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Polycystic ovary syndrome

Clinical presentation

POLYCYSTIC ovary syndrome (PCOS) affects 8-10% of women between menarche and age 45. The incidence is thought to be rising along with that of the metabolic syndrome.

Over the past 15 years, knowledge about the causes of PCOS and its associated long-term health problems has exploded. There is now an emphasis on the prevention of diabetes and vascular disease.

Understanding of a set of conditions with symptoms similar to those of PCOS — loosely termed hypothalamic amenorrhoea — has also improved, with new treatments in the pipeline.

Women aged 10-45 often present to their GP with androgenic symptoms, menstrual disturbances or both. Symptoms can include any combination of:

- Acne/rosacea.
- Hirsutism/alopecia.
- Frequent, infrequent, erratic or absent menstruation.

NIH criteria

All of:

- Oligo-ovulation
- Androgen effects or increased androgen levels

and

- Exclusion of endocrine tumours and hypothalamic causes

Rotterdam criteria

Two or three of:

- Oligo-ovulation or anovulation
- Androgen effects or increased androgen levels
- Polycystic ovaries on ultrasound

and

- Exclusion of endocrine tumours and hypothalamic causes

The woman may be concerned by her physical appearance or her future fertility prospects. Her GP will want to differentiate between a diagnosis of PCOS and other conditions.

Definitions of PCOS

PCOS is a vague diagnosis defined by two committees — the 'NIH criteria' and the 'Rotterdam criteria' (see box left).

The presence of ovarian cysts is not considered in the NIH criteria and not a necessity in the Rotterdam criteria. Furthermore, the treatment and outcomes for women with PCOS are not altered by the presence or absence of cysts.

The Rotterdam criteria are useful for selecting groups of like patients for controlled clinical trials.

There is some difficulty in defining the criteria for PCOS, as it is not a single disease entity. Rather, PCOS is the result of a number of pathophysiological factors, all of which need elucidation and treatment.

Many women with PCOS are obese and have difficulty achieving weight loss because of insulin resistance. They may resort to bulimia, a typical cause of hypothalamic amenorrhoea or oligomenorrhoea.

Up to 50% of women with PCOS suffer from stress or depression, which also cause hypothalamic menstrual disturbance. This may complicate the clinical picture, as PCOS and hypothalamic menstrual disturbance may therefore coexist in these patients.

An understanding of the factors that can disrupt the hypothalamic–pituitary–ovarian axis is central to the rational management of all menstrual disturbances.

The physiology of hypothalamic menstrual disturbance will therefore be covered in detail later.

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inside

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Aetiology and pathophysiology

What causes PCOS?

THE menstrual and androgen disorders in most women with PCOS are caused by insulin resistance and compensatory hyperinsulinaemia. This insulin resistance is primarily genetically determined.

Although an aggravating factor, obesity is not the primary cause of the insulin resistance, as non-obese women with PCOS are also insulin resistant.

Androgens may aggravate insulin resistance in women by an action in the liver similar to that of oestrogens and progestogens. However, androgens are not a major factor in the insulin resistance of PCOS, as blockade of androgen action by spironolactone, flutamide or finasteride reduces insulin resistance by only 15%.

However, another necessary causal factor is the presence of genes that permit hyperinsulinaemia to inhibit follicular development and to stimulate both ovarian and adrenal androgen production (figure 1).

Follicles usually only respond to LH stimulation above a diameter of 9mm. In PCOS, hyperinsulinaemia sensitises a 4mm immature follicle to respond prematurely to LH, which is already elevated by insulin stimulation of pituitary LH secretion.

Normally follicular development stops after LH-induced growth. If ovulation fails, both the theca and granulosa cells undergo apoptosis and the follicle disappears (upper part of figure 2).

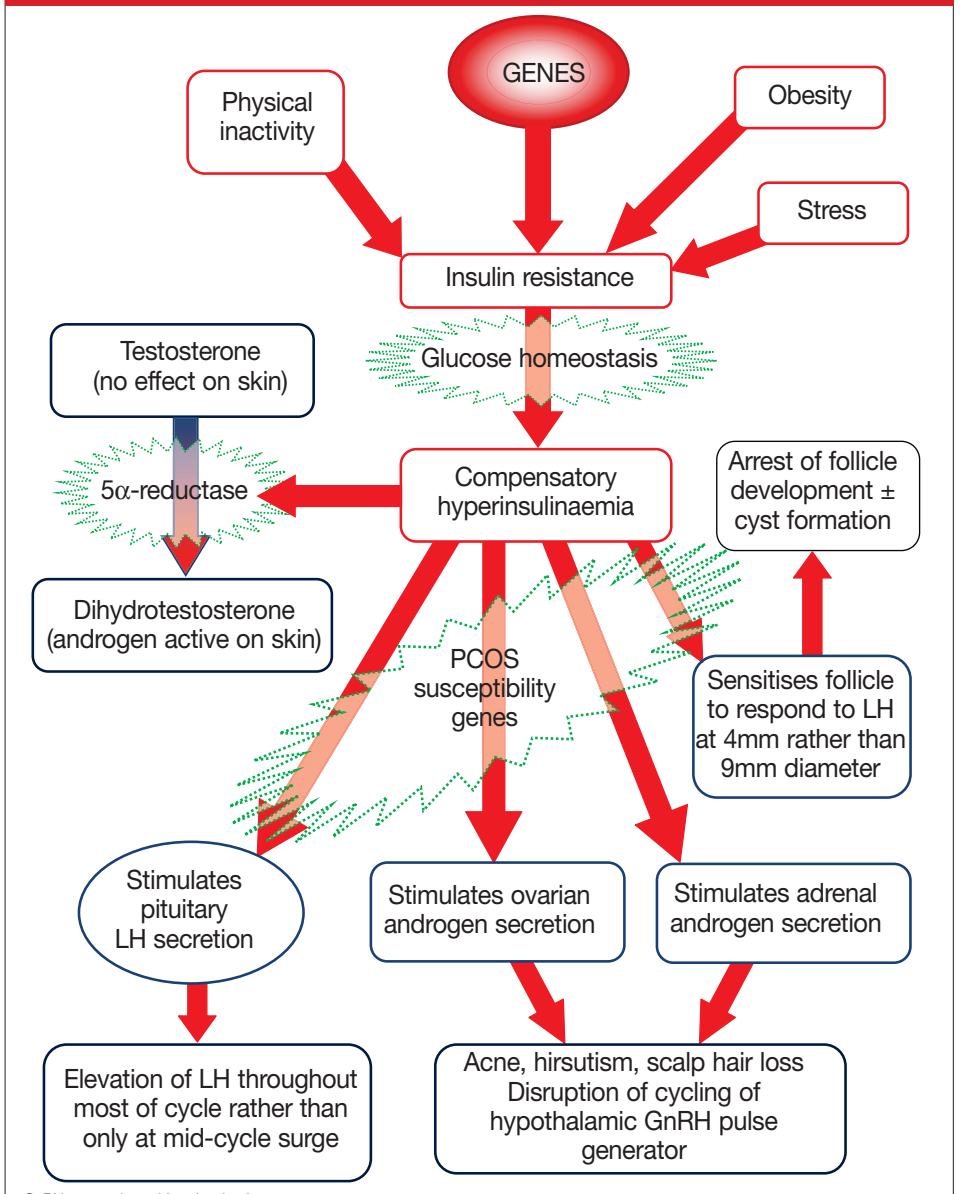
In PCOS, insulin prevents apoptosis of the follicular theca cells but allows apoptosis of the granulosa cells after failure of ovulation, leaving a cyst lined by theca cells. LH and insulin stimulate theca cells to produce androstenedione, most of which is taken up by adjacent granulosa cells then converted into oestrone and oestradiol. In the absence of granulosa cells, theca cells convert some of the androstenedione to testosterone and both hormones are secreted (lower part of figure 2).

Is insulin resistance partially responsible for obesity in PCOS?

It is likely than the thermodynamic concept of ENERGY IN = ENERGY OUT ± FAT STORED or BURNT is not the whole explanation of energy balance in PCOS.

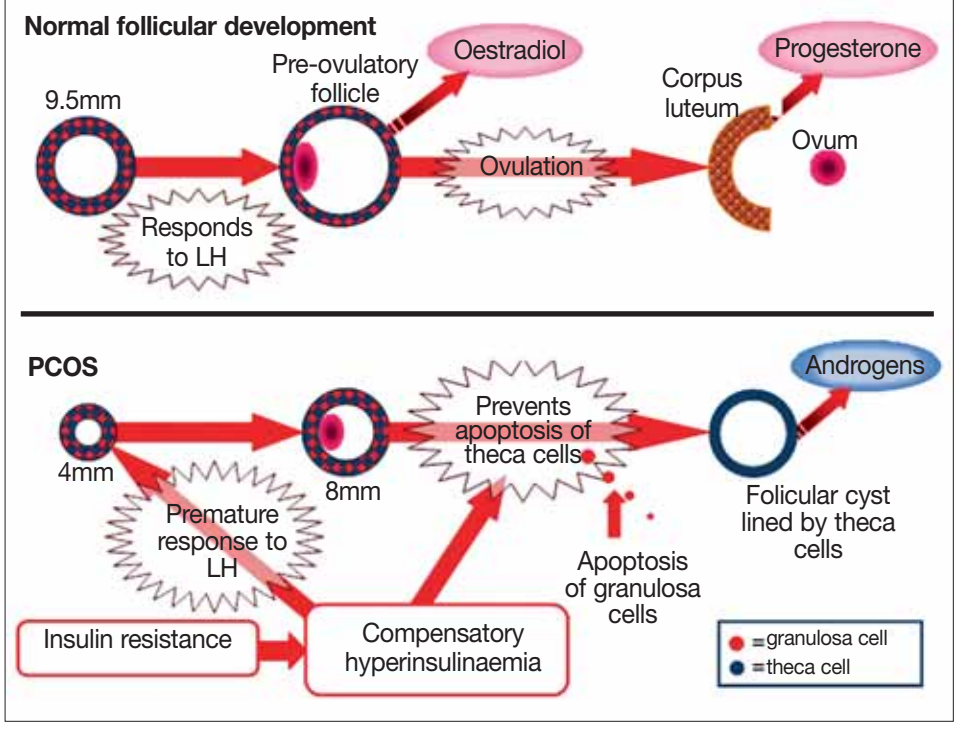
Inhibition of fat breakdown (lipolysis) is one of the most insulin-sensitive processes in the body. The usual meal-peak of insulin is around 40U/L. Fat breakdown is inhibited until insulin falls below 8-9 U/L 2-2.5 hours after a meal. Insulin-resistant individuals may not drop their insulin to levels sufficient to allow fat breakdown, making weight loss difficult (see figure 7, page 34).

Figure 1: Pathophysiology of PCOS.



GnRH = gonadotrophin-releasing hormone

Figure 2: Insulin effects on follicle development and cyst formation.



Recent brain PET scan studies of 16 obese insulin-resistant men and 16 matched, obese insulin-sensitive men reveal that insulin-sensitive men turn off their hypothalamic food-seeking centre after glucose infusion, but insulin-resistant men do not. The separate hypothalamic satiation centre is turned on after glucose infusion in both groups. In other words, insulin-resistant men will tend to seek food, despite adequate energy intake.

To achieve weight loss, overweight women with PCOS therefore need intensive help with exercise, diet and other insulin-lowering strategies.

Long-term comorbidities in PCOS and related conditions

Women with PCOS have increased risks of type 2 diabetes, gestational diabetes, vascular disease and endometrial carcinoma. By age 19, women with PCOS already have increased thickening of the arterial intima compared with controls. As tobacco smoking aggravates both vascular disease and bone loss, women should have these increased risks explained and be assisted to quit.

Endometrial carcinoma has been classically associated with PCOS and amenorrhoea. A recent Australian study confirmed this association with a fourfold increase of endometrial carcinoma in women with PCOS or a 2.2 times increase when adjusted for obesity.

This may be due to increased levels of oestrogen unopposed by progesterone (because of anovulation), and the growth- and cancer-stimulating effects of insulin. To place this risk in perspective, this study also showed that women with type 2 diabetes have a 5.5-fold increased risk of endometrial carcinoma, thought to be due to insulin stimulation.

Hypothalamic causes of menstrual disturbances

Reproductive function is controlled by the hypothalamic gonadotrophin-releasing hormone (GnRH) pulse generator, which controls pituitary secretion of FSH and LH. In women the GnRH pulse generator operates in a cyclic fashion over 26-34 days.

Any process that inhibits the GnRH pulse generator will impair follicular development and ovulation, often leading to the development of ovarian cysts. Women with hypothalamic amenorrhoea or oligomenorrhoea have increased bone loss, previously thought to be primarily due to reduced oestrogen levels but now known to be largely due to the direct effects of hypercortisolaemia on bone.

Stress hormones and neurotransmitters

The GnRH pulse generator is controlled by a variety of neurotransmitters but is inhibited by corticotrophin-releasing hormone (CRH), cortisol, beta endorphin and increased noradrenergic tone. CRH and cortisol secretion is increased by stress and depression. Some clinical situations in which CRH and cortisol inhibit the GnRH pulse generator are:

- Anorexia nervosa, bulimia and other causes of severe weight loss. After weight gain and resumption of menses, some women will later develop androgenic skin problems.
- Excessive physical training for 2-4 hours daily in ballet, gymnastics or athletics during adolescence. Recovery will occur after exercise is reduced and energy intake increased.
- Extreme stress in women working 10-14 hours a day. These women are frequently working in law, finance or securities trading or are PhD students. Occasionally severe relationship stress will have a similar effect.

Increased androgen levels

Increased androgen levels, for example in PCOS, congenital adrenal hyperplasia and androgen-treated female-to-male transsexuals, alter the cyclicity of the GnRH pulse generator and cause irregular cycles.

Incomplete maturation of the GnRH pulse generator

Incomplete maturation of the GnRH pulse generator results in delay of menarche until 14-16 years and is followed by oligomenorrhoea. Cycles usually become regular after the first pregnancy.

Often the patient's mother or sister(s) have a similar history. It is diagnosed by exclusion of stress-related conditions.

Diagnosing PCOS and related conditions

History

A THOROUGH and detailed clinical history (table 1, page 32) is the most important investigation in women experiencing menstrual disturbances and/or androgenic skin disorders. An adequate history in women with suspected PCOS is a time-consuming process that cannot be replaced by investigations.

Physical examination

Physical examination should include:

- Weight, height, BMI and blood pressure.
- Severity and distribution of acne or rosacea.
- Severity and distribution of hirsutism.
- Severity and distribution of alopecia.
- Signs of insulin resistance:
  - — pigmentation of the skin on the dorsal aspect of the knuckles and toes; usually fades after 40 years (figure 3, page 32)
  - — pigmentation of the skin on the eyelids
  - — pigmentation of the skin on the base of the axillae and neck (acanthosis nigricans) (figures 4, 5, page 32)
  - — skin tags.
- Signs of Cushing's syndrome: purple striae, proximal muscle weakness, thin skin and purpura.

Investigations in PCOS, exclusion of other endocrine diseases

Before embarking on investigations of a woman's menstrual or androgen problems, a GP should already have a good idea of its causation

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from the history and clinical examination.

Pelvic ultrasound

The main indication for pelvic ultrasound examination in women with PCOS is evaluation of the endometrium in menorrhagia and the exclusion of rare androgen-secreting ovarian tumours. Pelvic ultrasound should generally be omitted unless the clinical picture includes heavy bleeding or pelvic pain.

In reality, the presence or absence of ovarian cysts rarely alters treatment options except for laparoscopic ovarian diathermy. Furthermore, the discovery of ovarian cysts and the label 'polycystic ovary syndrome' will often cause much angst ('Are my ovaries diseased?', 'Can I ever have children?', 'Can the cysts be cut out?').

Oestradiol

Oestradiol level will be normal in most women with PCOS, but low to normal in women with hypothalamic problems.

Luteinising hormone and follicle-stimulating hormone

Although LH secretion is increased by hyperinsulinaemia, a diagnosis should not be based on the LH:FSH ratio, as it is an insensitive test. LH and FSH levels will be reduced in some hypothalamic disturbances but will be normal in others.

Prolactin

Hyperprolactinaemia from a pituitary adenoma is another cause of amenorrhoea. The prolactin test should be repeated after 20 minutes' quiet reading in the pathology centre. Persistent hyperprolactinaemia can be caused by stress and psychotropic drugs but warrants pituitary imaging by MRI. Pituitary CT should be avoided, as it will suggest a microadenoma in 20-25% of normal people.

Testosterone, sex hormone binding globulin and free androgen index

Testosterone, sex hormone binding globulin (SHBG) and free androgen index (FAI) should be measured in all women with androgenic skin problems and in those with menstrual disturbance without androgen problems. In women who are not taking hormonal preparations, SHBG is one of the best laboratory indicators of insulin resistance. SHBG values <38nmol/L in women and <28nmol/L in men are diagnostic of insulin resistance.

Women with androgenic skin problems will sometimes have normal testosterone and FAI levels. Their androgenic skin problems are caused by insulin-stimulated conversion of testosterone by 5-alpha-reductase to dihydrotestosterone, the androgen responsible for skin effects.

Figure 3: Pigmented knuckles.

Table 1: Things to ask about when taking a history

Age of menarche	An early menarche is common with insulin resistance, particularly in obese girls. A delayed menarche can also occur with insulin resistance or a hypothalamic disorder, and is more common than early menarche
Menstrual history	Infrequent menstruation suggests a hypothalamic disorder or insulin resistance. Frequent bleeding can occur as a result of anovulation in the presence of reasonable oestradiol secretion, insulin resistance, endometrial hyperplasia, polyps or carcinoma, or occasionally from endometrial atrophy
A history of recent onset of amenorrhoea and/or androgen effects	After adolescence, following a normal menarche and regular cycle, this raises the possibility of an endocrine (ie, hormone secreting) tumour of the ovaries, adrenals or pituitary. Endocrine tumours, except prolactinomas, are quite rare
A history of hirsutism since childhood	Suggests insulin resistance or congenital adrenal hyperplasia (rare). The latter is diagnosed by elevation of 17-hydroxyprogesterone in the follicular phase of cycle
Acne, particularly followed by hirsutism	Suggests insulin resistance
Weight gain	In childhood, during adolescence or later, this suggests insulin resistance. Weight gain caused by Cushing's syndrome is usually associated with purple striae, proximal muscle weakness, thin skin and bruising associated with minor trauma. Late-onset acne, hirsutism or menstrual disturbance are symptoms that warrant exclusion of ovarian, adrenal or pituitary tumours
Lowest adolescent weight	An estimate of this should be sought. The question 'What was your lowest weight between age 12 and 22?' is likely to elicit a more honest response than 'Have you ever had anorexia or bulimia?'
Regular physical training	A history of regular physical training for 2-4 hours daily in ballet, gymnastics or athletics can inhibit the hypothalamic GnRH pulse generator, leading to inhibition of LH and FSH secretion and amenorrhoea
Number of work or study hours	This should be sought, particularly for women working in law, finance or security trading or doing a PhD
History of depression and/or anxiety	Many women with PCOS suffer from mood disturbance. The increased secretion of corticotrophin-releasing hormone and cortisol inhibit the gonadotrophin-releasing hormone pulse generator. Excess cortisol secretion aggravates insulin resistance and makes weight loss difficult to achieve
Family history	A family history of type 2 diabetes, gestational diabetes, PCOS and infertility supports the diagnosis of insulin resistance

17-hydroxyprogesterone

The level of androgen 17-hydroxyprogesterone is elevated in congenital adrenal hyperplasia, both infantile and late onset. It is also secreted by the corpus luteum after ovulation, and blood must therefore be taken in the follicular phase of a woman's cycle.

DHEA, DHEAS and androstenedione

These androgens rarely add anything to the diagnosis and, in any case, in classic PCOS the source of the excess androgens is both the ovaries and the adrenal cortex.

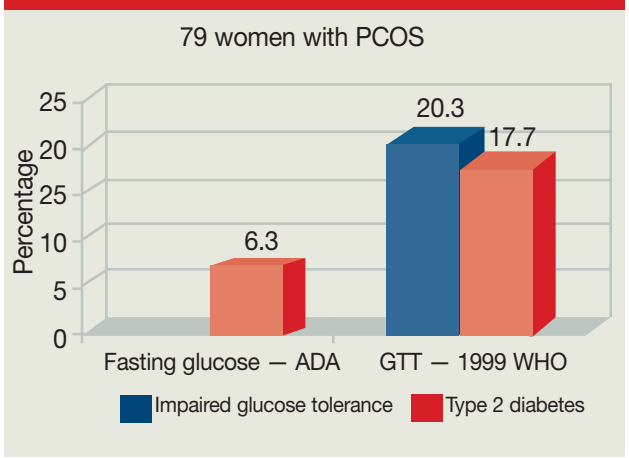
Glucose screening

As explained, all women with PCOS are insulin resistant.

Figure 4: Acanthosis nigricans in the axilla.

Figure 5: Acanthosis nigricans at the base of the neck.

Figure 6: Prevalence of type 2 diabetes and impaired glucose tolerance in PCOS identified by fasting glucose compared with a glucose tolerance test.



More than 50% of overweight women are vitamin D deficient.

Furthermore, in women aged 20-44 with PCOS, about 38% have either type 2 diabetes or impaired glucose tolerance. A two-hour glucose tolerance test is mandatory, even in non-obese women with PCOS, as a fasting glucose measurement will miss 85% of these abnormalities (figure 6).

Insulin resistance testing

The clinical finding of skin tags, pigmentation of the eyelids, elbows or knuckles or acanthosis nigricans in the axillae or at the base of the neck confirms insulin resistance.

The diagnosis of insulin resistance by the measurement of insulin levels during glucose tolerance testing, although controversial among some endocrinologists, may increase a woman's understanding of PCOS and her motivation for lifestyle change. Insulin resistance is confirmed by a fasting insulin >9mU/L, a peak insulin >60mU/L or a two-hour insulin higher than the one-hour value. Insulin resistant women who are exercising for 45-60 minutes, 5-7 days a week, will often lower their insulin levels, particularly the peak level, into the normal range. Insulin levels, if used, must be interpreted in the clinical setting.

In women who are not using hormonal contraception SHBG is a useful measure of insulin resistance.

Vitamin D

More than 50% of overweight women are vitamin D deficient. In addition to bone loss, vitamin D deficiency (<20-25nmol/L) leads to muscle weakness, thereby reducing exercise capacity, the ability to lose weight and aggravating insulin resistance. It therefore must be treated and monitored.

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Treatment of PCOS and hypothalamic disorders

TREATMENT of skin, menstrual and fertility problems with oral contraceptives or ovulation-induction agents will usually achieve prompt results, but at the expense of other health problems in the longer term. Treatment aimed at the underlying disease process will reduce the long-term risks of diabetes and vascular disease but will improve acne and infertility more slowly.

Treatment of insulin resistance

The treatment of insulin resistance is integral to the improvement of long-term health problems in women with PCOS. As insulin resistance is partly due to inherited factors, it cannot be eliminated but can be markedly improved with increased physical activity, weight loss and use of insulin sensitisers (figure 7), and by removing or reducing aggravating factors (work or relationship stress, mood disturbance or hormonal contraception).

Exercise

Regular physical exercise for 45 minutes, five days a week is central to the treatment of PCOS. Although a mixture of two-thirds aerobic and one-third resistance is probably optimal, the form of exercise that the woman finds enjoyable and compatible with her schedules will result in the greatest compliance. Upper-body exercise and outdoor exercise probably help mood disturbance. The box, above right, lists the immediate and long-term effects of exercise.

Diet

Low-GI, reduced-energy diets result in satisfactory weight loss in many women. A reduced carbohydrate diet is often necessary in severely insulin-resistant women. Any commercial diet plan that results in significant weight loss is acceptable, even though the rationale behind the diet may not be rational. Greater weight loss is achieved with frequent follow-up. The involvement of a scientifically trained dietitian is invaluable.

In overweight women with PCOS, 4-5kg weight loss can produce significant improvements in menstrual regularity, fertility and acne. Weight loss usually does not occur in the absence of physical exercise (see figure 7).

Insulin-sensitising medications

Metformin, an insulin-sensitising medication introduced for diabetes in 1957, has been used in PCOS since 1994, and its benefits were confirmed in 2002. Ovulatory cycles and conception usually occur 4-6 months after starting therapy. Acne and rosacea will mostly clear or improve significantly after 3-4 months. Any improvement in hirsutism is modest.

Metformin is often ineffective if used in the absence of dietary measures and should not be prescribed in the absence of lifestyle changes (see figure 7 — a good teaching aid for patients). Metformin usually facilitates weight loss when combined with lifestyle changes. In women not seeking conception, metformin can often be withdrawn after significant weight loss that improves insulin resistance and lowers insulin levels.

Young women are more sensitive to the gastrointestinal side effects of metformin such as nausea and diarrhoea, so the extended-release formulations (Diabex XR and Diaformin XR) are preferred initially. The dose is increased by 500mg each week up to a daily dose of 1500mg. These preparations have a 16-hour duration of effect and should be given before breakfast and dinner rather than once daily to achieve maximal response. The dose can be increased to 1000mg bd. Conventional metformin at doses up to 2500mg spread over three doses can be used when response to the extended-release formulation is inadequate. Metformin can lower vitamin B12 levels, which should be checked every six months.

Metformin reduces the high incidence of pregnancy miscarriage in PCOS and should be continued until 13 weeks' gestation, even though it is a Category C drug. It is unlikely the pharmaceutical industry will apply for revision of metformin's Category C status because of the cost of supportive studies, the low profit margin and the experience with the spurious litigation over the excellent pregnancy anti-emetic Debendox. Metformin is now widely used in the first trimester of pregnancy throughout the world with significant benefits and no apparent adverse effects on the fetus. Prescription of metformin for PCOS remains 'off-label'.

Other insulin-sensitising medications such as rosiglitazone and pioglitazone cause weight gain in humans and reduced litter numbers in rats. Although they improve symptoms of PCOS, these drugs are contraindicated.

Inability to achieve weight loss or regular menstruation with exercise, diet and metformin suggests there are other factors aggravating insulin resistance. Work or relationship stress, mood disturbance or hormonal contraception are the usual culprits.

Treatment of hypothalamic disorders

Women with anorexia nervosa and bulimia should be treated by experts in this field to increase the BMI to 20kg/m^2. Women who are involved in extreme physical training should reduce their weekly hours of exercise and increase their energy intake. Their haemoprotein, vitamin and mineral intake should be assessed.

IVF should not be offered to these women as 'a quick and easy way out', as fetal development will be suboptimal in a malnourished mother, with lifelong consequences.

Women whose amenorrhoea is caused by stress may benefit from cognitive behavioural therapy over a period of 6-18 months. Those with long work hours should reduce their hours or change employer.

Women whose hypothalamic amenorrhoea is more likely due to incomplete maturation of the hypothalamic GnRH pulse generator will usually need clomiphene or gonadotrophins (LH, FSH) to achieve their first conception, but will often have regular ovulatory cycles after that pregnancy.

As the neurotransmitters controlling the GnRH pulse generator are better understood, new therapies for hypothalamic amenorrhoea are emerging (table 2).

The contraceptive pill and other hormonal contraceptive agents

Oral contraceptive agents have been the mainstay of non-fertility treatment of PCOS and hypothalamic amenorrhoea for the past 45 years.

They have the proven advantages of providing regular predictable bleeding, control of menorrhagia and prevention of endometrial hypertrophy and carcinoma.

They have been prescribed in hypothalamic amenorrhoea in the hope of preventing the bone loss associated with low oestradiol levels. However, several recent controlled studies have shown that bone loss is due to increased cortisol secretion in hypothalamic amenorrhoea and that the pill does not prevent that bone loss.

Over the past 15 years the pill has been found to cause deterioration in glucose tolerance in women with PCOS (figure 8).

Because of concerns over

Figure 7: Additive effects of exercise, diet and metformin on the reduction in insulin levels.

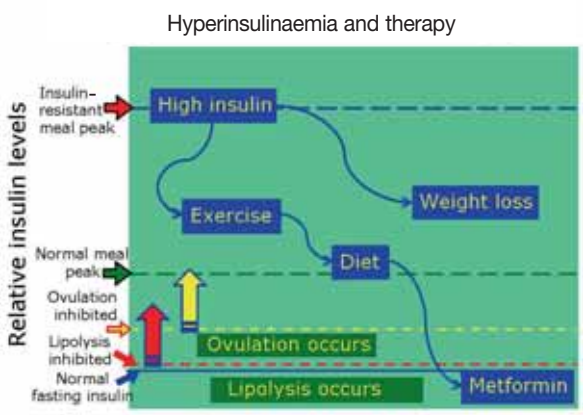
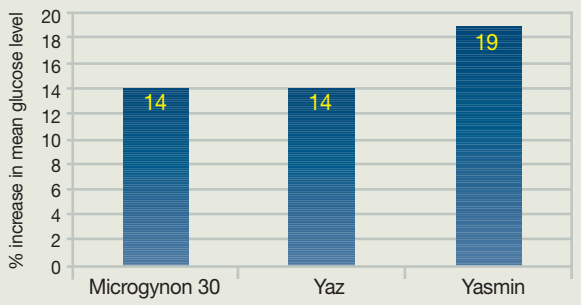


Figure 8: Increase in average glucose levels after six months therapy with common OCPs.



Oelkers W, et al. *Journal of Clinical Endocrinology and Metabolism* 1995; 80:1816-21.

Figure 9: Timeline of insulin resistance, insulin secretion, gestational diabetes, impaired glucose tolerance and type 2 diabetes.

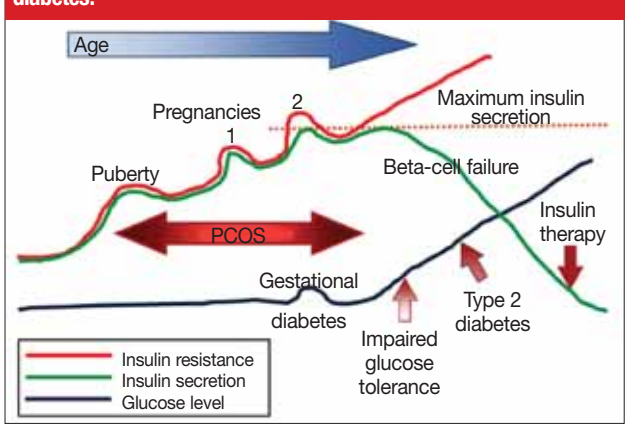


Table 2: Emerging therapies for hypothalamic amenorrhoea

Experimental drug	Mode of action
Naltrexone	Opioid receptor blocker
Acetyl-L-carnitine (ALC)	Central cholinergic, serotoninergic and dopaminergic systems
GABA-ergic medications	Inhibit CRH release
Benzodiazepine receptor agonists	Inhibit CRH release
Pivagabine (PVG)	GABA receptor type A, inhibits CRH release

Effects of physical activity

Acute effects of physical activity

- Physical activity increases glucose uptake into active muscles, with greater effect as the intensity of physical activity increases.
- Muscle contractions during physical activity stimulate blood glucose transport via a mechanism that is separate from, and additive to, insulin-stimulated blood glucose uptake into skeletal muscle at rest.
- Moderate physical activity acutely improves blood glucose and insulin action, the improvement in systemic insulin action lasting for 2-72 hours.
- Intense physical activity can cause transient hyperglycemia.
- Resistance exercise leads to lower fasting glucose for at least 24 hours in people with impaired fasting glucose levels.

Long-term effects of physical activity

- Aerobic and resistance training improve insulin action, blood glucose control and fat oxidation and storage in muscle.
- Resistance exercise improves skeletal muscle mass.
- Physical activity might improve systolic more than diastolic blood pressure.
- Physical activity and physical fitness are linked with reduced risk for all-cause and cardiovascular mortality.
- If relying on exercise alone for weight loss, up to 60 minutes a day of physical activity might be needed.
- Physical activity and fitness can decrease depression symptoms and improve health-related quality of life.

Prevention of gestational diabetes

- Physical activity might decrease the risk for the development of gestational diabetes.

Clinician–patient approach to hormone use in PCOS

- Assess and explain a woman's risk of type 2 diabetes and methods of prevention.
- Explain the complications and reduced life expectancy of type 2 diabetes.
- Explain that exercise, weight loss and metformin will clear or improve acne within 3-4 months and result in regular ovulatory cycles within 4-6 months.
- Explain that ovulatory cycles reduce the risk of endometrial carcinoma similarly to contraceptive pills and that the pill does not prevent osteoporosis in hypothalamic amenorrhoea.
- If no other contraception is acceptable:
  - use the lowest dose pill possible (Loette, Microgynon 20)
  - progestogen-only pills have been associated with a higher conversion to diabetes after gestational diabetes than combined contraceptive pills
  - perform a glucose tolerance test before and six months after starting the pill. If glucose levels rise, withdraw all contraceptive pills, Implanon, NuvaRing and Depo-Provera therapy
  - consider the use of a Mirena IUD even though a woman might be nulliparous.
- Take time and allow a woman to choose her therapy after informed discussion.

the long-term metabolic health of women with PCOS, a number of world authorities in PCOS recommend that contraceptive pills be avoided if possible. An approach incorporating their suggestions is outlined in the box on the previous page.

Other hormonal forms of contraception such as Implanon and the NuvaRing have similar effects on insulin resistance as the pill, while Depo-Provera is worse, usually resulting in 5-10kg weight gain.

Women who are frustrated with PCOS and the side effects of treatment often access and blog on several informed PCOS websites and are aware of these problems. Many have one or more parents or grandparents with diabetes and are very often fully aware of its complications. The timeline of insulin resistance, increased insulin secretion, impaired glucose tolerance (figure 9) is a very useful tool to place these relationships in perspective for a young woman.

In hypothalamic amenorrhoea, the GnRH pulse generator is partially or completely inhibited by the factors outlined earlier. Combined contraceptive pills exert their effect by inhibiting the GnRH pulse generator. The use of such drugs in this situation makes recovery even more difficult. Previously women were prescribed the pill to regulate their cycle, only to experience so-called post-pill amenorrhoea as a result of this uninformed approach.

Anti-androgen therapy for acne, hirsutism and male-pattern alopecia

If acne does not respond to the treatments outlined earlier, other therapies such as topical therapies, antibiotics, anti-androgens (table 3) or isotretinoin should be considered. If hirsutism is localised rather than generalised, local treatments such as waxing, electrolysis or laser are low-side-effect options.

Of all androgenic side effects, alopecia is the most resistant to treatment. It must be treated intensively at an early stage to achieve hair regrowth, using topical minoxidil and an anti-androgen.

Table 3: Anti-androgens available for androgenic skin problems

Drug	Usual starting dose	Comments	Precautions
Spironolactone	50mg bd	Polymenorrhoea (frequent menses)15%, amenorrhoea, occasionally hypotension if dose >100mg/day in hot weather.	Hypokalaemia is only usually seen with concomitant use of NSAIDs or in older ages.
Cyproterone	50mg daily	Causes weight gain. Benefit equivalent to that of spironolactone.	Suppresses LH, FSH and oestradiol. Use with contraceptive pill to address low oestradiol and associated bone loss.
Flutamide*	125mg daily (half of 250mg tablet)	2-3 times as effective as the others. Achieves scalp hair regrowth.	Two men on flutamide for Ca of prostate have developed Ca of breast. Avoid if mammogram or breast check abnormal, or if family history of breast carcinoma.
Finasteride*	5 mg daily	5-alpha-reductase inhibitor (reduces synthesis of dihydrotestosterone). Benefit equivalent to cyproterone and spironolactone. Rarely used.	10 men on finasteride for Ca of prostate have developed Ca of breast. Only use if others are not tolerated. Avoid if mammogram or breast check abnormal, or if family history of breast carcinoma.

*Not licensed for use in women Ca = cancer

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2. Glueck CJ, et al. Pregnancy outcomes among women with polycystic ovary syndrome treated with metformin. *Human Reproduction* 2002; 17:2858-64.

Online resources

- The Polycystic Ovarian Syndrome Association of Australia: www.posaa.asn.au
- The Jean Hailes Foundation for Women's Health: www.jeanhailes.org.au

Conflict of interest statement

Warren Kidson has not received subsidised travel, accommodation, gifts or gratuities from manufacturers of metformin, hormonal contraceptives or fertility drugs.

Fertility therapy

MOST women with PCOS or hypothalamic oligomenorrhoea will conceive with appropriate lifestyle changes, metformin and treatment of depression and stress. Women should be reassured of this fact.

Some will need clomiphene, gonadotrophin therapy or IVF. Discussion of these treatments is beyond the scope of this article. IVF should not be a first option. It is rewarding but irritating for a woman to conceive after 4-6 months of exercise, diet and metformin when she has previously had three or four failed or successful cycles of IVF.

Laparoscopic ovarian diathermy is proven to increase pregnancy rates in PCOS but this therapy can cause ovarian adhesions, causing obstructive infertility. Each laser burn destroys thousands of primordial follicles, and laparoscopic ovarian diathermy is followed by a fall in markers of ovarian reserve.

There do not appear to be any long-term studies of ovarian function after laparoscopic ovarian diathermy. This treatment should only ever be used to achieve conception, and only when other non-invasive therapies have failed.

Figure 10: Reduction in incidence of miscarriage by use of metformin.

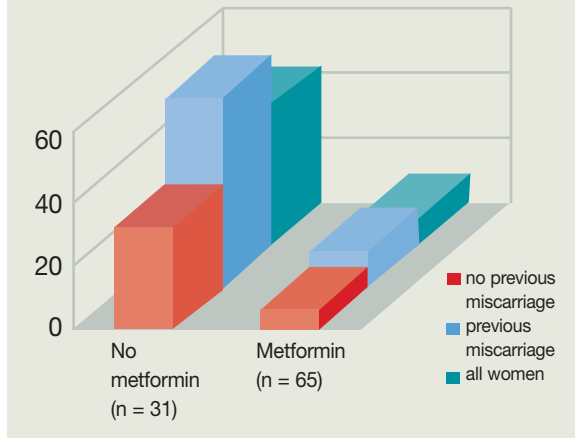
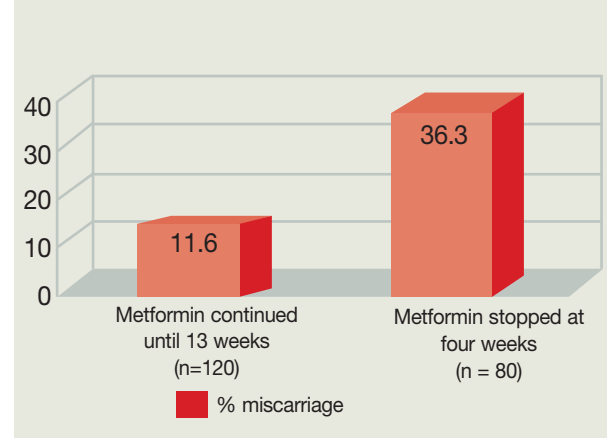


Figure 11: Miscarriage rates with cessation or continuation of metformin.



Management of pregnancy in PCOS

Pregnancy in women with PCOS carries a very high risk of miscarriage and gestational diabetes, often as early as 10-20 weeks. A glucose tolerance test should be performed at both 12 and 24 weeks and the results compared with the woman's pre-pregnancy glucose tolerance test. Vitamins D and B12 should be checked in early pregnancy.

Continuation of metformin through the first trimester reduces the risk of miscarriage by up to 80% (figure 10).

As metformin also improves egg quality in IVF, it was thought the reduced incidence in miscarriage with use of metformin was a pre-conception effect only. A study comparing outcomes when metformin was either discontinued at diagnosis of pregnancy or continued until 13 weeks confirmed a definite intra-pregnancy benefit (figure 11).[1,2]

Patient support

The Polycystic Ovary Syndrome Association of Australia and the Jean Hailes Foundation for Women's Health (see Online resources, above) provide educational and emotional support for women frustrated by PCOS.

Summary

KNOWLEDGE of the causes of PCOS and hypothalamic menstrual disturbances has increased over the past 15 years, leading not only to simpler therapies but to an awareness of the long-term health issues likely to afflict these women.

Women with these problems should be educated about their predicament and given every opportunity to be involved in decisions regarding their treatment.

The management of PCOS, like that for type 2 diabetes, requires multiple skills, including gaining knowledge of a woman's past health, emotional issues and career and family history, and the ability to implement lifestyle changes and stress reduction. As in type 2 diabetes, a woman's GP, more than any other health professional, is the practitioner best equipped to manage this increasing problem.

Author's case study

MS GA presented at age 24 with a history of excess facial hair from age 19. Menarche occurred at 12 years and the cycle was always regular.

Physical examination revealed a moderate increase in hair growth on the face, neck and legs and a mild increase in hair growth on the lower abdomen.

There was no acne or other abnormal findings. The patient was mildly overweight at 56kg and height was 153cm. BP was 140/80mmHg.

Investigations revealed normal values for testosterone, androstenedione, DHEA, DHEAS and 17-hydroxyprogesterone. SHBG was low (20nmol/L) and free androgen index was elevated at 7.1 (NR 0.37-03.41).

LH was markedly elevated compared with FSH (27 and 5.0mIU/L, respectively). Pelvic ultrasound revealed polycystic ovaries. A diagnosis of PCOS was confirmed.

GA had previously suffered menorrhagia when using spironolactone and was averse to the use of hormonal contraceptives as treatment for her hirsutism, which therefore remained untreated.

At age 26 she suffered an acute abdomen from a ruptured ovarian cyst. Her cycle varied between 30 and 38 days.

At age 30 GA returned some time after marriage because her cycle had lengthened to two-monthly. Her weight had increased to 65kg. The importance of diet and exercise was stressed. Repeated progesterone measurements were low, indicating anovulatory cycles. Ovulation was induced with clomiphene but conception did not occur.

At age 32 GA was referred for IVF and a glucose tolerance test diagnosed type 2 diabetes, with a two-hour glucose level of 12.5mmol/L (fasting glucose was 5.8mmol/L). Metformin was started and the importance of diet and exercise was stressed. Weight fell by 3.5kg and glucose values were typically between 4.7 and 8.2mmol/L, with an HbA_{1c} of 5.7%.

By age 38 GA had had 16 unsuccessful attempts at IVF, with only one pregnancy, which miscarried. She had steadfastly refused to exercise from the time of diagnosis of diabetes. After explanation of the benefits of exercise to GA's husband, he took her walking every evening. GA conceived at age 39 on her 17th IVF cycle.

GA's pregnancy was complicated by hypertension, treated with labetalol. Her diabetes remained well controlled on metformin 2200mg daily. A healthy daughter weighing 2.2kg was delivered by caesarean section at 38 weeks.

At age 40 GA asked what form of contraception I would recommend. I advised her that she was extremely unlikely to conceive at 40, having failed 16 cycles of IVF, and that I did not feel that contraception was necessary.

However, she presented just before her 41st birthday 6.5 weeks spontaneously pregnant. She had had much more physical exercise caring for her 15-month-old daughter than ever before. Her weight had fallen to 55.5kg, the lowest for years.

Her diabetes required insulin therapy during the second pregnancy, which was uncomplicated. Her healthy son was born at 38 weeks by caesarean section, weighing 2.5kg. GA and her husband were delighted with the outcome.

This case illustrates the dramatic effect that physical exercise and weight loss have on infertility in PCOS and highlights the necessity of regular glucose tolerance testing in women with PCOS, irrespective of age.

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GP's contribution

DR CELINA RAPPAPORT
Sydney CBD, NSW

Case study

MIA, a nurse aged 24 presented for a general check up complaining of increasing vaginal discharge that had become bloodstained. She had not been sexually active in the previous six months and had always used condoms. Menses were regular at 3/28-30 days and heavy for the first two days.

Vaginal swabs grew heavy gardnerella and moderate candida but cervical chlamydia PCR was negative. She requested fasting bloods. Lipids and TSH were within normal limits, BSL was 4.7mmol/L, Hb was 130g/L, ferritin was 7µg/L and vitamin D was 40nmol/L.

She used Zidoval cream PV, and started on vitamin D supplements, as she was doing night shifts in a palliative care hospital.

Mia returned five months later complaining of intermittent PV loss, sometimes red, sometimes pink, in between her regular cycles. She mentioned that she was suffering from anxiety and had trouble falling asleep, lacked motivation and energy. She had joined the local gym but was struggling to get there.

Pap smear was negative but pelvic ultrasound showed a normal-sized uterus with endometrial thickening measuring up to 24mm. Left ovary measured 8.2mL with a 2cm cyst, and the right ovary was 16.1mL with a polycystic appearance. A repeat FBC revealed Hb had dropped to 111, and her ferritin remained low at 7µg/L.

She was referred to a gynaecologist and subsequently had a hysteroscopy and uterine biopsy. She was also referred to a nutritionist for dietary advice, as her weight in 2007 was 59.6kg (BMI 22.7) and had risen to 67.1 in four years (BMI 25.5)

Past history included asthma as a child, and atopic eczema (her allergist had noted 'pigmentation' in her axilla and neck due to her chronic eczema).

Mia had never been on the pill, and there was no known family history of diabetes, vascular or fertility problems. Menarche was at 14 followed by regular 3-4/30-day menstrual cycle. She had never had acne. Although she noticed she had 'hairy legs' she never worried about it.

Progress: endometrial curettings showed functional endometrial polyp and late secretory phase endometrium. SHBG was 25nmol/L (normal range 30-110) and her LH and FSH were in the normal range as was the testosterone and free androgen index.

Questions for the author

Here we have an overweight woman with regular, heavy menstrual cycles, with a low vitamin D level, iron-deficiency anaemia, insulin resistance (low SHBG), normal fasting BSL endometrial hyperplasia, depression and a polycystic-looking ovary. Does Mia have PCOS or a hypothalamic cause for her symptoms?

Mia most likely has PCOS rather than a hypothalamic disorder, in view of the low SHBG, endometrial hyperplasia and skin pigmentation.

Should she have a formal glucose tolerance test ?

All women with PCOS should have this test, even if not obese, as a fasting glucose will miss 65% of those who already have diabetes, and will not detect anyone with impaired glucose tolerance.

Should she go on the pill to avoid anaemia and subsequent endometrial hyperplasia/ endometrial polyps? Or will she be at risk of deterioration in her glucose tolerance?

Most women with PCOS will develop regular ovulatory cycles about 4-6 months after starting exercise and metformin, so that future endometrial hyperplasia will not be a problem.

However, heavy irregular bleeding may continue before achieving this result, and a woman may need to be on the pill for six months. Anaemia can exacerbate lethargy and make establishing a regular exercise program difficult. The pill should be withdrawn after six months or the test repeated to check that glucose tolerance has not deteriorated on the pill.

Despite starting to exercise at the gym, and modifying her diet, Mia's weight isn't shifting. Is this the right time to add in metformin?

Yes. I start metformin with diet and exercise, to facilitate weight loss rather than cause Mia more frustration.

Metformin can be withdrawn once weight loss has been achieved, although weight will increase again if exercise is not continued.

General question for the author

In women with PCOS, the pill has been found to cause deterioration in glucose tolerance. Extrapolating from that, should perimenopausal and menopausal women with a past history of PCOS/ hypothalamic amenorrhea avoid HRT?

Perimenopausal and menopausal women with a past history of hypothalamic amenorrhoea should be offered HRT, as they will most likely have reduced bone mineral density.

Several studies have shown that HRT improves insulin resistance.

This paradoxical situation suggests that either hormone deficiency has a greater effect on insulin resistance than the suppressive doses in hormonal contraception, or that menopausal oestrogen deficiency leads to reduced muscle strength or reduced mental drive for exercise. A past history of PCOS is not a contraindication for HRT.

How to Treat Quiz

Polycystic ovary syndrome — 24 June 2011

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY
www.australiandoctor.com.au/cpd/ for immediate feedback

1. Which TWO statements are correct?
a) Oligo-ovulation without clinical androgenisation excludes a diagnosis of polycystic ovary syndrome (PCOS)
b) A diagnosis of PCOS requires the exclusion of endocrine tumours and hypothalamic causes
c) The presence of polycystic ovaries is necessary for a diagnosis of PCOS
d) PCOS and hypothalamic menstrual disorders may coexist

2. Which THREE statements are correct?
a) The menstrual and androgen disorders in most women with PCOS are caused by insulin resistance and compensatory hyperinsulinaemia
b) Obesity is the primary cause of the insulin resistance of PCOS
c) PCOS is caused primarily by genes that result in insulin resistance
d) The genes that cause PCOS allow hyperinsulinaemia to inhibit follicular development and ovulation

3. Which TWO statements regarding PCOS are correct?
a) The genes that cause PCOS allow hyperinsulinaemia to stimulate ovarian and adrenal androgen production
b) Insulin facilitates fat breakdown and weight loss
c) Insulin-resistant men tend to seek food despite adequate energy intake
d) The increased risk of endometrial carcinoma in women with PCOS is entirely attributable to increased oestrogen unopposed by progesterone

4. Which TWO statements are correct?
a) Women with PCOS have increased risks of type 2 diabetes, gestational diabetes and vascular disease
b) Hypothalamic menstrual disorders are not associated with the development of ovarian cysts
c) The bone loss that occurs with hypothalamic amenorrhoea is primarily due to reduced oestrogen levels
d) Stress-related hormones and neurotransmitters inhibit the hypothalamic GnRH pulse generator

5. Which TWO statements are correct?
a) Inhibition of the GnRH pulse generator can occur with any cause of severe weight loss, depression, excessive physical training or extreme work stress
b) Frequent or heavy uterine bleeding excludes PCOS
c) Recent onset of amenorrhoea and/or androgen effects following a normal menarche and regular cycles is typical of insulin resistance
d) Hirsutism since childhood may be due to insulin resistance or congenital adrenal hyperplasia

6. Which TWO statements are correct?
a) Pelvic ultrasound should be routinely performed in all women with suspected PCOS
b) Women with heavy bleeding or pelvic pain and possible PCOS should be investigated with pelvic ultrasound
c) The LH/FSH ratio should be used to make a diagnosis of PCOS
d) Reduced levels of sex-hormone-binding globulin (SHBG) are a good indicator of insulin resistance in patients not using hormonal contraception

7. Which TWO statements are correct?
a) Women with androgenic skin problems due to PCOS may have normal testosterone levels and normal free androgen index
b) In women with PCOS, fasting glucose level is an accurate measure of impaired glucose tolerance or type 2 diabetes
c) In insulin-resistant women, regular exercise can lower insulin levels into the normal range
d) Oral contraceptives and ovulation induction address the longer-term health problems (diabetes, vascular disease) associated with PCOS

8. Which TWO statements are correct?
a) The insulin resistance of PCOS can be improved by physical activity, weight loss and insulin sensitisers
b) Aggravating factors for insulin resistance include stress, depression, or hormonal contraception
c) Moderate physical activity does not improve blood glucose and insulin sensitivity in the short term
d) Weight loss can usually be achieved in PCOS with diet alone

9. Which TWO statements are correct?
a) Metformin is used in PCOS primarily to reduce glucose levels
b) Ovulatory cycles and conception are typically achieved within two months of starting metformin
c) Acne and rosacea will mostly clear or improve significantly after 3-4 months of metformin therapy in combination with diet and exercise
d) Metformin can lower vitamin B12 levels, which should be checked every six months

10. Which TWO statements are correct?
a) Metformin is effective in normalising insulin levels, independent of weight loss and exercise
b) Metformin should be discontinued as soon as the woman conceives
c) The pill can cause deterioration in glucose tolerance in women with PCOS
d) The anti-androgen cyproterone should be used at a dose of 50mg daily and co-prescribed with a contraceptive pill

CPD QUIZ UPDATE

The RACGP requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2011-13 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education

HOW TO TREAT Editor: **Dr Giovanna Zingarelli**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Giovanna Zingarelli**

NEXT WEEK The next How to Treat tackles child and adolescent obesity. The authors are **Dr Shirley M Alexander**, staff specialist; **Professor Louise A Baur**, consultant paediatrician; **Susie Burrell**, weight management dietitian; **Kerryn Chisholm**, weight management dietitian; **Joanne Henderson**, weight management clinical nurse consultant; **Ronalda Hoffman**, senior social worker; **Sophie Knott**, physiotherapist; **Gerri Minshall**, weight management clinical psychologist; **Dr Srinidhi JV Rao**, weight management registrar; and **Susan Sampson**, clinical nurse consultant — all from the Children's Hospital at Westmead, Sydney.