Polycystic Ovarian Syndrome

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Polycystic Ovarian Syndrome (PCOS) is a common but under-diagnosed endocrine and metabolic condition. First described in the 1930s and termed Stein Leventhal syndrome, PCOS has evolved from being considered a menstrual and cosmetic problem into a complex metabolic and hormonal imbalance.

Cause

Polycystic Ovarian Syndrome affects 5–10% of women and appears to be genetically determined. Family studies have demonstrated a high frequency of affected individuals leading to a hypothesis of autosomal dominant transmission. The diverse range of PCOS phenotypes suggest that inheritance may be polygenic. The insulin receptor gene is thought to be the likely culprit. Interestingly, men may also carry the gene(s) and may present with balding before the age of 40 years.

Pathogenesis

Many studies have implicated insulin resistance as the primary defect in women with PCOS. Theca cells within the ovaries are excessively responsive to the insulin leading to stimulation of androgen production. High levels of estrogen produced by the ovaries have a feedback effect on hypothalamic-pituitary function to stimulate LH secretion. The tonically high LH levels adversely affect ovulation and fertility. The insulin resistance may also alter glucose tolerance and weight management. (Table 1)

Weight gain may be excessive in 50% of women with PCOS leading to further androgen and insulin production from the adipose tissue.

Presentation

Polycystic Ovarian Syndrome has been traditionally considered a disorder of the reproductive years. However, evidence is emerging that signs of an imbalance may be present at other stages of our life. For instance, intra-uterine growth retardation, early puberty and the metabolic syndrome later in life may all represent manifestations of PCOS.

Hirsutism is considered the best marker of androgen excess in women, but studies have indicated that up to 85% of women with adult acne may have PCOS. This is likely to be the area where the bulk of under-diagnosis is seen.

Symptoms of PCOS

- *Acne.*
- *Hirsutism.* This can be present from soon after puberty but may become more obvious at menopause with the relative decline in estrogen.
- *Weight gain.* This tends to be distributed primarily about the abdomen creating an 'apple' shape rather than the typical female 'pear' shape.
- *Irregular periods.* It is estimated that 80% of women with oligomenorrhoea have PCOS. An important clinical point is often overlooked in women with regular periods. The presence of regular cycles does not mean that ovulation is reliably occurring. Up to 25% of women with regular periods may in fact be anovulatory.
- *Alopecia.* This is fortunately uncommon, affecting just 3% of women with PCOS. Hair loss is in an androgenetic pattern.
- *Infertility* as a result of irregular ovulation.

Longer-term complications include:

- *Type 2 diabetes.* There appears to be a 40% risk of either IGT or type 2 diabetes developing in women with PCOS. The progression from normal to abnormal glucose tolerance may be rapid. The risk of type 2 diabetes is greatest in those women who are anovulatory, obese and who have a family history of type 2 diabetes.
- *Endometrial hyperplasia.* This increases in frequency in anovulatory women due to unopposed estrogen exposure. Whether endometrial cancer is increased remains controversial.

There remains some debate over the connection between PCOS and other conditions such as coronary artery disease, miscarriage and pregnancy complications. The increased miscarriage rate seen in women with PCOS may reflect excessive body weight rather than the hormone imbalance itself. Research is currently underway to explore this further.

Table 1

Abnormality	Effect
Elevated androgens	Acne Hirsutism
Elevated estrogen	Dysfunctional bleeding Endometrial hyperplasia
Elevated LH	Anovulation Elevated prolactin
Insulin resistance	Metabolic syndrome

Diagnosis

Over the past two years, consensus conferences have reviewed the diagnostic criteria for this syndrome and new recommendations[1] have made the diagnostic process much clearer (Box 1).

It is important to remember that PCOS is a syndrome and therefore has no single diagnostic test. It is essential to exclude other conditions that may present with similar symptoms, particularly the late onset variant of congenital adrenal hyperplasia. This, apart from one marker hormone, is clinically indistinguishable from PCOS. Thyroid dysfunction, Cushing's syndrome or hyperprolactinaemia may be obvious from history taking and examination.

The following criteria are recommended for diagnostic purposes. Two of the three criteria are required.

- History of oligo- or anovulation
- Biochemical or clinical signs of hyperandrogenism
- Polycystic appearing ovaries on ultrasound scan.

In working through this process, several important caveats exist. An ultrasound scan may not show cysts in up to 40% of women with confirmed PCOS and so can be misleading. The scan is likely to be normal if performed in a woman taking the oral contraceptive pill. Furthermore the appearance of peripheral cysts may be seen in a number of endocrine conditions and is not specific for PCOS. It is useful to try to arrange the scan for the follicular phase of the menstrual cycle (preferably day 3–5) and to request a transvaginal approach to improve the chances of a positive result. One ovary fitting the definition is consistent with polycystic appearing ovaries.

Investigations should ideally be performed during the follicular phase of the cycle and in the morning. Even with perfect timing a small proportion of women with PCOS will have normal (usually high-normal) androgen levels.

Insulin is not recommended as part of the routine set of investigations.

A gynaecological examination is recommended if there has been erratic bleeding or if there is concern about virilisation. It is extremely useful to grade the hirsutism using a tool such as the Ferriman and Gallwey Index.[3] This index grades androgen-dependent hair growth on a 0–4 scale and gives an objective baseline assessment that can be used to monitor response to treatment.

Treatment[2]

Lifestyle

Attention to diet and exercise is a crucial part of managing PCOS. Input from our dietician colleagues can be very useful. Clinical studies have shown that a combination of cardio and resistance work is ideal for weight loss.

Cosmetic therapies

Electrolysis or laser hair removal are useful methods of reducing the hirsutism. Multiple treatments are required and cost may be prohibitive. Shaving, waxing and depilatory creams may also be helpful.

Combined oral contraceptive pill

This can be effective in regulating menstrual cycles and controlling acne. Androgen production from the ovaries is reduced and the increase in hepatic production of SHBG lowers the free testosterone and FAI levels. Recent clinical trials suggest that some oral contraceptives may adversely affect metabolic indices particularly in overweight women. At this stage no clear recommendations with regard to the most appropriate agent are available. Keeping an eye on the lipid profile and glucose levels after starting the oral contraceptive helps to identify those not responding as anticipated.

Anti-androgen therapy

Spironolactone, cyproterone acetate or flutamide are available in New Zealand. These agents have been extensively studied in short-term trials and are helpful with managing acne, hirsutism or alopecia. They have beneficial effects on metabolic indices particularly when used in combination with metformin. They should be used with appropriate contraceptive cover. Improvement in acne may be seen as early as 4–6 weeks after initiation of therapy. However reduction in hirsutism is slower over 12–18 months. Therapies will reduce androgenetic hair growth by an average of 80%.

Box 1

How to diagnose PCOS

- Exclude other hormone disorders

AND

- Satisfy 2 of the following 3 criteria:
  - Oligo- or anovulation
  - Clinical or biochemical evidence of hyperandrogenism
  - Polycystic appearing ovaries on pelvic ultrasound.

Table 2. The following is a suggested list of appropriate blood tests:

Test	Tips
Total testosterone	Increased in 75% of women
Free testosterone/free androgen index	Increased in 90-95%
LH/FSH ratio	>2 in 60-70%
Estradiol	Helps to exclude premature ovarian failure
Prolactin	Increased in 25-40%
17(OH) progesterone	Marker for late onset CAH. If >15 specialist referral is recommended
Oral glucose tolerance test	This is especially useful in overweight women in whom the fasting glucose level may be misleadingly normal.
Lipids	Helpful in the diagnosis of the metabolic syndrome.

Table 3

Drug	Dose	Side effects
Spironolactone	100–200mg daily	Diuresis, GI upset, hypotension, is a 'sulphur drug'
Cyproterone acetate	50mg daily for 10 days/month (with OC) ***OR*** 50mg daily with estradiol 2mg daily ***OR*** 50mg daily for 14 days with estradiol 2mg daily	Fatigue, irritability, alteration in liver function, low libido
Flutamide	250mg daily	GI upset, photosensitivity, urine discoloration, alteration in liver function

Progestin therapy

This can be considered in those women with menstrual dysfunction when the use of the oral contraceptive pill is inappropriate.

Metformin

The primary role for metformin is as an ovulation induction agent. Within six months of beginning metformin 80% of women with PCOS are ovulating more frequently and conception rates of 40–45% have been reported. It may be useful in helping control acne and trials have suggested a role in treating hirsutism. It has some impact on central adiposity when used in conjunction with an appropriate diet and exercise programme. Anti-androgen agents are frequently used with metformin to augment the metabolic benefits of metformin therapy. Lipid profile improves with treatment. However metformin's role in the prevention of long-term sequelae such as type 2 diabetes or coronary disease remains unclear. Increasingly evidence suggests it may be useful during pregnancy to reduce miscarriage risk, toxaemia and gestational diabetes. Further data are awaited to clarify this.

The glitazone family of drugs, used in the management of type 2 diabetes, have been shown to act as ovulation induction agents. However their safety in pregnancy remains unclear. The weight gain seen with these agents also limits their use in PCOS.

Clomiphene

This may be added to metformin to enhance conception rates or used alone. The risk of multiple pregnancies is 5–8%.

Ovarian drilling

Surgery has no role in the general management of PCOS but may be useful as adjunctive fertility treatment. As with older surgical techniques, such as wedge resection, adhesions and loss of ovarian tissue are important complications. The effect of ovarian surgery is short-lived. More dramatic surgery such as oophorectomy does not cure what is a systemic condition and should be avoided.

Follow-up

Women with PCOS require long-term surveillance. In addition to assessing the effects of treatment on skin and hair growth, review of metabolic indices such as lipid and glucose profiles, is helpful. Liver function should be monitored in those prescribed cyproterone or flutamide. Vitamin B12 levels may drop with metformin and potassium may increase with spironolactone therapy. An ultrasound scan should be considered in those women with persistent oligo-amenorrhoea to exclude endometrial thickening.

Key Points

- Polycystic-appearing ovaries may be seen in 20–25% of the female population. Polycystic ovary syndrome affects 5–10% of women.
- A range of menstrual, cosmetic and metabolic abnormalities occur in PCOS.
- PCOS is associated in the long-term with an increased risk of type 2 diabetes and endometrial hyperplasia.
- Symptoms may present at any stage of life but the diagnosis is usually made after puberty.
- Diagnosis depends on excluding other hormone disorders and then satisfying two of three consensus criteria.
- Effective therapies are available, including lifestyle changes and medications.

Conclusion

PCOS is a common endocrine disorder with important symptoms and long-term complications. It is almost certainly under-diagnosed and under-treated in our community. A range of effective therapeutic options are available and allow this condition to be well managed in general practice.

References

1. Rotterdam ESHRE/ASRM 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(1):19-25
2. Norman RJ, Wu R, Stankiewicz MT. MJA Practice Essentials. Polycystic Ovary Syndrome. MJA 2004 180:132-137.
3. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol 1961, 21:1440-1447

Useful resources

1. www.pcosupport.org (US-based PCOS Association)
2. www.jeanhailes.org.au (excellent Melbourne-based women's health site)