The unfolding story of polycystic ovary syndrome

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Dramatic changes are afoot in the management of PCOS in light of our increasing knowledge of the pathophysiology and long term natural history of the condition.

Polycystic ovary syndrome (PCOS) is the most common endocrine problem in women, occurring in 5 to 10% of premenopausal women. The syndrome is difficult to define as it has a spectrum of presentations. Its natural history is uncertain and it has a complex pathophysiology, which largely remains elusive.

Until recently, PCOS was thought to be specific to the gynaecological arena. Now it is recognised that this disorder is associated with insulin resistance in 30 to 60% of cases (varying in different racial groups). The risk of progression to abnormal carbohydrate metabolism and type 2 diabetes is starting to be evaluated, as is antidiabetogenic therapy (oral hypoglycaemics) for both prevention and treatment. Although our understanding is still in its infancy, an exciting new area of preventive health is opening up.

What is PCOS?

PCOS has a heterogeneous clinical picture, characterised by the association of chronic anovulation and menstrual irregularity, obesity and hyperandrogenism (without a specific underlying disease of the adrenal or pituitary glands).

Table 1 shows the distribution of symptoms characteristic of PCOS (found singly or in combination) in the large UK study by Balen and colleagues of 1741 women with polycystic ovaries (PCO) on ultrasound.[1] The European (including UK) literature defines PCOS as the characteristic ultrasound appearance in combination with one

IN SUMMARY

- **Polycystic ovary syndrome (PCOS) is the commonest endocrine problem for women, occurring in 5 to 10% of premenopausal women.**
- **A 'polycystic ovarian' ultrasound pattern occurs as an incidental finding in about 20% of the normal female population.**
- **PCOS is a heterogenous clinical picture, characterised by the association of menstrual abnormality (due to chronic anovulation), obesity and hyperandrogenism.**
- **About 40% of women with PCOS are obese. Weight loss is the first line of therapy for regulating menstruation, reducing body hair in hirsutism and inducing ovulation in fertility therapy.**
- **About 30 to 60% of women with PCOS have insulin resistance and hyperinsulinaemia, and are at risk of developing type 2 diabetes mellitus.**
- **Although there is much observational evidence, there is, as yet, no definitive high quality evidence to support the use of metformin in treating PCOS. Definitive studies are needed to assess its use in anovulation, and for women with androgen excess and vascular risk factors.**

or more of the criteria listed in Table 1. The US literature uses a tighter definition, requiring the combination of menstrual irregularity and hyperandrogenism, and does not utilise ovarian morphology.

The most severe example of PCOS is the Stein–Leventhal syndrome. In 1935, Stein and Leventhal described the abnormal ovaries, enlarged and sclerocystic, relating to a clinical syndrome consisting of 'menstrual irregularity, featuring amenorrhoea, a history of sterility, masculine type hirsutism, and less consistently, retarded breast development and obesity'.[2]

It is now thought that there is a continuum or spectrum of presentations ranging from the most severe, as just described, to the asymptomatic or 'normal' woman, who only has the characteristic PCO appearance on ultrasound. This incidental ultrasound finding is present in approximately 20% of the normal population (16 to 33% of studied populations). It is likely that genetic factors, as yet to be well defined, place a woman in this spectrum. A trigger, perhaps increased food intake and obesity, hyperandrogenism or decreased physical activity, may push her from an ovulatory balance into a situation where PCOS is expressed.[1] Movement is thought to occur in both directions along this spectrum.

The anovulatory state of PCOS manifests with a range of clinical presentations – irregular heavy menses, amenorrhoea and hirsutism. The serious consequences of anovulation are infertility and a threefold risk of developing endometrial cancer. Several clinical series have reported an association of endometrial carcinoma with PCOS. Discussion of infertility in PCOS is beyond the scope of this article.

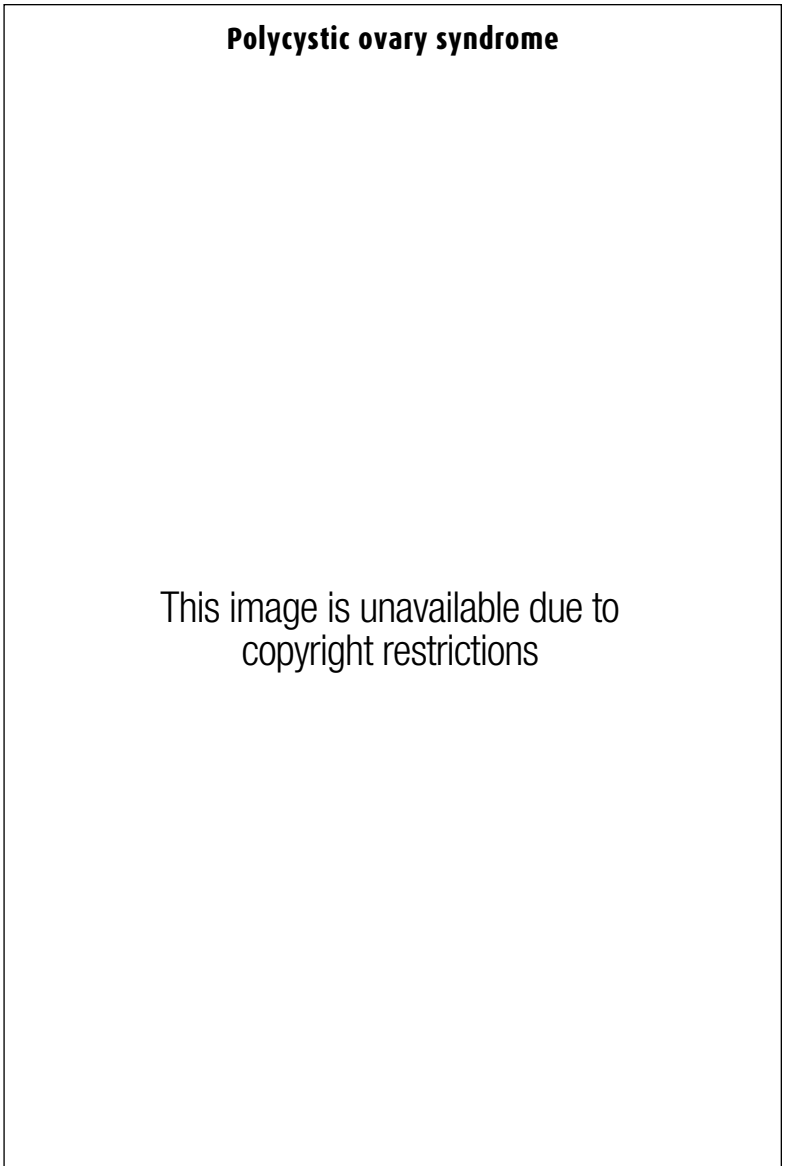
With the new appreciation of the role of insulin resistance comes an understanding of the increased risk of developing type 2 diabetes. Obesity is often difficult to manage. An increased risk of developing premature cardiovascular

Table 1. Prevalence of PCOS symptoms in a UK study[1]

• Polycystic ovaries on ultrasound	100%
• Menstrual cycle disturbance	66%
• Amenorrhoea	19%
• Obesity	38%
• Infertility	20%
• Hyperandrogenism (hirsutism, acne)	70%
• Raised serum luteinizing hormone	38%
• Raised serum testosterone	29%

(n=1741 women)

Polycystic ovary syndrome



Polycystic ovary syndrome, the commonest endocrine problem for women, is a heterogenous clinical picture characterised by the association of menstrual abnormality (due to chronic anovulation), obesity and hyperandrogenism.

disease has been postulated, but there is not yet epidemiological evidence of this.

Acne is seen in about one-third of PCOS patients. The severity correlates with the increased sebaceous secretion stimulated by the increased androgenic environment.

There is no evidence to date to suggest a greater risk of breast cancer in women with PCOS than in the general population.

Insulin resistance and long term health in PCOS

The most exciting and indeed revolutionary change in direction of thinking about PCOS was initiated by Burghen, Givens and Kitabchi's work in 1980.[3] In their study of women with PCOS, most were found to be hyperinsulinaemic and to have a glucose metabolism resistant to the stimulatory effects of insulin. This has had many repercussions relating to the understanding of the pathophysiology of PCOS, and for the treatment and long term health of sufferers.

The model to date in PCOS is that insulin resistance, the reduced glucose response to a given amount of insulin, occurs mainly in muscle (as in type 2 diabetes), but is also present in the liver in obese PCOS women. Insulin resistance leads to hyperinsulinaemia because insulin secretion rises to maintain normal glucose levels. The hyperinsulinaemia may then stimulate lipid storage and alter lipoprotein and cholesterol metabolism. Hyperinsulinaemia has also been shown to stimulate ovarian androgen production, as the ovary retains its sensitivity to insulin. However, because PCOS is a heterogeneous condition defined by a symptom complex, not all women with PCOS have insulin resistance and fit into this model.

Women with PCOS and hyperinsulinaemia have largely been shown to have a high prevalence of hyperlipidaemia (elevated cholesterol and triglycerides) and decreased HDL-cholesterol levels. Although a progression with time to type 2 diabetes in women with PCOS has been shown,[4,5] evidence showing an increased prevalence of hypertension is more tenuous. These features of PCOS, i.e. hyperlipidaemia, central obesity and asymptomatic impaired glucose tolerance, are very similar to the metabolic syndrome or syndrome X, where patients are known to have an increased risk of developing hypertension, type 2 diabetes and ischaemic heart disease.

Cardiovascular disease

Of great hypothetical concern for women with PCOS is the presence of risk factors for cardiovascular disease – hyperlipidaemia, hyperinsulinaemia and central obesity. In a retrospective cohort study of 33 Swedish women with PCOS reviewed up to 30 years later, Dahlgren and colleagues estimated a sevenfold increase in developing myocardial infarction for the whole cohort between ages 40 and 61 years.[5] In a study by Birdsall and colleagues of women aged less than 60 years with ischaemic heart disease, coronary angiography showed that 46% of all the women with a significant abnormality had PCOS.[6]

Despite these preliminary studies and the initial hypothesis that women with PCOS are at greater risk of developing cardiovascular disease, the most definitive study to date does not support an increased mortality rate from circulatory disease. This study, by Pierpoint and colleagues, looked at 786 women diagnosed with PCOS in the UK between 1930 and 1979 and followed up for an average of 30 years.[7] No significant increase in mortality rate from circulatory disease was found, and the mortality from all causes was no higher than the national rate for women of the same age.

Type 2 diabetes

As mentioned earlier, it is well recognised that insulin resistance, and the resultant hyperinsulinaemia, is the underlying disorder of PCOS in many women, and that women with PCOS are believed to have an increased risk of type 2 diabetes. However, there is a paucity of longitudinal studies. Epidemiological evidence is from the two long term studies of Dunaif and Dahlgren.[4,5] Dahlgren's study showed that 15% of the group of 33 Swedish women with PCOS developed type 2 diabetes, compared with 2.3% of controls. Norman and Clark, in a recent prospective study from Adelaide, showed that women with PCOS convert from initially normal glucose tolerance to impaired glucose tolerance or type 2 diabetes at a rate of approximately 3% per year (30% in 10 years).[8]

Interestingly, although Pierpoint's study showed no increase in the mortality rate in women with PCOS compared with the national rates for women, type 2 diabetes is mentioned as an underlying and contributory cause of death with an elevated odds ratio of 3.6 (6 *v.* 1.7 deaths: p=0.002). The extent that type 2 diabetes contributes to morbidity and mortality in women with PCOS is as yet unclear (it is also not known how many women with type 2 diabetes have PCOS). It is well known that increased obesity is associated with an increased risk of glucose intolerance and type 2 diabetes. However, the extent to which PCOS contributes to glucose intolerance, apart from obesity, is also not known.

Genetic basis of PCOS

The search for candidate genes for PCOS continues. The task is limited by the diverse clinical presentation of PCOS, the lack of a secure male phenotype and the failure to agree on a definition. These factors suggest a multigenic disorder with varying penetration. The literature suggests that PCOS clusters in families, with a gene or group of genes linked to a PCOS susceptibility.

Genes being investigated include those involved in steroid hormone synthesis and action (e.g. the gene in androgen

biosynthesis at CYP11A, the cholesterol side chain cleavage gene at CYP19, the gene encoding P450 aromatase, and at the follistatin locus) and those involved in the secretion, action and signalling of insulin (e.g. *insulin* VNTR).

Investigating PCOS

The main investigative tests used in assessing PCOS are listed in Table 2.

Ultrasound

PCO is a well defined and recognised ultrasound entity (Figure 1). Ultrasound shows an enlarged ovary with a circlet or necklet of small follicles around the periphery (at least 10 follicles, each 2 to 8 mm in diameter), which correspond to subcapsular follicular cysts. The stromal echogenicity is increased. The ovarian pattern can be difficult to view transabdominally, especially with obese individuals, and the transvaginal approach is, therefore, preferable. Results will vary with the radiologist's experience in gynaecological practice.

PCO ultrasound findings are also seen where there is incomplete follicular development, such as in early to mid-adolescence, or failure to ovulate, such as in hyperprolactinemia, increased adrenal androgen production, bulimia and recovery from anorexia nervosa.

Obesity

About 30 to 50% of women with PCOS are obese. It is useful to try to quantify the degree of obesity as a baseline measurement. The most commonly used measurement of obesity is the body mass index (BMI), i.e. weight in kg/square of the height (in metres). This correlates fairly well with body fat, apart from at the extremes of height. An elevated BMI correlates with an increased rate of hirsutism, cycle disturbance and infertility.

An increased waist to hip ratio (WHR) is associated with PCOS, and also with visceral obesity and the metabolic syndrome.

Oligomenorrhoea and amenorrhoea

About 65% of women with PCOS will have menstrual irregularity because their normal menstrual cycle, with its exquisitely regulated follicular and ovulatory mechanism, will have been knocked out of kilter. However, the converse is that about 35% of women with PCOS will have a regular cycle.

An elevated luteinizing hormone (LH) level is pathognomonic of PCOS. The follicle stimulating hormone (FSH) level remains at a normal level. The LH and FSH levels are best reviewed in the hormonal nadir of the menstrual cycle, preferably on day two of the cycle (if periods are occurring). From a fertility point of view, a mid-luteal serum progesterone elevation confirms ovulation. As ovulation is 14 days before the following period, the traditional 'day 21 serum progesterone level' may be too early to confirm ovulation in a long cycle: a day 28 or day 35 level may be more useful. A serum prolactin level is worth performing as hyperprolactinaemia can cause both oligomenorrhoea and anovulation.

Amenorrhoea is present in about 20% of women with PCOS. Other causes, such as hyperprolactinaemia, weight, stress, medications, premature menopause and, rarely, hypothalamic–pituitary causes, need to be excluded. (It is also worth measuring the beta human chorionic gonadotrophin [β-hCG] level, just in case of pregnancy.) Specialist referral is advisable.

Table 2. Investigations in PCOS

- Pelvic ultrasound
- Weight, body mass index and waist–hip ratio
- Cycle day two LH and FSH; serum prolactin; mid-luteal progesterone and rubella serology in the infertile patient
- Serum testosterone; DHEAS; sex hormone binding globulin and free androgen index
- Two-hour oral glucose tolerance test with insulin levels
- Fasting serum lipid levels

Hyperandrogenism

Review of serum testosterone and dehydroepiandrosterone sulfate (DHEAS) levels allows screening for testosterone-producing tumours, congenital adrenal hyperplasia and Cushing's syndrome. The free androgen index (FAI), the ratio of total testosterone to sex hormone binding globulin (SHBG), is a measure of testosterone physiological activity and a useful clinical benchmark.

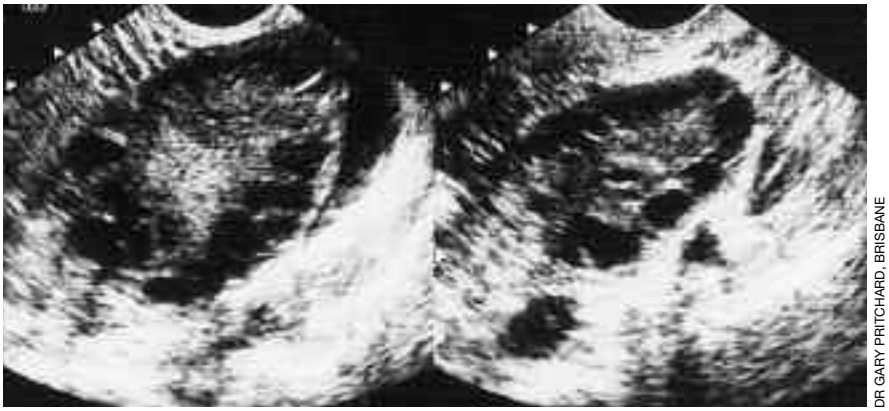


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Figure 1. The typical polycystic ovarian ultrasound pattern, showing small follicles around the periphery of each ovary corresponding to subcapsular follicular cysts, and increased stromal echogenicity.

Hyperinsulinaemia

It would seem reasonable to screen all women with PCOS for carbohydrate intolerance and hyperinsulinemia, so that appropriate management can be instituted.

Insulin levels taken during the oral glucose tolerance test (GTT) (fasting, and at one and two hours) will detect most insulin-resistant women. Kidson suggests that women with PCOS should have an oral GTT at diagnosis and at five-yearly intervals.[9] He also suggests that the parents of women with PCOS should have a GTT, and that a woman's siblings' glucose tolerance should be tested if a parent is shown to be diabetic.

Hyperlipidaemia

Screening is suggested for the conventional vascular risk factors – smoking, hypertension, sleep apnoea and hyperlipidaemia.

Management

Abnormal uterine bleeding

The persistently mildly elevated oestrogen, which is unopposed due to anovulation, stimulates a disordered build-up of the endometrium in PCOS, resulting in abnormal bleeding that ranges from amenorrhoea to heavy and irregular bleeding.

Both cyclic progesterone and the low dose oral contraceptive pill provide a progestogenic effect aimed at producing a stable secretory endometrium with regular withdrawal bleeding. Endometrial hyperplasia and carcinoma must be excluded before treatment is initiated. The endometrium can be evaluated with ultrasound, where an increased endometrial thickness is found in endometrial hyperplasia and carcinoma. If the ultrasound is abnormal, definitive histology is indicated with uterine curettage. In young women, where contraception is desired, the use of an oral contraceptive is the better choice, as sporadic ovulation can occur. Gynaecological referral is helpful.

Low dose oral contraceptives have a minimal effect on carbohydrate metabolism and most hyperinsulinaemic, hyperandrogenic women can be expected to respond favourably to treatment. However, a recent uncontrolled study showed a deterioration in glucose tolerance with the use of a combined oral contraceptive containing desogestrel, suggesting the need for further evaluation of specific oral contraceptives in PCOS. Serial review of glucose tolerance in hyperinsulinaemic women is recommended.

Obesity

Considerable evidence shows that weight loss in women with PCOS can lead to the return of menses, ovulation and fertility. Usually a weight loss of 5% or greater (not even requiring loss into the normal range) will produce regular menstruation and also reduce plasma androgens, decrease serum insulin and increase SHBG. The problem for these women is that weight loss is difficult to maintain and dietary modification can be a difficult long term solution.

Some hope is raised, however, from Clark and colleagues' work in a group of women with PCOS attending an Adelaide infertility clinic, where the emphasis was on lifestyle management rather than diet.[10] Women were encouraged to join a weekly group for six months. Gentle exercise was undertaken for one hour and in the second hour, dietary and medical advice were combined with other interesting activities and group discussions. There was a dramatic improvement in menstrual patterns in more than 90% of the obese, oligomenorrhoeic women undergoing this lifestyle modification program – and 40% conceived spontaneously. In most of the women, weight loss has been sustained.

Hyperandrogenism

Acne

Mild acne is usually treated topically with keratolytics such as azaleic acid (Acnederm Medicated Lotion, Skinoren) or with antibacterial agents such as clindamycin 1% lotion (ClindaTech, Dalacin T), erythromycin 2% gel (Eryacne 2%), and benzoyl peroxide. More severe acne requires oral antibiotics (tetracyclines, erythromycin and trimethoprim [Alprim, Triprim]) and retinoids. Isotretinoin produces long term remission in more than 70% of the most severe cases of acne, but is teratogenic and requires adequate contraception.

Antiandrogens such as spironolactone (Aldactone, Spiractin) and cyproterone acetate (Andocur, Cyprone, Procur) are indicated in women with a marked premenstrual accentuation of acne or when antibiotic treatments have failed.

Some oral contraceptive pills can exacerbate acne. To lessen this, use of a combined pill that is higher in oestrogen and lower in progestogen is suggested (with a preference for the progestogen to be cyproterone acetate [Diane-35, Brenda-35, Juliet-35], desogestrel [Marvelon 28] or norethisterone [Brevinor, Norimin]).

Hirsutism

Weight loss by obese, hirsute women often leads to a reduction in body hair growth and should be attempted before any drug therapy is instituted.

Physical removal of excessive hair is the easiest and most common method of treatment, although ongoing and repetitive treatment is required. Shaving, plucking, depilatory creams, bleaching, electrolysis and laser treatments may be used. Electrolysis is a proven method of hair removal, but is very operator dependent and folliculitis, hyperpigmentation and scarring are not uncommon. Laser treatment often requires several treatments to give acceptable results and with the available lasers, hair is not destroyed permanently. Side effects of laser treatment include erythema, hyper- and hypopigmentation, blistering and pain.

The antiandrogens cyproterone acetate and spironolactone suppress hair growth, but need to be taken long term. They will not affect the terminal hair already

present and an effect is not seen until after six months of continuous use. Cyproterone acetate antagonises the androgen receptor in the skin and acts as a weak progestogen. It is usually taken in the contraceptive pill formulation Diane-35, Brenda-35 or Juliet-35, or at a higher dosage in a reverse sequential regimen with cyclical oestrogen therapy. Specialist referral is recommended. Side effects include weight gain, gastrointestinal upset, headache and depression. As there is a risk of emasculating the male fetus, a contraceptive regimen must be used.

As an initial treatment, Diane-35 and Marvelon 28 (which contains desogestrel) have been shown to be effective in treating hirsutism.[11,12] Contraceptives containing an increased dose of norethisterone or levonorgestrel may exacerbate hair growth.

The oral aldosterone antagonist spironolactone acts by interfering with testosterone production and decreasing 5-alpha-reductase (which converts testosterone into the more active metabolite, dihydrotesterone at the level of the hair follicle). It is used daily at a dosage of 100 to 200 mg per day, with or without the oral contraceptive pill, and does not cause weight gain nor depression, although it can produce menstrual irregularity, gastrointestinal disturbance, headache and breast tenderness. Ovulation may be restored with the use of spironolactone and this must be considered beforehand. Due to its potassium-sparing diuretic effect, hyperkalaemia may be a risk if it is combined with a potassium-sparing diuretic, ACE inhibitor or NSAID.

Hyperinsulinaemia – the emerging role of metformin

In the past 10 years, many nonrandomised studies in women with PCOS have shown that the antidiabetogenic agent metformin improves insulin resistance, decreases serum insulin and androgen levels, and increases SHBG. The findings were not universal, usually short term (studied over periods of four to six months) and influenced by the degree of obesity. Two randomised studies have supported these findings, and two others have found no difference. Three randomised, placebo-controlled studies found metformin to induce ovulation in a significant number of obese, anovulatory, PCOS women.[13] Another, however, found it had no effect on ovulation.[14] Although evidence seems to be mounting in favour of metformin, this is only at a lower and less convincing level of evidence. High quality evidence at the level of randomised control (or above) is preliminary and in conflict, and to date does not support the use of metformin.

Metformin has gastrointestinal side effects, including diarrhoea and vitamin B_{12} malabsorption. The serious side effect of lactic acidosis, seen in diabetes, has not been described in PCOS.

The working group set up by the Endocrine Society of Australia, the Australian Diabetes Society and the Australian Paediatric Endocrine Group suggests that the literature 'supports a trial of metformin in patients with anovulation, androgen excess and vascular risk factors, as these abnormalities may be reduced'.[15] The group also notes that the long term effects of treatment with metformin on vascular risk factors, morbidity and mortality are unknown. It must be emphasised that the long term 'natural history' of PCOS, its morbidity and mortality, is also unknown because of the limited epidemiological data available. The same working party also states, 'Given the present lack of long term safety data and demonstrable efficacy in a large number of patients, we recommend that metformin use be supervised by an endocrinologist or physician with expertise in the area.'

Before widespread use of metformin in PCOS is accepted, there is an urgent need for more clinical trials to define its indications in appropriate subgroups of women with PCOS and its long term effects.

Hyperlipidaemia

Hyperlipidaemia should improve with the dietary and lifestyle modifications instituted for weight loss. If, however, it persists, referral for drug therapy is appropriate.

Conclusion

Increasing obesity correlates with an increased rate of cycle disturbance, infertility and hirsutism. Weight loss has been shown to improve menstrual patterns and decrease serum androgen and insulin levels, and is the first line therapy in these areas. Lifestyle modification involving dietary advice, exercise and weight loss has been shown to improve menstrual patterns in 90% of obese PCOS women.[10] Dietitian support and the use of commercial programs for weight reduction, lifestyle and exercise may be helpful.

We are moving into an unfolding and very exciting era in the understanding of the pathophysiology and long term natural history of PCOS, which has the potential to lead on to dramatic changes in management and health for women with this syndrome. MT

A list of references is available on request to the editorial office.

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