Polycystic ovary syndrome

Prevalence
PCOS is one of the commonest endocrinopathies in women, affecting 5–10% of women in the reproductive age worldwide. The prevalence tends to vary depending on ethnicity and the criteria used to define PCOS. In the United States, prevalence rates of 5–10% have been quoted. PCOS also appears to be commoner in Mexican-American than White or African-American women. It has also been reported that prevalence rates are higher in those with gestational diabetes, those who have premature adrenarche and in those with first-degree relatives who have PCOS. Prevalence data for PCOS in South Africans are not available.

Diagnosis
PCOS is in essence a diagnosis of exclusion once other ovulatory and androgen-excess disorders have been ruled out (Table I). Late onset 21 hydroxylase deficiency, androgen secreting neoplasms, drug induced hyperandrogenism and Cushing’s syndrome at most account for 10% of women with androgen excess.

Table I: Disorders that can mimic PCOS

| Androgen-excess disorders that can mimic PCOS |
|---------------------------------------------|
| 1. Late onset non-classic 21 hydroxylase deficiency |
| 2. Idiopathic hirsutism |
| 3. Syndromes of severe insulin resistance e.g. HAIR-AN syndrome |
| 4. Ovarian androgen-secreting tumours |
| 5. Use of anabolic or androgenic drugs |
| 6. Cushing’s syndrome |

| Ovulatory disorders that mimic PCOS |
|-----------------------------------|
| 1. Hypothalamic and pituitary disorders causing amenorrhoea |
| 2. Premature ovarian failure |

| Other disorders |
|-----------------|
| 1. Thyroid dysfunction |
| 2. Hyperprolactinaemia |

disorders need to be considered especially when chronic anovulation occurs (with PCOM) and overt androgen excess is absent. The WHO has divided anovulation into 4 categories:

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Class 1: Hypogonadotrophic hypogonadal anovulation

This accounts for about 10% of ovulatory disorders. Women have low to low normal FSH concentrations with low serum oestradiol concentrations due to decreased GnRH or pituitary unresponsiveness to GnRH.

Class 2: Normogonadotrophic normoestrogenic anovulation

This group accounts for 85% of ovulatory disorders. Women may secrete normal gonadotrophins and oestrogens but FSH secretion during the follicular phase is subnormal. This subgroup includes women with PCOS.

Class 3: Hypergonadotrophic hypogonadism

This is the smallest group (5% of ovulatory disorders). The primary causes are premature ovarian failure and ovarian resistance.

Hyperprolactinaemic anovulation

Increased prolactin levels inhibit gonadotrophins and oestrogen secretion. These patients may have regular anovulatory cycles or oligo/amenorrhoea. Their serum gonadotrophins are usually normal.

Hypothalamic amenorrhoea or functional amenorrhoea (HA), which falls into group 1, accounts for up to 48% \(^{16}\) of secondary amenorrhoea and is often related to metabolic, psychological or physical stressors or weight loss related to limited caloric intake or excessive physical exercise. It is a diagnosis of exclusion, much like PCOS. Typically they do not bleed following withdrawal of progesterone therapy as they do not produce enough oestrogen (unlike PCOS). PCOM may be seen in this entity \(^{17}\) although recent texts have characterised the ovaries as more multifollicular than polycystic and the increased stromal area typical in PCOM is not present. \(^{18}\) The diagnosis can be problematic as both PCOS and HA are diagnoses of exclusion and the decision to which takes precedence over the other is unresolved. The cause is thought to be a disrupted GnRH pulse frequency and amplitude secondary to the underlying stressors or diseases which cause anovulation. The aetiology of the PCOM is not thought to be extra ovarian but rather increased endogenous ovarian androgen synthesis.\(^{18}\)

Rarely pituitary or hypothalamic disease may cause hypogonadotrophic hypogonadism resulting in anovulation although features of androgen excess or PCOM may be absent in these instances.

Premature ovarian failure (POF) is diagnosed if ovarian failure occurs before the age of 40 in the absence of any demonstrable genetic abnormality. It is characterised by elevated gonadotrophins with decreased oestrogen concentration and amenorrhoea. The exact cause has not been defined but it is linked to other autoimmune disorders and may be part of the polyendocrine syndrome. Antibodies to gonadotrophins and gonadotrophin receptors have been found but mutations in the LH and FSH receptors have also been documented. Other known causes are genetic aberrations involving the X chromosome and iatrogenic causes e.g. following surgery, chemotherapy etc.\(^{19}\). PCOS and POF both can present with oligo/amenorrhoea and POF thus needs to be excluded in the workup of such a patient. The controversy, as will be discussed below, is whether these ovulatory disorders should be considered to be similar in presentation to PCOS in the absence of androgen excess (despite the presence of ovulatory dysfunction or PCOM).

Controversies regarding diagnostic criteria for PCOS

There have been three different sets of criteria set forth by different bodies\(^{20,21}\) and all have met with some degree of controversy. \(^{22-24}\) The first arose via an NIH expert conference in 1990.\(^{20}\) This set of criteria requires all of the following to fulfill the diagnosis of PCOS: i. Presence of anovulation, plus ii. Clinical and / or biochemical evidence of hyperandrogenism, and iii. Exclusion of other related disorders e.g. hyperprolactinaemia, thyroid disease, congenital adrenal hyperplasia (CAH) etc.

The presence of polycystic ovaries on ultrasound was considered suggestive but not diagnostic in this set of criteria as it was thought to have low specificity (25% of normal women can have PCOM and up to 25% of women with the syndrome may not have PCOM).\(^{22-25,27}\)

Using the NIH definition it was thus possible to isolate 3 clinical phenotypes of PCOS:

- **Group 1:** Clinical hyperandrogenism (hirsutism), biochemical hyperandrogenism and anovulation
- **Group 2:** Biochemical hyperandrogenism and anovulation
- **Group 3:** Clinical hyperandrogenism (hirsutism) and anovulation

Interestingly in a US cohort of patients, the Group 1 phenotype occurred most commonly, followed by Group 2 and 3 (50%, 30% and 20% respectively). Group 1 also had the highest fasting insulin levels and Group 3 had the lowest.\(^{20}\)

In May 2003 another expert conference was hosted in Rotterdam sponsored by European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine.\(^{8}\)

The diagnostic criteria that emerged from this conference were the presence of **two or more of the following:**

- Oligo- or anovulation
- Clinical (hirsutism, acne or androgenic alopecia) and/or biochemical evidence of androgen excess
- Polycystic ovaries

It also required the exclusion of other related disorders.

By expanding the NIH criteria, the Rotterdam criteria now identified 2 additional phenotypes of PCOS (Figure 1) viz.

- Women with demonstrable polycystic ovaries (PCOM) with clinical and/or biochemical androgen excess but no anovulation
- Women with PCOM and anovulatory cycles but no evidence of androgen excess

Disagreement has persisted regarding whether these two additional phenotypes (Figure 1, areas 2 and 3) actually do have classical PCOS, or whether they actually represent a milder form-fruste of PCOS. Subsequent studies have demonstrated that these women with PCOM but without overt hyperandrogenism (whether ovulatory or not), are either similar to control women without PCOM or have significantly fewer metabolic features than PCOM women who are also hyperandrogenaemic. These women may have slightly higher (albeit within the normal range) androgen, fasting insulin and LH levels, and lower SHBG levels. Therefore they probably form part of the spectrum of PCOS disorders but the significance of these findings on future metabolic risk and fertility remains to be determined.\(^{26-30}\)
The Rotterdam criteria also make it difficult to differentiate between patients with PCOM and hypothalamic-pituitary amenorrhea from non-obese women with PCOS. In addition, only women who fulfill the NIH criteria have been shown to be at high risk for some of the complications associated with PCOS e.g. the metabolic syndrome.

Another criticism of the Rotterdam criteria was that it has significant implications for research as it expanded the already heterogeneous nature of this population of patients. In addition it makes ultrasonography essential, and significantly increases the population implications for research as it expanded the already heterogeneous group of women, but whose risk for infertility and metabolic syndrome is lower.

It is noteworthy that all three sets of diagnostic criteria did not include obesity, measurements of insulin resistance (IR) or hyperinsulinaemia, or elevated lutenising hormone (LH) levels. These latter features are present only in approximately 50% of PCOS patients.

**A clinical approach to the diagnosis of PCOS**

1. **Assessment of ovulatory dysfunction**

   Approximately 75% of women with PCOS have menstrual irregularities suggestive of anovulation. This includes oligomenorrhoea (defined as less than 8 menstrual cycles per year, or cycles that are longer than 35 days) and amenorrhoea (the absence of menstrual cycles for > 3 months without pregnancy). However 20–30% of oligoanovulatory women with PCOS can present with apparent eumenorrhoea (i.e. subclinical oligoanovulation). Therefore eumenorrhoeic women with other features of PCOS should have multiple determinations of serum progesterone (drawn between Day 20–24 of their menstrual cycle) to accurately categorise their ovulatory status.

2. **Assessment of clinical hyperandrogenism**

   Hirsutism is the commonest clinical manifestation of androgen excess in PCOS. Overall 60–75% of patients with PCOS will have hirsutism but there is wide variation based on ethnicity and degree of obesity. Its assessment should therefore be ethnic specific. Most studies have examined Caucasian and African-American women where mean Ferriman Gallwey scores in excess of 5–8 have been considered abnormal. East Asian women have a lower prevalence of hirsutism while the prevalence and severity of hirsutism in women with PCOS of Southern Asian origin (Bengali, Gujerati, or Dravidian Indian) is greater when compared to Caucasians.

   In the latter study this was found to be correlated with greater insulin resistance (as manifested by higher fasting insulin levels and lower insulin sensitivity). The differences in the presence and degree of hirsutism are potentially the result of differences in the sensitivity of the pilosebaceous unit to circulating androgens. The subjectivity in the assessment of hirsutism is confounded further by the fact that there are no normative data for different populations. In addition the evaluation system is subjective and most patients will have depilated before presentation thus making scoring difficult.

   Other clinical features of hyperandrogenism are acne in younger women and female-pattern alopecia (thinning at the crown with preservation of the anterior hairline) in older women although, in general, these signs are considered to be less reliable markers of hyperandrogenism. As with hirsutism, there are ethnic differences in the prevalence of acne (also higher in Asian-Indians).

   The prevalence of PCOS in women with hirsutism is 75–80%, whereas 20–40% with acne alone have PCOS. About 10% of women with alopecia only will have PCOS.

3. **Assessment of biochemical hyperandrogenism**

   About 70% of patients with PCOS diagnosed by NIH criteria will have elevated serum free testosterone levels. Measurement of free testosterone using radioimmunoassay is inaccurate and using a direct method of measurement such as equilibrium-dialysis can be expensive and complex. Most experts recommend measuring serum total testosterone and sex hormone binding globulin (SHBG) followed by a calculation of the free testosterone using either the...
free androgen index (Testosterone/SHBG x 100) or, the mass action equation.

Most total testosterone assays are geared more towards measuring male range (higher) values and are complicated by age and reproductive stage (total testosterone levels tend to decrease as menopause approaches and then remain elevated in older age). Total testosterone levels are also dependent on SHBG levels, which are often low in PCOS women and elevated in women taking the contraceptive pill. Moreover, many manufacturers do not have accurate normative data for females. Thus the measurement of total testosterone alone is of little value in PCOS.

The measurement of androstenedione may detect an additional 10% of hyperandrogenaemic women and is not recommended routinely at this time. It may have utility in the patient suspected of having hyperandrogenaemia when the free testosterone is normal. Dehydroepiandrosterone measurements also have limited clinical use as it has significant diurnal and inter-individual variation and can be elevated by any degree of stress. Measurements of its sulphated metabolite (DHEA-S) are preferred. Elevated DHEA-S levels are found in 25-35% of women with PCOS, and it is the sole biochemical androgen abnormality in approximately 10%. Very high levels of DHEA-S may be a marker of adrenocortical disorders, but DHEA-S levels do not always reflect adrenal steroidogenesis.

4. Assessment for polycystic ovarian morphology (PCOM)

Ovarian morphology is assessed preferably by trans-vaginal ultrasound (TVUS) as the definition of PCOM has been revised on the basis of this technique. The Rotterdam definition of polycystic ovaries uses the criteria set forth by Dewailley et al.46 PCOM can be established in the follicular phase when at least one ovary has ≥ 12 follicles measuring 2–9 mm in diameter and/or the ovarian volume is > 10 cm³ in at least one ovary. Subsequent studies have shown the threshold for ovarian volume can be reduced to >7.5 cm³. The follicles are usually tightly spaced along the periphery of the ovary with increased stromal volume (the “pearl necklace” sign). However the previous measurement of stromal volume (which previously was regarded as being specific for PCOM) has been replaced by ovarian volume as a good surrogate.8

Adolescent girls can be evaluated using transabdominal ultrasound with assessment of ovarian volume only, as accurate determination follicle number is less reliable via this route.47 A transabdominal ultrasound will also in most cases exclude an ovarian or uterine abnormality. The ovarian volume is the parameter of greatest ultrasound will also in most cases exclude an ovarian or uterine abnormality. The ovarian volume is the parameter of greatest importance. The transabdominal criteria for a polycystic ovary as defined by Adams et al48 is where, in plane 10 follicles is > 10 cm³ in at least one ovary instead of a single plane was based on a report showing 99% specificity and 75% sensitivity for this value in differentiating between PCOS and normal individuals.46

Recently a surrogate measure of follicle pattern known as stroma-total area ratio was shown to have a 100% sensitivity and specificity for polycystic ovaries.50

The ultrasonographic definition of PCOM does not apply to women on the oral contraceptive pill as it can alter the ovarian appearance. Patients need to be counselled to discontinue the pill for 8 weeks before scanning is undertaken.

The term polycystic ovary to describe this morphology is a misnomer because there are no dominant cysts or follicles larger than 10 mm because of anovulation. If there is a follicle that is > 10 mm, the scan will need to be repeated in the following cycle. A study from Cape Town demonstrated no correlation between the severity of ovarian morphology and the endocrine or metabolic manifestations of PCOS.

Newer modalities like 3-D ultrasound and MRI have been explored and while good correlation between 3-D and 2-D measurements were found, 3-D is more expensive and requires more training.47,52 The cost of MRI imaging limits its use despite reported good sensitivity.

As noted previously, PCOS is a functional disorder that does not depend on the presence of polycystic ovaries, and the absence of PCOM does not exclude the diagnosis. Approximately 20–30% of asymptomatic women < 35 years of age will have PCOM; it is estimated that about 20% of these women will actually have PCOS by NIH definition; the other associations with PCOM are listed in Table II. Conversely, 10–25% of patients with PCOS by NIH definition will not have PCOM on ultrasonography.21,33,38

| Table II: Circumstances and conditions associated with polycystic ovarian morphology* |
|---------------------------------------------------------------|
| i. Up to 30% of females with normal menses and normal androgens |
| ii. Normal pre-pubertal children                              |
| iii. Normal girls in the first few years following puberty     |
| iv. Adrenal hyperplasia                                       |
| v. Long term use of oral contraceptives                        |
| vi. Autoimmune oophoritis                                     |
| vii. Periovarian adhesions                                    |
| viii. Primary hypothyroidism                                  |
| ix. Long term androgen use in female to male transsexuals     |
| x. Hyperprolactinaemia                                        |

*Most of these are probably co-incidental.

As mentioned previously, up to 30% of females with normal androgens and normal menses can have PCOM.47,53 It has also been suggested that some women with PCOM and normal ovulatory cycles may have higher LH, androgen and insulin levels as well as lower SHBG levels (albeit in the normal range) when compared with control women without PCOM.44 This phenotype may therefore represent the mildest form of PCOS.

In pre and peri-pubertal females, histological studies have revealed features similar to PCOM. There is increased volume, a multifollicular rather than multicystic appearance, hyperplasia with luteinisation, atretic follicles and cortical fibrosis. This is predominantly due to the fact that this is a period where a high follicular turnover does not exist and is a transitional period typical of early pubertal development.55
Studies in women with chronic use of oral contraceptives have also shown features suggestive of PCOM. The overall appearance may appear polycystic but the ovarian volume in these women may be decreased. It has been postulated that the use of contraceptives over a long period allows follicular development to continue but growth stops.

PCOM may also be seen with patients with tubo-ovarian inflammatory disease and peri ovarian adhesions. It has been suggested that these patients have greater numbers of atretic follicles and cystic corpora lutea possibly due to congestion of the ovary and interruption of the ovarian blood supply. The literature surrounding this is scanty. Autoimmune oophoritis has been documented to have PCOM as well. It is thought that the increased gonadotrophins, secondary to the ovarian pathology, are possibly responsible for the cystic changes. This morphology may also be seen in women with congenital adrenal hyperplasia and in those with hyperandrogenism in the absence of cyclical irregularity.

5. Differentiating PCOS from other androgen-excess and ovulatory disorders

Other common androgen excess disorders are: Cushing’s syndrome, androgen secreting tumours, non-classical congenital adrenal hyperplasia (NC-CAH), HAIR-AN (hyperandrogenism-insulin resistance-acinanthosis nigricans) syndrome and drug-induced hyperandrogenism. These are mostly acquired disorders so there is usually a post-pubertal period of normal menstrual cycles without symptoms of hyperandrogenism. In contrast, PCOS often has an adolescent onset (not infrequently post-menarche) and affects most of the woman’s reproductive life.

Although Cushing’s syndrome can share many of the clinical features of PCOS (menstrual irregularities, acne and hirsutism as well as evidence of PCOM), other signs consistent with Cushing’s syndrome are usually evident. In view of the low prevalence of this disorder in patients with PCOS, a 24 hr urinary free cortisol can be measured only if the clinical examination warrants it. Serum cortisol measurements are notoriously unreliable in the presence of oral contraceptive use because of elevated cortisol binding globulin levels.

Androgen secreting tumours are usually ovarian in origin but occasionally arise from the adrenal glands. Clinically these patients have rapid onset of virilisation with clitoromegaly and breast atrophy, features which are rarely found in PCOS. In addition androgen levels are markedly elevated with elevations in both testosterone and DHEA-S levels.

21-hydroxylase deficient non-classical congenital adrenal hyperplasia occurs due to mutations in the CYP 21 gene resulting in abnormal 21-hydroxylase activity and a shift towards androgen overproduction. As with Cushing’s syndrome, many symptoms are shared with PCOS (hirsutism, oligo-anovulation, infertility, acne and hyperandrogenaemia). However symptoms tend to be milder and frank virilisation and hirsutism are rare. Screening for this disorder involves measurement of basal 17-hydroxyprogesterone levels in the morning during the follicular phase of the menstrual cycle (normal value is < 6 nmol/L). If the screening hydroxyprogesterone level is elevated, then a synacthen test is performed. 17-Hydroxyprogesterone levels > 45 nmol/L 60 min following intravenous synacthen is diagnostic of NC-CAH. Some carriers may have slightly raised values following the test but the levels are usually below 30 nmol/L. Screening for this condition is recommended especially in the high risk population group of Ashkenazi Jews and Europeans of Latin descent. 3-BHSD and 11β-hydroxylase deficient CAH are rare and routine screening is not recommended.

Other conditions that can present with hyperandrogenism and/or chronic anovulation are:

- **Thyroid disease.** Although it is uncommon to mistake the menstrual disturbance of thyroid disorders with PCOS, the disorder is common, screening is simple and inexpensive, and the disorder is easily treated. Thyroid function testing is therefore recommended.
- **Hyperprolactinaemia.** Although one can find mild elevations of prolactin in 20–30% of women with PCOS (< 30 ng/ml), severe hyperprolactinaemia has been known to mimic PCOS.
- **HAIR-AN Syndrome:** About 3% of hyperandrogenic women suffer from this severe form of insulin resistance (IR) characterised by severe hyperandrogenism (and often virilisation) and severe acanthosis nigricans. The ovarian morphology is one of hyperthecosis, and ovarian/ovulatory dysfunction is common. The severe IR may be associated with lipodystrophy. Other forms of insulin resistance syndromes (types A and B) may also produce features similar to the HAIR-AN syndrome. As a result of the severe IR, progression to type 2 diabetes and the development of hypertension and dyslipidaemia with increased cardiovascular risk is common. Fasting insulin levels are usually in excess of 80μU/ml and 2-hour post-glucose insulin levels are > 300μU/ml (unlike PCOS where fasting insulin levels are higher than obese control subjects without a diagnostic threshold). This is probably the only clinical indication for measuring insulin levels in the context of PCOS.

### Metabolic consequences of PCOS

1. **Obesity** accompanies PCOS in 30–50% of patients in the US.61 This may exacerbate insulin resistance and metabolic abnormalities. Increased visceral adiposity is reflected by an increased waist circumference (> 88 cm) or waist to hip ratio. These are often associated with hyperandrogenism, IR, dyslipidaemia and glucose intolerance. Recent data suggests that although obesity increases the prevalence rates of PCOS to a modest degree, the metabolic consequences of obesity may precipitate a genetically susceptible individual to express the PCOS phenotype.

2. **Insulin resistance** is defined as a reduction in insulin-mediated glucose disposal and is measured (for research purposes) by the euglycaemic-hyperinsulinaemic clamp or a frequently-sampled glucose tolerance test. The prevalence of IR in the general population varies from 10–25% and 50% of women with PCOS (both obese and non-obese) have IR. Conversely and more importantly, although IR is more common among women with PCOS, 50% of women with PCOS do not have IR. Therefore the common prevailing belief among medical practitioners (personal observation) that IR is universally present and the “cause” of PCOS is a myth.

Some studies have found the prevalence of insulin resistance to be closer to 75%. The difference in prevalence rates in different...
In any event, a biochemical measure of IR is not a criterion for the diagnosis of either the insulin resistance (metabolic) syndrome or PCOS. There is also no evidence that biochemical indices of IR (other than plasma glucose values derived from a GTT) offer any therapeutic or prognostic value in women with PCOS; neither does it predict weight loss (insulin resistant subjects with PCOS). The assessment of IR is therefore a clinical one based on conventional criteria for the diagnosis of either disorder. The biochemical assessment of insulin levels and its derived indices currently has no merit in clinical practice and increases the cost of managing this condition unnecessarily.

3. There are increased rates of impaired glucose tolerance (IGT) and diabetes mellitus in women with PCOS. The underlying abnormality is postulated to be insulin resistance. These women may often have normal fasting glucose and HbA1c levels but are glucose intolerant following a glucose challenge. By the fourth decade 31% of PCOS females have IGT and 7.5% have type 2 diabetes. Overall, the risk of type 2 diabetes in PCOS women is increased 7-fold when compared to controls. This is obviously influenced by a family history of diabetes, obesity and age. The compensatory hyperinsulinaemia drives many of the phenotypic changes seen, including ovarian hyperandrogenism (elevated insulin drives ovarian theca cell androgen production) and acanthosis nigricans.

A 2 hr OGTT can be used to assess glucose tolerance in all patients with PCOS, although there are those that only advocate screening for diabetes if patients have additional risk factors for diabetes i.e. obesity, history of gestational diabetes, type 2 diabetes in a first degree relative, high-risk ethnic origin. Insulin resistance is not a diagnostic criterion of this disorder and there is little to recommend insulin measurements outside research purposes.

4. Increased cardiovascular risk has been postulated in patients with PCOS. Cardiovascular risk factors are increased including hyperlipidaemia, increased circulating androgens, insulin resistance and increased levels of inflammatory markers. Hypertriglyceridaemia, increased VLDL and LDL and decreased HDL are postulated to predispose to increased cardiovascular risk. There are also reports that increased coronary artery calcification and increased PAI-Type 1 may contribute to this risk. Endothelial function and vascular function is also altered in women with PCOS and vascular compliance has been reported to be decreased. There have also been suggestions that there is an increased rate of metabolic syndrome in these patients but it is unclear if this is secondary to the increased rates of obesity and its consequent metabolic complications. However all of these are surrogate markers and despite their presence, it remains to be proven (prospectively) that women with PCOS are at increased risk for cardiovascular-related morbidity and mortality.

5. Obstetric and gynaecological: PCOS is the leading cause of anovulatory infertility and is an independent risk factor for the development of gestational diabetes, pregnancy induced hypertension, pre-eclampsia and increased fetal loss. The developmental competence of the oocyte is one of the early factors that affect embryonal development, establishment and maintenance of pregnancy and fetal development. Defects in glucose metabolism due to selective insulin resistance at the level of the ovaries could adversely affect the flow of glucose, pyruvate and purines in the oocyte leading to an altered meiosis and abnormal oocyte maturation. This could contribute to the anovulatory disturbances and increased early pregnancy loss associated with PCOS. In addition hyperinsulinaemia is postulated to decrease endometrial secretory proteins that play a role in implantation and maintenance of the pregnancy. High LH levels, elevated PAI-I levels induced by hyperinsulinaemia and obesity are some other explanations given for early pregnancy loss. The studies however have not been definitive and thus the evidence for a definite relationship remains weak.

A higher than expected risk of pre-eclampsia (PE) has been reported in a few studies. With regards to pregnancy induced hypertension (PIH), studies have found conflicting results. Some have found an increased incidence of PIH and PE, while others have found no relationship. Thus the relationship between hypertensive disorders of pregnancy and PCOS is not definite.

The incidence of PCOS in women with gestational diabetes (GDM) is much higher than normal controls and this was true even when weight was accounted for. Thus patients with PCOS should be screened for GDM.

Chronic anovulation can lead to unopposed endometrial stimulation by oestrogen and may lead to an increased risk of endometrial hyperplasia and a possibly increased risk of endometrial cancer. Thus one of the aims of therapy is to improve the frequency of ovulation and also improve fertility.

6. Sleep apnoea: There is an increased prevalence of sleep apnoea noted that also appears to correlate with insulin resistance.
Review: Polycystic ovary syndrome

Theories of aetiology

The aetiology of PCOS is unknown but various theories have been put forth to explain the myriad of abnormalities encountered.

1. Abnormalities in the hypothalamic-pituitary axis (HPA) and uncontrolled ovarian steroidogenesis
   These HPA abnormalities cause abnormal secretion of gonadotropin releasing hormone (GnRH) and LH, resulting in increased ovarian androgen production. LH stimulates the theca cell in ovary to synthesise androgens and FSH is responsible for the granulosa cell synthesising oestrogen via its actions on aromatase activity. Increased GnRH pulse frequency favours increased LH levels. Women with PCOS tend to have increased LH:FSH ratios. It is postulated that an increased GnRH frequency and low levels of progesterone (that normally decreases this pulsatility) from infrequent ovulation is the catalyst.

2. Insulin resistance
   Insulin drives increased androgen production from the ovary and adrenal and may alter gonadotrophin secretion.
   It is also thought to also be responsible for decreased SHBG synthesis in the liver thus increasing free testosterone in the circulation.
   In patients with PCOS, it has been revealed that there is selective tissue insulin sensitivity (skeletal muscle is resistant but ovary and adrenal are sensitive). Ovarian insulin sensitivity to the prevailing hyperinsulinaemia is thought to be one of the mechanisms that drive ovarian androgen production. Body mass index, hyperandrogenaemia and clinical hyperandrogenism are independent predictors of insulin resistance.

3. Ovarian follicular defect
   Women with PCOS have 2 to 6-fold more primary, secondary and small antral follicles when compared to normal ovaries. Abnormal androgen signalling is thought to be responsible for the increase in follicle number. It has also been postulated that follicles grow very slowly due to possibly deficient growth signals from the ovary.
   There have been some studies showing a positive association between follicle number and androgen concentrations.

The pathophysiological focus has thus shifted from the ovary to the hypothalamic-pituitary-gonadal axis, to defects in insulin action (currently favoured by many) as the possible aetiological factor in PCOS. It is possible that all three processes may interact with varying degrees in each individual to create this heterogeneous disorder. Familial aggregation has been recognised but genetic analysis has not found a culprit candidate gene although many have been associated with PCOS. In addition environmental factors are thought to play a role as well. Animal studies have shown that exposure to androgens in pregnancy induces a PCOS-like syndrome and a similar effect in humans can only be postulated.

The treatment of PCOS

Patients with PCOS will usually present to the practitioner with one or more dominant symptom of the disorder (obesity, hirsutism, acne, infertility, menstrual irregularity etc). It is important to choose therapies that are not only effective in addressing the patient’s most distressing symptom, but also attempt to improve the long-term outcomes of the disorder.

1. Lifestyle modification
   Weight loss improves SHBG concentrations, decreases testosterone and improves menstrual function and conception rates. It has also been shown to improve insulin sensitivity. Weight loss of 2-5% has been associated with improved androgen levels, ovulation rates and insulin sensitivity in obese anovulatory women. Caloric restriction rather than specific macronutrient manipulation has been the key determinant of success.
   The effect of metformin on weight loss has been controversial and it is currently not approved by the FDA for the treatment of obesity or for PCOS. However a few studies have demonstrated that metformin combined with lifestyle measures may be more effective in lowering weight than lifestyle and placebo alone.

2. Management metabolic risk factors
   Screening for diabetes and other cardiovascular risk factors (the metabolic syndrome) should be conducted in view of its prevalence in this population as discussed above. The management of glucose intolerance, dyslipidaemia and hypertension should follow current guidelines for these disorders. Patients should also be screened for sleep apnoea and referred for sleep studies when clinically indicated.

3. Management of clinical hyperandrogenism
   a. Oestrogen-containing oral contraceptives (OC)
      All combined OC’s contain ethinyl oestradiol. Oestrogen suppresses LH and thus ovarian androgen production. Ethinyl oestradiol also increases hepatic synthesis of SHBG, thereby decreasing free testosterone levels. OC’s with low doses of cyproterone acetate or diospirenone (Diane-35® and Yasmin® respectively) are particularly effective in the treatment of hirsutism and acne because of their anti-androgenic properties (vide-infra), and because they attenuate the oestrogen-stimulated increase in SHBG to a far lesser extent than other progestogens. However some studies have reported the potentially adverse effects of oestrogen-containing OC’s on insulin resistance, dyslipidaemia, coagulability and vascular reactivity, and the long-term consequences of the OC in PCOS remain debatable.
   b. Antiandrogens
      All anti-androgens can cause pseudohermaphroditism of the male fetus and should therefore not be used without adequate contraception.
      i. Spironolactone is an aldosterone antagonist which competitively inhibits the androgen receptor at higher doses, and inhibits 5α-reductase activity to a lesser extent. It is effective in improving hirsutism scores in 50% of patients with PCOS when used alone. Doses of 100–200 mg/d are recommended. A Cochrane review in 2003 found spironolactone 100 mg/day to be superior to finasteride 5 mg/day and low dose cyproterone acetate 12.5 mg/day (first 10 days of cycle). Oral contraceptives and spironolactone are synergistic and response rates can increase by 75% with the use of this combination. In a recent study, this combination was compared to flutamide alone and both were found to be equally effective in treating hirsutism.
      ii. Cyproterone acetate (CPA) is a progestogenic anti-androgen which competitively blocks the androgen receptor, inhibits 5α-reductase activity and suppresses gonadotrophin and testosterone levels. It has a long half-life and doses of 50–100 mg/d are usually administered from day 5 to 15 of the menstrual cycle (with or without ethinyl oestradiol [OC] from day 5 to 25 to maintain cyclicity). The dose can be...
Drugs that improve insulin resistance (metformin and thiazolidinediones) have been used to treat hirsutism as well. Drugs that improve insulin resistance (metformin and thiazolidinediones) have been used to treat hirsutism as well.

Flutamide is a non-steroidal pure anti-androgen which inhibits the androgen receptor in a dose-dependent manner. It has equal, if not better efficacy than spironolactone, CPA, finasteride and GnRH agonists in the treatment of hirsutism. The most frequently used dose in randomised trials is 500 mg/d but some studies have suggested equal efficacy with 250 mg.108 Flutamide can also cause liver dysfunction, and may even result in liver failure and death. However hepatotoxicity has not been noted at doses up to 375 mg/d. It is not registered for the treatment of hirsutism and generally not recommended due to its association with liver failure.

Flutamide remains the cornerstone for the management of the components of the metabolic syndrome. In obese PCOS individuals, weight loss is far more effective in improving insulin sensitivity than pharmacotherapy.115

Overall recommendations for the treatment of hirsutism

A reasonable approach would be to use spironolactone and topical efflornithine as a first-line treatment for hirsutism. A CPA or drospirenone-containing OC would be a reasonable choice for the patient who also has acne or demands menstrual cyclicity, particularly if they are not obese and have a low risk for venous thromboembolism. Finasteride should be reserved for patients who are unresponsive or intolerant of the above, and should be combined with an OC (because of fetal risk). Flutamide is no longer recommended for the treatment of hirsutism because of its liver toxicity, although some authors have found it to be particularly effective if used supra even at lower doses.

Metformin should not be used as monotherapy for hyperandrogenic symptoms, but should be added when other indications exist (IGT or diabetes), or it may be added to the OC in obese individuals (to offset the potential adverse metabolic consequences of the OC).

Combination treatments for hirsutism also appear to be promising as suggested by a meta-analysis which demonstrated that a combination of spironolactone or finasteride with an OC was more effective than monotherapy with an OC. Similarly, flutamide plus metformin was superior to metformin monotherapy.109

In terms of the clinical response to therapy, it should be noted that the more obese subjects show smaller responses to therapy, and that those with more severe hirsutism have a larger reduction in Ferriman-Gallwey scores.113

4. The management of menstrual dysfunction

The options for the treatment of irregular menstrual cycles and/or to prevent endometrial proliferation (caused by chronic unopposed oestrogen in PCOS), are to use a cyclic progestogen (e.g. medroxyprogesterone acetate 10mg from day 5 to 25) or a combined oral contraceptive pill. The ideal oral contraceptive remains elusive as there are no head to head trials for PCOS, but pills containing anti-androgenic progestins (e.g. synthetic progestogens such as CPA and drospirenone) have the added advantage of improving acne and hirsutism. It has been argued that the monophasic OC may be preferred as it lends itself continuous use (i.e. no placebo days thus allowing no reduction in oestradiol or SHBG levels, and no spike in gonadotrophins that could stimulate ovarian androgen synthesis). Theoretically the dose of ethinyl oestradiol should be in the range of 30–35 μg so as to suppress ovarian follicular activity and stimulate hepatic SHBG synthesis. The risks of the oral contraceptives are their tendency for increased clotting events. In a patient with a strong personal or family history of clotting disorders a progestin only pill could be recommended. The latter is not recommended routinely because of unpredictable breakthrough bleeding.

Although metformin therapy has been associated with increased menstrual regularity it is not universally effective in this regard, and should therefore not be used as primary therapy for women wishing to menstruate regularly. Some authors do argue that it is better than the OC in that it poses no risk for dyslipidaemia and actually helps improve the metabolic profile.114
Metformin acts by decreasing the hepatic glucose output and it has some peripheral insulin sensitising properties. It decreases insulin levels, which potentially assists in minimising theca androgen production. However, its anti-androgen action is inferior to specific anti-androgen compounds. Metformin is being widely prescribed as a weight loss drug for PCOS. However, a 2003 meta-analysis of all metformin trials in PCOS demonstrated no net effect on weight loss.116 It has also been shown to improve some intermediate and surrogate markers of cardiovascular disease and risk.114 However the long-term significance of these findings remains uncertain.

Metformin has a proven role for the prevention of type 2 diabetes in those with IGT, and in the management of type 2 diabetes. These two situations would constitute definite indications for metformin therapy in PCOS. When used in the absence of IGT and type 2 diabetes the target doses proposed have been variable ranging from 1500 mg–2550 mg and there are no guidelines as to how long it could/should be used for.

Thiazolidinediones increase insulin sensitivity in muscle, liver and adipose tissue. It also improves ovarian steroid biosynthesis and decreases insulin levels which assist in lowering hyperandrogenaemia. There have been some studies showing improved hyperglycaemia markers as well.117 There is a concern regarding its use in pregnancy and thus is not used in women trying to conceive. Other negative effects are its association with weight gain, fluid retention and distal fractures in women. It has limited efficacy in improving hirsutism.115 Its main role is as adjunctive therapy in patients with IGT or type 2 diabetes when metformin is ineffective or not tolerated.

6. The management of infertility

The treatment of infertility associated with PCOS is beyond the scope of this article. Of note is the recent consensus on infertility treatment related to PCOS sponsored by the European Society of Human Reproduction and Embryology. The American Society for Reproductive Medicine has recommended clomiphene citrate as first line therapy for ovulation induction.118 A recent meta-analysis of metformin use for infertility in PCOS has shown that it improves ovulation but not pregnancy rates when compared to placebo except when it is used with clomiphene.119

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