome, hyperprolactinaemia, thyroid disease and use of exogenous androgens.

Lifestyle interventions aimed at reducing body mass index and improving insulin sensitivity are central to the initial and ongoing management of women with polycystic ovary syndrome. The women need advice about reducing the calories in their diet as well as advice and support in increasing physical

activity. Modest weight loss of about 5% of the initial body weight can improve the menstrual cycle and studies confirm improvements in ovulation rates and fertility. Women with polycystic ovary syndrome also need advice on long-term behavioural change to manage their increased risk of cardiovascular disease. Those who smoke should be offered assistance to help them quit. When drug therapies are required, the choice of medication is influenced by whether the patient's main complaint is menstrual irregularity, infertility, acne or hirsutism.

Menstrual problems

In women presenting with menstrual problems, it is important to clarify the diagnosis (including the exclusion of pregnancy) and ask if they need contraception or are planning pregnancy. For those with oligomenorrhoea who are not planning pregnancy, the combined oral contraceptive pill may be appropriate. However, which combined oral contraceptive pill is best for women with polycystic ovary syndrome is unknown.

Combined contraceptive pill

The combined oral contraceptive pill controls the menstrual problems by establishing regular withdrawal bleeds and reducing menstrual flow. It also reduces hyperandrogenism and long-term use reduces the risk of endometrial cancer.

The combined oral contraceptive pill does not address the pathophysiology of polycystic ovary syndrome or improve the insulin resistance that usually underlies the hyperandrogenism. It has been reported to aggravate insulin resistance in women with polycystic ovary syndrome as well as those without this phenotype. However, in the general population the combined oral contraceptive pill has not been associated with an increased risk of type 2 diabetes mellitus. There is also no convincing evidence of an increased risk of diabetes when the combined oral contraceptive pill is used in women with polycystic ovary syndrome.

Of concern is the long-term risk of cardiovascular disease in women with polycystic ovary syndrome. At present, there is no evidence to suggest that they experience more cardiovascular events while taking the combined oral contraceptive pill. However, women over the age of 35 who smoke should not be prescribed the combined oral contraceptive pill because of the substantially increased risk of myocardial infarction. This risk is also increased in women with hypertension, and it is not known if control of hypertension reduces the risk.

Progestogens

The effect of progestogens on metabolic risk factors varies and is not well understood. Although there are no studies regarding the use of the progestogen-only levonorgestrel intrauterine system in women with polycystic ovary syndrome, it may be useful in affording endometrial protection in women who also require contraception. Erratic bleeding is a problem especially in the first three months, and 50% of women have infrequent bleeding at six to nine months.

Depot medroxyprogesterone acetate also results in amenorrhoea in 50% of women at 12 months, but it may produce erratic bleeding as well as metabolic disturbances affecting lipids and glucose tolerance. As depot medroxyprogesterone acetate is associated with a delayed return to fertility, other contraceptive methods should be considered in women with polycystic ovary syndrome who are planning pregnancy.

In women who present with menstrual disturbance and who are not planning a pregnancy, and who do not require contraception, cyclic progestogens can be used to regulate the endometrium and control irregular bleeding. Medroxyprogesterone 10–20 mg daily for 14 days each month, or norethisterone 5 mg daily for 14 days each month may be used. However, the optimal regimen for protection against endometrial cancer in women with polycystic ovary syndrome is not known.

Infertility

When women with polycystic ovary syndrome present to their general practitioners because of difficulty conceiving, history, physical examination and laboratory investigations for infertility, including analysis of their partners' semen, should be performed. If lifestyle measures such as weight loss are unsuccessful, metformin therapy can be considered.

Metformin is an oral biguanide insulin sensitiser. It is inexpensive and safe, but should not be prescribed if there is significant renal impairment or other contraindications. Renal function should be checked before treatment. As metformin does not promote insulin secretion, hypoglycaemia does not occur (except very rarely if taken with alcohol and no food). Prominent adverse effects include diarrhoea, nausea and vomiting.

In clinical trials, metformin has been used in doses of 500 mg two to three times a day, or 850 mg twice daily. Metformin improves menstrual patterns and ovulation rates and this effect, if it occurs, is seen within two to three months.¹ Trials in primary care are lacking and specialist societies do not recommend initiation of metformin therapy by general practitioners.² 'Off-label' prescribing of metformin for polycystic ovary syndrome should be discussed with the patient and documented.

General practitioners who do prescribe metformin to restore ovulation need to plan how they will monitor their patient to determine when pregnancy has occurred. Prompt discussion with the woman's obstetrician regarding management of

the metformin therapy in pregnancy is necessary. There are a limited number of non-randomised studies describing a reduction in spontaneous miscarriages in women with polycystic ovary syndrome who continue metformin.

Specialist referral is appropriate if metformin and lifestyle measures have not been effective in restoring fertility in six months. Clomiphene or additional fertility treatments may be required.

When managing women with type 2 diabetes during their reproductive years, it is prudent to ask about menstrual history, contraception and fertility before treatment with metformin as one may inadvertently treat concomitant polycystic ovary syndrome and then need to manage a pregnant patient with diabetes.

Acne and hirsutism

Treatment of acne or hirsutism that cannot be cosmetically controlled involves reducing androgen concentrations, or blocking the actions of androgens (antiandrogens), or inhibiting the action of 5 α reductase. Antiandrogens are teratogenic and male fetuses may potentially be feminised. When these treatments are prescribed for women, effective contraception is essential.

The combined oral contraceptive pill is effective in managing acne, and preparations containing ethinylestradiol and cyproterone (antiandrogen) are frequently prescribed. Oestrogens stimulate the hepatic production of sex hormone binding globulin, resulting in increased binding of testosterone and thus reducing the level of active free testosterone. Gonadotrophin suppression leads to suppression of ovarian androgen synthesis. The reduction in free androgen levels improves acne over three to six months. However, the combined oral contraceptive pill is less effective in the management of hirsutism.

When hirsutism is managed medically, treatment for three to six months is needed before the effect is apparent. Local cosmetic treatments are necessary during this time. Drug therapies are not curative. Options are:

- a combined oral contraceptive pill containing ethinylestradiol and cyproterone acetate
- a different combined oral contraceptive pill plus cyproterone acetate 25–100 mg per day in a reversed sequential regimen for 10 days per month
- spironolactone (antiandrogen) 50–100 mg per day.^{3,4}

Liver function tests should be checked prior to the prescription of cyproterone acetate, and at six-monthly intervals.

Spironolactone should not be used in patients with renal impairment, and renal and potassium status should be checked before therapy and after three months.

Flutamide, a potent antiandrogen, and finasteride, a 5 α reductase inhibitor, have been used overseas to treat women with

hirsutism. However, they are not in general use in Australia. Flutamide may cause hepatotoxicity, while finasteride is teratogenic.

Management of long-term risks

Insulin resistance is important in the development of the metabolic syndrome and is associated with an increased risk of cardiovascular disease. There are no long-term clinical studies to assess the benefit of metformin in reducing adverse cardiovascular outcomes in women with polycystic ovary syndrome.⁵ However, the findings of the Diabetes Prevention Program Research Group (which found lifestyle changes were more effective than metformin in reducing the incidence of type 2 diabetes in people at high risk) suggest that clinicians should persist in working with their patients to achieve lifestyle changes that will reduce body mass and improve insulin sensitivity.⁶

References

1. Harborne L, Fleming R, Lyall H, Norman J, Sattar N. Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. *Lancet* 2003;361:1894-901.
2. Norman RJ, Kidson WJ, Cuneo RC, Zacharin MR. Metformin and intervention in polycystic ovary syndrome. *Med J Aust* 2001;174:580-3.
3. Van der Spuy ZM, le Roux PA. Cyproterone acetate for hirsutism (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
4. Farquhar C, Lee O, Toomath R, Jepson R. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne (Cochrane Review). In: The Cochrane Library, Issue 3, 2004. Chichester, UK: John Wiley & Sons, Ltd.
5. Stadtmauer LA, Wong BC, Oehninger S. Should patients with polycystic ovary syndrome be treated with metformin? Benefits of insulin sensitizing drugs in polycystic ovary syndrome – beyond ovulation induction. *Hum Reprod* 2002;17:3016-26.
6. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393-403.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

9. In polycystic ovary syndrome, the combined oral contraceptive pill has more effect on acne than on hirsutism.
10. Metformin is the drug of choice in the treatment of polycystic ovary syndrome if there are no contraindications to its use.

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Agalsidase beta

Fabrazyme (Genzyme)

5 mL vials containing 5 mg powder for reconstitution

20 mL vials containing 35 mg powder for reconstitution

Approved indication: Fabry's disease

Australian Medicines Handbook section 10.6

Lysosomal storage diseases are caused by inborn errors of metabolism. The lack of a specific enzyme results in the substrate accumulating inside lysosomes. Fabry's disease results from an X-linked recessive genetic defect which causes a deficiency of α -galactosidase A. This deficiency leads to the accumulation of globotriaosylceramide in the lysosomes in blood vessel walls. Patients usually die of cerebrovascular disease, myocardial infarction, heart failure or renal failure.

Agalsidase beta is a recombinant form of α -galactosidase A

produced by genetically engineered Chinese hamster ovary cells. To replace the deficient enzyme requires an intravenous infusion, for at least two hours, every two weeks.

The infused agalsidase is taken up by endothelial lysosomes and has an elimination half-life of 45–100 minutes. As agalsidase is broken down by peptide hydrolysis, impaired liver or renal function may have little effect on clearance.

As the incidence of Fabry's disease is less than 1 in 100 000 births, clinical trials involve only a few patients. In a placebo-controlled trial 29 adult patients were treated with agalsidase beta for 20 weeks. After 11 infusions, 69% of this group had no microvascular endothelial deposits of globotriaosylceramide in more than 50% of the capillaries seen on renal biopsy. Deposits were also significantly reduced in the skin and the heart. There was also a significant reduction in the amount of globotriaosylceramide in the urine.¹