Polycystic ovaries (PCO) & polycystic ovarian syndrome (PCOS)

Definition

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Whilst polycystic ovaries (PCO) describes the ultrasonic diagnosis, the term polycystic ovary syndrome (PCOS) is used if the ultrasound appearance is combined with clinical symptoms of hyperandrogenemia, such as oligomenorrhea, hirsutism acne, seborrhoea or obesity.

The definition of PCOS—that any two out of three parameters (morphology, hyperandrogenism (clinical or biochemical) and oligo/amenorrhoea) were sufficient to diagnose PCOS—was universally agreed upon at the ESHRE ASRM Consensus Conference on PCO in Rotterdam, 2003.

The ultrasound criteria were also clarified. The critical finding to diagnose PCO in ultrasound examination of the ovaries is the presence of multiple peripheral small cysts. The Consensus Conference concluded that the presence of 12 peripheral cysts in at least one ovary was sufficient for diagnosis. There is also usually an increase in ovarian volume, and change in ovarian dimensions with the ovary being more spherical. The role of imaging can be read in detail in the chapter by Dewailly *et al*.[1]

Summary for treatment of anovulatory PCOS patients

1.	Weight loss and exercise
2.	Clomiphene citrate
3.	Clomiphene + Metformin
4.	Ovarian Cautery/ laparoscopy
5.	Gonadotrophin (rFSH) injections
6.	InVitro Fertilization
Remember:	Check partner's semen analysis
Consider:	Baseline GTT/Insulin levels Baseline Lipid studies (cholesterol and triglycerides)

Prevalence

The incidence of PCO and PCOS depends very much on the population being surveyed and the criteria used to diagnose the condition. True population studies have been reported from hospital employees, family planning clinics, volunteers and from general practice registers. These have been excellently reviewed by Balen and Michelmore[2] and vary between 17 and 22 per cent. We have carried a study of the wives of men who were referred for IVF with obstructive azoospermia, with 23 out of 100 sequential referrals demonstrating polycystic ovaries on baseline ultrasound examination, and about half of these women qualified as PCOS.[3]

Thus it appears that almost a quarter of the female population has the appearance of PCO on ultrasound, but the natural history of these women is poorly understood.

Longitudinal studies of women who are diagnosed with PCO are required to evaluate the probability of developing symptoms and biochemical abnormalities and to identify significant factors that may precipitate the development of these abnormalities.

Inheritance

It has been recognised that PCOS has a familial tendency, suggesting a genetic basis for its inheritance. It is likely that there is an interaction of environmental factors with a small number of causative genes.[4] A number of candidate genes have been investigated including genes coding for steroidogenic enzymes (CYP 11a, CYP 19, CYP 17) genes involved with insulin secretion and action (Insulin gene including VNTR, Insulin receptor gene and Glycogen synthetase gene) and Follistatin.[5]

Short term problems

The commonest presentation to gynaecologists is menstrual irregularities and infertility, with one study reporting more than 65 per cent of women presenting having PCO.[2] Whilst other problems need to be considered, the primary treatment given by gynaecologists is ovulation induction.

Ovulation Induction (OI)

Lifestyle changes

It has been reported that if obese women with PCOS enter a lifestyle program consisting of exercise and weight reduction, ovulatory cycles can be restored. The initial studies of Clarke and Norman of a 'Lifestyle, Fertility Fitness program'[6] found that 90 per cent of participants lost 5 per cent body weight and 90 per cent ovulated, with 60 per cent becoming pregnant within 18/12. Whilst lifestyle change to healthy living is to be encouraged, other groups have not found the exercise/diet program as effective.

Clomiphene citrate

The first line of pharmacological treatment is probably still the use of clomiphene citrate. With careful administration of a slowly escalating dose, ovulation rates of 70-85 per cent and pregnancy rates of 40-50 per cent can be achieved[7] with low multiple pregnancy rates. The minimal effective dose should be used, starting with 25mg/day for five days, increasing incrementally, monitoring response by at least monthly luteal oestradiol and progesterone estimations.

Insulin-sensitising drugs

The most widely used insulin sensitising agent is Metformin. Metformin is administered in a dose of 500mg-1700mg daily. Side effects are mainly gastrointestinal including diarrhoea, nausea, vomiting or abdominal bloating. In patients with impaired renal function, lactic acidosis can occur. A systematic review of the use of Metformin for ovulation induction for PCOS–up to 60 per cent of women ovulate over 3-6 month period.[8] A recent Cochrane review of insulin-sensitising drugs for polycystic ovary syndrome concludes that metformin is an effective treatment for anovulation in women with PCOS, either as a first agent, but it is more effective in combination with clomiphene citrate.[9]

OI with gonadotrophins

The use of daily follicle-stimulating hormone (FSH) injections to induce ovulation has been available since the 1960s. Although initial treatment involved pituitary gonadotrophins, this changed to the urinary preparation in 1985 with the diagnosis of CJD. These have now been superseded by the use of recombinant FSH. The principle of treatment has not changed, with incremental increase of FSH dose until there is a follicular response, as diagnosed by rising serum oestradiol and/or ultrasound. Special care needs to be taken with PCOS patients as they are at higher risk of Ovarian Hyperstimulation Syndrome (OHSS). It is therefore recommended that the dose of FSH is only increased by 30 per cent every 7-10 days.

Laparoscopic ovarian drilling

Although there have been sporadic reports of laparoscopic ovarian surgery restoring ovulation, it was not until the report of Gjonnaess that following the laparoscopic unipolar diathermy of the ovaries in 8 to 15 areas 92 per cent of patients ovulated with an 80 per cent pregnancy rate10 that this treatment achieved popularity. Many small series of successful cases have been reported. The use of laser including CO2, argon Nd-Yag and KTP have all been described, but show little advantage over unipolar diathermy.[11]

A Cochrane review of 14 trials of laparoscopic 'drilling' or laser for ovulation induction in anovulatory PCOS compared to gonadotrophin ovulation induction was carried out by Farquhar et al in 2001.[12] They identified eight studies including seven randomised controlled trials (RCT). The main outcomes measured included ovulation rate and pregnancy rate whereas secondary outcomes were miscarriage rate, multiple pregnancy, and OHSS. They concluded that the value of ovarian drilling as primary treatment is undetermined. For Clomiphene-resistant patients, there are insufficient numbers to show difference on pregnancy rate or ovulation rate have been studied. None of the modalities of drilling showed any advantage but multiple pregnancy rates are reduced in pregnancies after ovarian drilling.

Therefore the only conclusion that can be reached is that there is no difference in terms of these clinical outcomes for the two treatment regimens, except for the reduction of multiple pregnancies following surgical treatment. We have carried out a cost comparison study of laparoscopic ovarian cautery in the private hospital system in Australia, and ovulation induction using gonadotrophins.[13] Costs included the cost of hormones, biochemistry and medical/surgical costs. The cost of ovarian cautery was $AU1180 whereas the cost of typical cycle ovulation induction with HMG was $AU1401 and with recombinant FSH $AU1800. This means that surgical treatment is slightly cheaper and also enables several cycles of ovulation to attempt conception.

Biochemical Changes

Insulin resistance

The basic biochemical abnormality in PCOS is both insulin resistance and impaired pancreatic b cell function. This can lead hyperinsulinaemia and frank diabetes mellitus.

Androgen excess

The universal endocrine abnormality of polycystic ovary syndrome is the excessive circulation of androgens, and this is responsible for the symptoms and signs of polycystic ovary syndrome, such as menstrual irregularities, hirsutism, acne and alopecia. Hyperangrogenemia may also be responsible for weight gain in about 50 per cent of cases.[14] It has also been shown that women who have polycystic ovaries on ovarian ultrasound, but have no overt symptoms of PCOS, may still have hyperandrogenemia on biochemical analysis.[15]

Long-term effects

It is now widely accepted that women with PCOS have a significantly increased risk of diabetes. There has also been concern that PCOS may contribute to the risk of developing cardiovascular disease (CVD). The reason for this is that many of the biochemical disturbances, such as insulin resistance and hyperandrogenism and the resultant unfavourable changes in blood lipids which are associated with PCOS, are recognised risk factors. It has also been reported that women with PCOS have increased atherosclerosis as diagnosed on ultrasound measurement of the intima-media thickness of the carotid arteries.[16] However the Pierpoint study[17] showed no increase in deaths due to circulatory diseases or ischaemic heart disease in the PCOS group compared to the population as a whole. Consequently whilst there is a theoretical risk, there is little hard evidence that PCOS increases cardiovascular disease. The next question is whether women with PCO on ultrasound but without biochemical or clinical changes have an increased risk of long-term complications. This question is not yet able to be answered.

Lipid abnormalities have long been recognised as a risk factor for CVD. The abnormalities reported in women with PCOS include depressed high density lipoprotein (HDL) Cholesterol, elevated low density lipoprotein (LDL) Cholesterol, and raised triglyceride levels. These abnormalities are believed to be related to the insulin resistance/hyperinsulinemia.[18] It is also believed that chronic inflammation is a predisposing factor for CVD. It has been reported that C reactive protein levels are elevated in PCOS, which correlates with obesity and insulin resistance but not hyperandrogenemia.[19]

Early pregnancy loss and PCOS

It has been reported that the chance of early pregnancy loss in women with PCOS is significantly higher than the community.[20] This is thought to be associated with the raised levels of luteinising hormone (LH) associated with PCOS.[21] Unfortunately, a randomised prospective controlled study of 106 women with PCOS who have had at least three spontaneous abortions, using LH suppression with GnRH agonist did not improve pregnancy outcome, the outcome having been excellent for subjects and controls.[22]

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