Management of polycystic ovarian syndrome

L.W. CHO AND STEPHEN L. ATKIN

Patients with polycystic ovarian syndrome can be challenging as they usually present with multiple problems that may include weight gain, irregular periods, acne, hirsutism or infertility. Treatment should be tailored to the needs of the patient in a holistic manner. In this review, the authors detail the reproductive, metabolic and cardiovascular aspects of polycystic ovarian syndrome and how these features can be managed in general practice.

Dr L.W. Cho, MRCP, Specialist Registrar in Diabetes and Endocrinology, Hull Royal Infirmary; **Professor S.L. Atkin**, FRCP, PhD, Head of Academic Endocrinology, Diabetes and Metabolism, University of Hull.

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting 6–7 per cent of women of reproductive years.[1–4] It is likely to be increasing in line with the expected increase in obesity seen in the population. It is a heterogeneous clinical syndrome characterised by chronic anovulation leading to irregular periods, and clinical or biochemical hyperandrogenism resulting in hirsutism and acne.[5] Many women with PCOS may appear to have metabolic syndrome in view of the higher reported incidence of hypertension, abnormal lipids, visceral obesity and elevated insulin levels in this population.[6]

Box 1. Conditions to be excluded before making a diagnosis of PCOS.

- Thyroid dysfunction
- Congenital adrenal hyperplasia
- Hyperprolactinaemia
- Androgen-secreting tumours
- Cushing's syndrome

Box 2. Criteria for the diagnosis of PCOS.[7]

The presence of two of:

- Oligo- and/or anovulation
- Clinical and/or biochemical features of hyperandrogenism
- Polycystic ovaries

And exclusion of other aetiologies (see Box 1)

Diagnosis of PCOS

A diagnosis of PCOS can be made only after other conditions have been excluded (Box 1). We would recommend a baseline screen of thyroid function tests, serum prolactin, 17-hydroxyprogesterone, and a free androgen index (FAI = total testosterone divided by sex hormone-binding globulin [SHBG] x 100 to give a calculated free testosterone level). Only if there is a suspicion of Cushing's syndrome should two 24-hour urinary cortisol measurements be performed. If these results are unremarkable (though the FAI may be elevated), you can progress to establishing the diagnosis of PCOS.

In 2003, a consensus on the diagnostic criteria for PCOS was drawn up: the presence of two out of the three features listed in Box 2 indicates a diagnosis of PCOS.[7]

Many women with PCOS have a total testosterone level at the upper limit of normal, but an elevated FAI as a result of low SHBG. The elevation of the free component of testosterone can therefore contribute to a clinical presentation of hyperandrogenism. The official definition of the polycystic ovary is either 12 or more peripheral follicles, or increased ovarian volume >10cm^3 (Figures 1 and 2). If the ultrasound scan shows a follicle >10mm in diameter, it should be repeated at a time of ovarian quiescence in order to calculate volume and area.[7] In our unit we tend to diagnose on the basis of a history of irregular periods and a raised FAI as this is cheaper and easier, reserving ultrasound for difficult cases or for research purposes.

It is important to note that the raised luteinising hormone/follicle-stimulating hormone (LH/FSH) ratio is no longer a diagnostic test for PCOS due to its inconsistency, and should not be requested.[8]

Pathophysiology

The cause of PCOS is unknown, but it is very likely to have a genetic component. The underlying problem appears to be insulin resistance, which is an important target for the treatment of the condition. Simplistically, the high insulin levels[9] reduce the SHBG and increase androgens from the

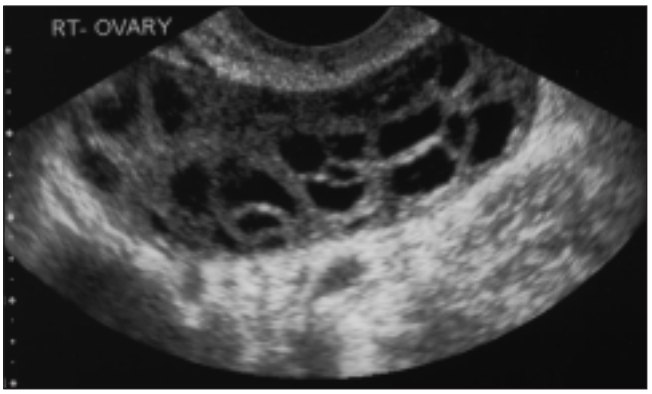

Figure 1. Ultrasound of a polycystic ovary showing multiple follicles in a peripheral distribution.

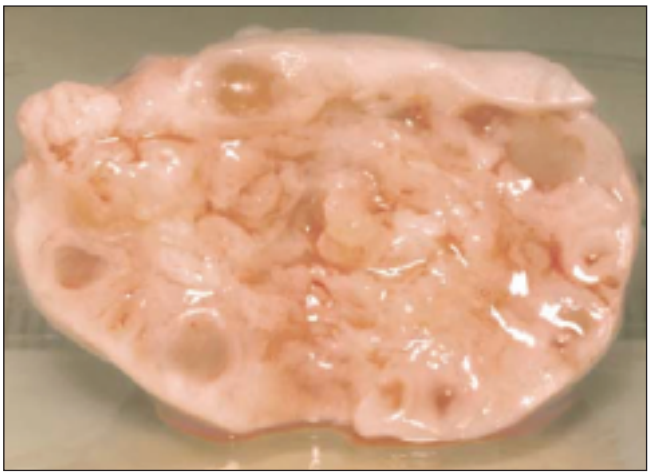

Figure 2. Gross anatomical specimen showing peripheral follicles in a polycystic ovary.

ovary, leading to higher testosterone levels and irregular periods, infertility, acne and hirsutism (Figure 3). This is compounded by obesity, which causes an increase in insulin resistance, making the problem worse.

Manifestations of PCOS

Symptoms often begin around puberty, or after weight gain or stopping the oral contraceptive pill, but can present at any time. Patients with PCOS normally have amenorrhoea or oligomenorrhoea with fewer than eight periods per year and, as the cycles are often anovulatory, infertility results. Hirsutism is common and can be accurately documented using the Ferriman-Gallwey criteria,[10] though in clinical practice this is of little use. Twenty-five per cent of women also suffer from acne or male-pattern alopecia, but virilisation is not a feature of PCOS. The prevalence of obesity in PCOS varies widely and may be responsible in some instances for the PCOS phenotype 'coming out'.

The chronic anovulation of PCOS may be associated with an increased risk for endometrial hyperplasia and endometrial cancer,[11] but this remains controversial: in a study of women 22–31 years after an ovarian wedge biopsy for PCOS, none had any endometrial problems.[12]

It would appear that many women with PCOS fulfil the criteria for metabolic syndrome in view of a higher reported incidence of hypertension, dyslipidaemia, visceral obesity, insulin resistance and hyperinsulinaemia in this population.[6] They have a high risk of progression to impaired glucose tolerance and type 2 diabetes, as shown in one study where 35 per cent of patients with PCOS had impaired glucose tolerance and 10 per cent had type 2 diabetes by the age of 40.[13] Sleep apnoea is an independent risk factor for cardiovascular disease and is found to be more common in PCOS,[14,15] so it may be worth asking the partner if the patient snores. The presence of cardiovascular risk factors of obesity, insulin resistance and an abnormal lipid profile may predispose women with PCOS to coronary heart disease, although this remains controversial. Cardiovascular disease studies in PCOS have been inconclusive, with some suggesting increased cardiac events and others suggesting no increase compared with women without PCOS.

Investigations

The aims of the investigations are to exclude serious underlying disorders, confirm the diagnosis and screen for complications.

History and examination

Virilisation is more likely if testosterone is >5nmol/l and there has been rapid progression of hirsutism. If virilisation is present and the testosterone is >7nmol/l, an androgen-secreting tumour needs to be excluded before PCOS can be confirmed. Gynaecological examination is required rarely and only to exclude other causes of, for example, abnormal bleeding.

Ultrasound scanning

Whether the presence of polycystic ovaries on ultrasound scanning should be used to diagnose PCOS is still debatable. About 20 per cent of normal women have polycystic ovaries on ultrasound[16] and more than 10 per cent of women with PCOS do not have polycystic ovaries.[17] However, ultrasound may be necessary if there is doubt regarding the diagnosis or the possibility of an androgen-secreting tumour, which is usually either adrenal or ovarian in origin. For adequate visualisation of the ovaries, a transvaginal ultrasound would be preferred if there are no contraindications.

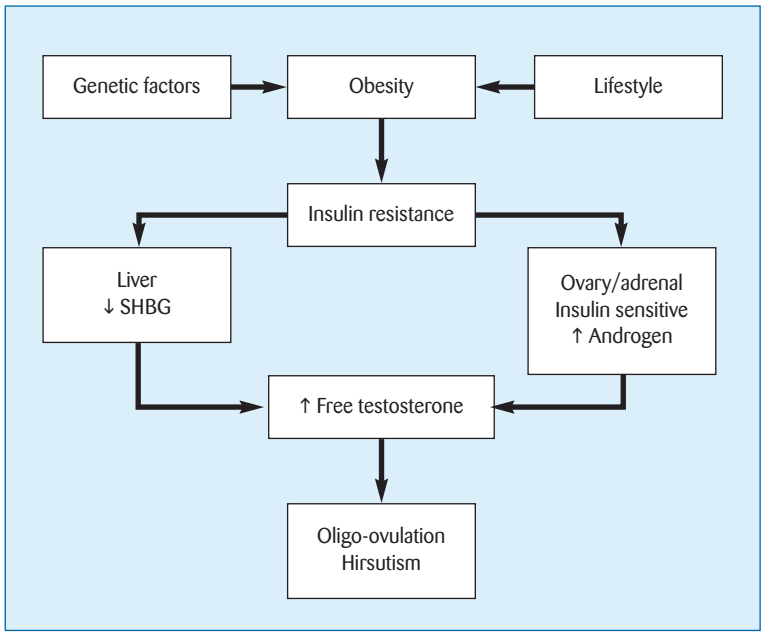

Figure 3. Insulin resistance in polycystic ovarian syndrome.

Biochemical tests

We tend to measure the FAI to confirm biochemical hyperandrogenaemia, as in many cases total testosterone may be at the upper limit of the normal assay in these women, but because of a reduced SHBG they have a higher level of bioactive testosterone. A glucose tolerance test should be considered to exclude type 2 diabetes if the patient has a fasting blood glucose level >5.6mmol/l, is over the age of 40 years and obese (body mass index [BMI] >30kg/m^2), or is obese with a family history of type 2 diabetes. Endometrial biopsy is not routinely requested, but may be used to investigate unexplained vaginal bleeding.

Management of PCOS

Effective treatment of patients with PCOS requires that the specific goal(s) of therapy be first established. Individual goals may include weight management, fertility, treatment for hirsutism and/or acne, achieving a regular menstrual cycle, and the prevention of the long-term consequences associated with PCOS (type 2 diabetes and possibly cardiovascular disease).

Obesity

It should be emphasised that weight management is the cornerstone in the treatment of PCOS.[18] Although obesity is not thought to be the cause of PCOS, it can make the individual features worse or reduce the effect of therapy.[19] It has been reported that loss of around 5 per cent of body weight results in spontaneous resumption of ovulation,[20] improvement in fertility,[21] increased SHBG and reduced basal level of insulin.[22,23]

Anti-obesity drugs such as orlistat and sibutramine have been shown to reduce hyperandrogenaemia[24,25] and would be a suitable add-on to insulin sensitisers such as metformin in the treatment of patients with PCOS. Rimonabant, which is a new endocannabinoid receptor blocker, has shown promise in reducing weight and improving cardiovascular risk profile in obese subjects,[26] but there are currently no data on its use in PCOS.

Menstrual dysfunction

Amenorrhoea may be associated with endometrial carcinoma and therefore it is recommended that women should have at least four menstrual bleeds per year. This can be achieved by using the low-dose combined oral contraceptive. Alternatively, a short course of either medroxyprogesterone or norethisterone will give a withdrawal bleed every three months (but will obviously not provide contraception). Metformin treatment is increasingly used to restore regular periods and will give an ovulatory rate of around 60 per cent. The levonorgestrel intrauterine device (Mirena) can be used as first-line treatment for correction of the anovulatory unopposed proliferative endometrial change, circumventing the significant problems associated with the oral products (acne, bloating, mood depression, ovarian cysts), although these symptoms are uncommonly seen for progestagens given for 10 days every three months.

Infertility

It should be remembered that there are three potential causes of infertility among patients with PCOS: the first might be directly related to the PCOS through a lack of ovulation as follicles fail to develop beyond 10mm;[27] the second might be an additional factor, such as tubal problems; and the third might be due to a male factor.

As most cycles are anovulatory, induction of ovulation may be required. However, it cannot be emphasised enough that encouragement of weight loss may help any treatment strategy and a weight loss of about 5 per cent can restore ovulation.[28,29]

The next line of treatment that is increasingly used is the insulin sensitiser metformin. Not all GPs are comfortable using metformin as it is not licensed for use in the treatment of PCOS and a referral to secondary care may be warranted. Studies have suggested that metformin will result in an ovulatory rate of between 29 and 75 per cent. It should be noted that women with a BMI greater than 37kg/m^2 may respond less well to metformin treatment. Other treatments used, particularly in secondary care,

include clomiphene citrate, with or without metformin,[30,31] and thiazolidinediones such as pioglitazone and rosiglitazone as a method to reduce insulin resistance in place of metformin.

Metformin is often used as first-line therapy to see if ovulatory cycles can be restored, as it is not associated with ovarian hyperstimulation and the need for ultrasound monitoring for the first cycle. If this fails, the fertility agent clomiphene is usually initiated. Studies have suggested that the combination of metformin and clomiphene is more effective than either alone. This was not found, however, in a recent study that suggested that clomiphene added to metformin, which had been recently started, had no additional benefit on ovulatory rate over clomiphene alone.[32] In patients who remain anovulatory or fail to achieve pregnancy with clomiphene and metformin, treatment such as ovarian drilling (for slim patients) or gonadotrophin therapy may be considered. Wedge resection of the ovaries has now been abandoned due to the risk of pelvic adhesions, subfertility and loss of ovarian tissue.

Hirsutism

Hirsutism should ideally be quantified using the Ferriman-Gallwey score,[10] with a score of over eight indicating hirsutism, although this is often not practicable. Licensed treatments include:

- oral contraceptive pills;
- oestrogen plus cyproterone acetate (Dianette);
- cosmetic measures (*eg* laser, electrolysis, bleaching, waxing and shaving);
- eflornithine (Vaniqa) for facial hirsutism.

Usually, a combination of methods is required to achieve an acceptable cosmetic result. Non-licensed treatments that may be used depending on individual practice, but are often seen more in specialist centres, include:

- spironolactone, initially 50mg twice daily – check biochemical profile two weeks after initiating therapy;
- anti-androgens, *eg* flutamide (25mg three times daily) and finasteride (5mg daily) – adequate contraceptive measures are essential;
- metformin as an insulin sensitiser – this has been shown to be an effective option for treatment of hirsutism, with an 11 per cent reduction in testosterone levels.[33]

Use of insulin sensitisers

It should be emphasised that metformin is not licensed for use in PCOS. Patients need to be advised of this, and it should be documented in the notes that this has been discussed. Metformin (500mg three times daily) is effective in improving the metabolic aspects of PCOS as well as increasing menstrual regularity and hirsutism.[33] However, metformin causes a significantly high incidence of nausea and vomiting. To minimise these side-effects, we would recommend a starting dose of 500mg taken with a meal for the first week; if tolerated, the dose can be increased to 500mg twice daily for the second week, and finally three times daily on the third week at breakfast, lunch and dinner. There are inadequate data to recommend the use of metformin during pregnancy, although no specific neonatal complications have been described in the literature.

The thiazolidinediones, troglitazone (removed from clinical use due to its association with liver failure), pioglitazone (up to 45mg daily) and rosiglitazone (up to 8mg daily), have been shown to have positive cardiometabolic effects and to reduce hyperandrogenaemia and hirsutism, as well as regulating the menstrual cycle in women with PCOS.[34–36] However, they cause weight gain, which can be an undesirable side-effect in this population. These treatments are again unlicensed and tend to be restricted to specialist units.

Long-term management

It has been suggested that women with PCOS may have a higher cardiovascular risk than weight-matched controls with normal ovarian function.[37] They have increased cardiovascular risk factors such as obesity, hyperandrogenism, hyperlipidaemia and hyperinsulinaemia. Their abnormal lipid profiles consist mainly of raised triglycerides and total and low-density lipoprotein cholesterol.[38–40] The effect of PCOS on high-density lipoprotein cholesterol, however, is controversial,[38,39,41] and evidence on hypertension is also less consistent.[41] The elevation of risk factors in women with PCOS at an earlier age than among women without PCOS may therefore put them at an increased risk of developing accelerated atherosclerosis, resulting in myocardial infarction.[38,40,42] In the Nurses' Health Study, menstrual cycle irregularity was associated with an increased risk of non-fatal and fatal coronary heart disease, although no clinical or biochemical androgen data were available for confirmation of a diagnosis of PCOS.[43]

In spite of the increase in cardiovascular risk factors, morbidity and mortality from coronary heart disease among women with PCOS in a long-term study have not proved to be as high as predicted.[44] Furthermore, the available studies to date are small in size – non-randomised controlled trials and prospective end-point studies are lacking. Nevertheless, from a clinical perspective, clinicians should continue to identify cardiovascular risk factors in women with PCOS and treat these accordingly. While it seems prudent to assess the cardiovascular risk factors of a patient with PCOS (including blood pres-

sure, 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 of patients.

Women with PCOS are, however, at risk of developing type 2 diabetes. Fasting blood sugars have been shown to be insensitive at diagnosing diabetes and therefore it seems sensible to perform an oral glucose tolerance test on women at particularly high risk (see section on biochemical tests). It has been suggested that high-risk Southeast Asian women should be considered for an oral glucose tolerance test if they have a BMI of more than 25kg/m^2 because of their increased insulin resistance at a lower BMI compared to a Caucasian population. For those patients diagnosed with impaired glucose tolerance, annual fasting blood glucose would be warranted.

Summary

Patients with PCOS may be referred to an endocrinologist, gynaecologist or dermatologist depending on their main presenting complaint. PCOS is a multisystem condition and therefore treatment will involve a multidisciplinary approach.

The UK-based PCOS support group can be found through the website http://www.verity-pcos.org.uk

KEY POINTS

- Polycystic ovarian syndrome (PCOS) is a common endocrine condition.
- Weight management is an important aspect in women with PCOS who are overweight and pharmacological help may be required.
- Insulin-sensitising agents are being increasingly used and have a place in the treatment of PCOS.
- Apart from the reproductive, menstrual and dermatological aspects of PCOS, many affected women have features of metabolic syndrome.
- Management of patients with PCOS needs to be individualised with prior identification of specific goals in a holistic manner.

References

1. Knochenhauer ES, Key TJ, Kahsar-Miller M, *et al.* Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab* 1998; **83**: 3078-82.
2. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, *et al.* A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. *J Clin Endocrinol Metab* 1999; **84**: 4006-11.
3. Asuncion M, Calvo RM, San Millan JL, *et al.* A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. *J Clin Endocrinol Metab* 2000; **85**: 2434-8.
4. Azziz R, Woods KS, Reyna R, *et al.* The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004; **89**: 2745-9.
5. Franks S. Polycystic ovary syndrome. *N Engl J Med* 1995; **333**: 853-61.
6. Glueck CJ, Papanna R, Wang P, *et al.* Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. *Metabolism* 2003; **52**: 908-15.
7. European Society for Human Reproduction and Embryology/ American Society for Reproductive Medicine-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril* 2004; **81**: 19-25.
8. Cho LW, Jayagopal V, Kilpatrick ES, *et al.* The LH/FSH ratio has little use in diagnosing polycystic ovarian syndrome. *Ann Clin Biochem* 2006; **43**: 217-9.
9. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. *J Clin Endocrinol Metab* 1980; **50**: 113-6.
10. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. *J Clin Endocrinol Metab* 1961; **21**: 1440-7.
11. Dockerty MB, Jackson RL. The Stein-Leventhal syndrome: analysis of 43 cases with special reference to association with endometrial carcinoma. *Am J Obstet Gynecol* 1957; **73**: 161-73.
12. Dahlgren E, Johansson S, Lindstedt G, *et al.* Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. *Fertil Steril* 1992; **57**: 505-13.
13. Ehrmann DA, Barnes RB, Rosenfield RL, *et al.* Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999; **22**: 141-6.
14. Gopal M, Duntley S, Uhles M, *et al.* The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in patients with polycystic ovarian syndrome. *Sleep Med* 2002; **3**: 401-4.
15. Fogel RB, Malhotra A, Pillar G, *et al.* Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001; **86**: 1175-80.
16. Polson DW, Adams J, Wadsworth J, *et al.* Polycystic ovaries – a common finding in normal women. *Lancet* 1988; **1**: 870-2.
17. Hahn S, Bering van Halteren W, Roesler S, *et al.* The combination of increased ovarian volume and follicle number is associated with more severe hyperandrogenism in German women with polycystic ovary syndrome. *Exp Clin Endocrinol Diabetes* 2006; **114**: 175-81.
18. Norman RJ, Davies MJ, Lord J, *et al.* The role of lifestyle modification in polycystic ovary syndrome. *Trends Endocrinol Metab* 2002; **13**: 251-7.
19. Holte J. Disturbances in insulin secretion and sensitivity in women with the polycystic ovary syndrome. *Baillieres Clin Endocrinol Metab* 1996; **10**: 221-47.
20. Crosignani PG, Colombo M, Vegetti W, *et al.* Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. *Hum Reprod* 2003; **18:** 1928-32.
21. Norman RJ, Noakes M, Wu R, *et al.* Improving reproductive performance in overweight/obese women with effective weight management. *Hum Reprod Update* 2004; **10**: 267-80.
22. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* 1999; **84**: 1470-4.
23. Tolino A, Gambardella V, Caccavale C, *et al.* Evaluation of ovarian functionality after a dietary treatment in obese women with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2005; **119**: 87-93.

24. Jayagopal V, Kilpatrick ES, Holding S, *et al.* Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. *J Clin Endocrinol Metab* 2005; **90**: 729-33.

25. Sabuncu T, Harma M, Nazligul Y, *et al.* Sibutramine has a positive effect on clinical and metabolic parameters in obese patients with polycystic ovary syndrome. *Fertil Steril* 2003; **80**: 1199-204.

26. Pi-Sunyer FX, Aronne LJ, Heshmati HM, *et al.* Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 2006; **295**: 761-75.

27. Fujiwara T, Sidis Y, Welt C, *et al.* Dynamics of inhibin subunit and follistatin mRNA during development of normal and polycystic ovary syndrome follicles. *J Clin Endocrinol Metab* 2001; **86**: 4206-15.

28. Clark AM, Ledger W, Galletly C, *et al.* Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod* 1995; **10**: 2705-12.

29. Clark AM, Thornley B, Tomlinson L, *et al.* Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998; **13**: 1502-5.

30. Kocak M, Caliskan E, Simsir C, *et al.* Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. *Fertil Steril* 2002; **77**: 101-6.

31. Malkawi HY, Qublan HS. The effect of metformin plus clomiphene citrate on ovulation and pregnancy rates in clomiphene-resistant women with polycystic ovary syndrome. *Saudi Med* J 2002; **23**: 663-6.

32. Moll E, Bossuyt PM, Korevaar JC, *et al.* Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *BMJ* 2006; **332**: 1485.

33. Harborne L, Fleming R, Lyall H, *et al.* Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003; **88**: 4116-23.

34. Brettenthaler N, De Geyter C, Huber PR, *et al.* Effect of the insulin sensitizer pioglitazone on insulin resistance, hyperandrogenism, and ovulatory dysfunction in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004; **89**: 3835-40.

35. Sepilian V, Nagamani M. Effects of rosiglitazone in obese women with polycystic ovary syndrome and severe insulin resistance. *J Clin Endocrinol Metab* 2005; **90**: 60-5.

36. Cataldo NA, Abbasi F, McLaughlin TL, *et al.* Metabolic and ovarian effects of rosiglitazone treatment for 12 weeks in insulin-resistant women with polycystic ovary syndrome. *Hum Reprod* 2006; **21**: 109-20.

37. Wild RA. Polycystic ovary syndrome: a risk for coronary artery disease? *Am J Obstet Gynecol* 2002; **186**: 35-43.

38. Talbott E, Guzick D, Clerici A, *et al.* Coronary heart disease risk factors in women with polycystic ovary syndrome. *Arterioscler Thromb Vasc Biol* 1995; **15**: 821-6.

39. Conway GS, Agrawal R, Betteridge DJ, *et al.* Risk factors for coronary artery disease in lean and obese women with the polycystic ovary syndrome. *Clin Endocrinol (Oxf)* 1992; **37**: 119-25.

40. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 2001; **111**: 607-13.

41. Wild S, Pierpoint T, McKeigue P, *et al.* Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol (Oxf)* 2000; **52**: 595-600.

42. Dahlgren E, Janson PO, Johansson S, *et al.* Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. *Acta Obstet Gynecol Scand* 1992; **71**: 599-604.

43. Solomon CG, Hu FB, Dunaif A, *et al.* Menstrual cycle irregularity and risk for future cardiovascular disease. *J Clin Endocrinol Metab* 2002; **87**: 2013-7.

44. Wild S, Pierpoint T, Jacobs H, *et al.* Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)* 2000; **3**: 101-5.