POLYCYSTIC OVARIAN SYNDROM

PCOS

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- Polycystic ovary syndrome is the most common endocrine disorder to affect women during their reproductive years.

The symptoms of PCOS include menstrual cycle disturbance and features of hyperandrogenism (hirsutism, acne,alopecia), with associated fertility problems, obesity and psychological issues. There is significant heterogeneity of presentation, such that signs and symptoms manifest across a spectrum and their severity may vary

DEFINING PCOS

- the European Society of Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) held a consensus meeting in Rotterdam. They proposed that the diagnosis of PCOS should be made, once appropriate investigations have been done

- performed to exclude other causes of menstrual disturbance
- and androgen excess, if two out of three criteria are met – the

so-called ‘Rotterdam Criteria’:

- **1 the presence of clinical or biochemical features of**
- **hyperandrogenism;**
- **2 oligo-ovulation or anovulation (in other words a menstrual cycle disturbance);**
- **3 polycystic ovaries on ultrasound.**
- This definition of PCOS requires the exclusion of specific underlying diseases of the adrenal or pituitary glands (e.g.hyperprolactinaemia, acromegaly, congenital adrenal hyperplasia, Cushing’s syndrome, androgen-secreting tumors of the ovary or adrenal gland) which could predispose to similar ultrasound and biochemical features and also the exclusion of other causes of menstrual cycle irregularity secondary to hypothalamic, pituitary or ovarian dysfunction

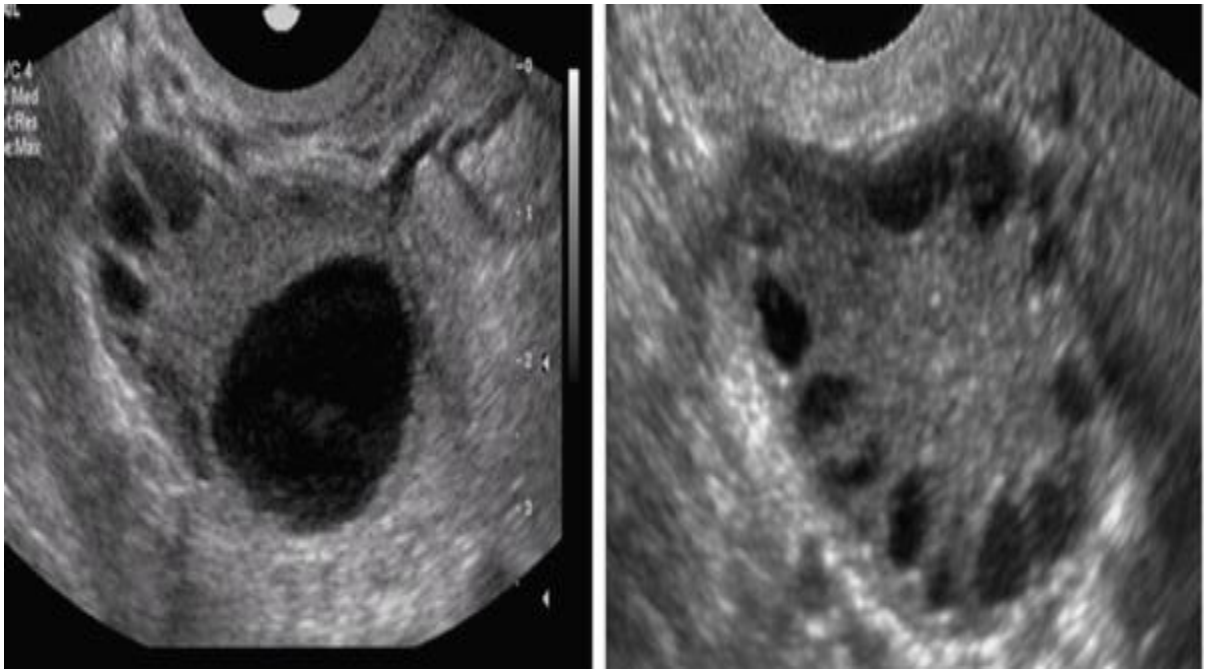
The spectrum of clinical manifestations of PCOS

Symptoms •

- ● Hyperandrogenism (hirsutism, acne, alopecia)
- ● Menstrual disturbance
- ● Infertility
- ● Obesity
- ● Asymptomatic, with polycystic ovaries on ultrasound scan
- Possible late sequelae
- ● Type 2 diabetes mellitus
- ● Dyslipidaemia
- ● Hypertension
- ● Cardiovascular disease
- ● Endometrial carcinoma
- Serum endocrinology
- ↑ Androgens (testosterone and androstenedione)
- ↑ LH, normal FSH
- ↑ Fasting insulin (not routinely measured; insulin resistance
- assessed by GTT)
- ↓ Sex hormone binding globulin, results in elevated ‘free
- androgen index’ (FAI)
- ↑ Oestradiol, oestrone
- ↑ Anti-Müllerian hormone

ULTRASOUND

- Polycystic ovaries are commonly detected by pelvic ultrasound, with estimates of the prevalence in the general population being in the order of 20–33 per cent. The morphology
- of the polycystic ovary was also defined in the ESHRE/ASRM consensus as an ovary with 12 or more follicles measuring 2–9 mm in diameter and/or increased ovarian volume
- (>10 cm3).



EPIDEMIOLOGY AND PREVALENCE

- The prevalence of PCOS in the general
- population has not been definitively determined and appears to vary considerably studied and the diagnostic criteria being employed and has ranged from 4 per cent to 26 per cent between populations

PCOS tends to run in families, although there is not a single gene or pathway that causes the syndrome; however there may be genetic factors that affect expression and presentation – whether because of racial differences in the colour and distribution of hair or variations in hormone production and receptor activity. For example women from the Far East (e.g. Japan) with PCOS do not present with excess bodily or facial hair despite having dark hair and elevated testosterone levels, whereas those from Mediterranean countries or South Asia with similar hormone profiles may have profound hirsutism

PCOS AND METABOLIC ABNORMALITIES

Women with PCOS are characterised by the presence of insulin resistance, central obesity and dyslipidaemia, which appears to place them at a higher risk of developing diabetes as well as cardiovascular disease. There are a number of environmental factors that may influence the expression of the syndrome, in particular a tendency to insulin-resistant states induced by overeating and under-exercising

- n **PCOS**, elevated insulin (also in the case of insulin resistance) stimulates the growth and reproduction of granulosa cell that surround the oocyte, which leads to increased production of male (testosterone) and female (estrogen) hormones. Healthy ovaries produce smaller amounts of male sex hormones (androgens), but convert it into estrogen (female hormone). In the case of IR, enhanced production of androgen exceeds the capacity of the ovaries and therefore there is excess of androgen. Eventually, all this leads to disorders of ovulation, oily skin, hair, excessive body hair, acne ...

- Although the insulin resistance may occur irrespective of BMI, the common association of PCOS and obesity has a synergistic deleterious impact on glucose homeostasis and can worsen both hyperandrogenism and anovulation. It has been suggested that rather than BMI itself it is the distribution of fat that is important, with android obesity being more of a risk factor than gynaecoid obesity. Hence the value of measuring waist:hip ratio, or waist circumference, which detects abdominal visceral fat rather than subcutaneous fat. It is the visceral fat which is metabolically active and when increased results in increased rates of insulin resistance, type 2 diabetes, dyslipidaemia and hypertension. Waist circumference should ideally be less than 79 cm, whilst a measurement that is greater than 87 cm carries a significant risk. Exercise has a significant effect on reducing visceral fat and reducing cardiovascular risk – indeed a 10 per cent reduction in bodyweight may equate with a 30 per cent reduction in visceral fat

MANAGEMENT OF PCOS

Obesity •

- The management of women with PCOS should be focused
- on the patient's particular problems. Obesity worsens both
- symptomatology and the endocrine profile and so obese
- women (BMI >30 kg/m2) should be encouraged to lose
- weight, by a combination of calorie restriction and exercise.
- Weight loss improves the endocrine profile and the Meal replacement therapy or low-calorie diets may be appropriate; it is often helpful to refer to a dietitian, if available. An increase in physical activity is essential, preferably as part of
- the daily routine. Thirty minutes per day of brisk exercise is
- encouraged to maintain health, but to lose weight, or sustain
- weight loss, 60 to 90 minutes per day is advised likelihood of ovulation and a healthy pregnancy

- Furthermore there are no medications that have been shown to assist with long-term weight reduction. Bariatric surgery is used increasingly because of the global epidemic of obesity and certainly has a role in the management of obese women with PCOS. It is recommended by some that anyone with a BMI of more than 40 kg/m2 should be referred for consideration for bariatric surgery. If there are co-morbidities, such as diabetes, then the BMI cut-off for surgery is lower at 30–35 kg/m

Menstrual irregularity

- The simplest way to control the menstrual cycle is the use of a low-dose COCP. This will result in an artificial cycle and regular shedding of the endometrium. It is also important once again to encourage weight loss. As women with PCOS are thought to be at increased risk of cardiovascular disease
- a ‘lipid-friendly’ combined contraceptive pill should be used.
- The third-generation oral contraceptives are lipid friendly
- but present the potential disadvantage of venous thromboembolism, particularly in overweight women. Dianette® and Yasmin® are both COCPs that respectively contain the antiandrogens cyproterone acetate and drospirenone, which is a derivative of spironolactone, although any COCP will help suppress ovarian hyperandrogenism and concurrently achieve an elevation in SHBG production and thereby help suppress the free androgen levels.

Alternatives to the COCP •

- include a progestogen, for example medroxyprogesterone acetate (Provera), for 12 days every 1–3 months to induce withdrawal bleed, or simply the insertion of a Mirena intrautrin Levonogesteril system.

- In women with anovulatory cycles the action of estradiol
- on the endometrium is unopposed because of the lack of
- cyclical progesterone secretion. This may result in episodes
- of irregular uterine bleeding, and in the long term endometrial hyperplasia and even endometrial cancer ().
- An ultrasound assessment of endometrial thickness provides a bioassay for oestradiol production by the ovaries and conversion of androgens in the peripheral fat. If the endometrium is thicker than 10 mm a withdrawal bleed should be induced and if the endometrium fails to shed then endometrial sampling is required to exclude endometrial hyperplasia.

Hyperandrogenism and hirsutism

The bioavailability of testosterone is affected by the serum concentration of SHBG. High levels of insulin lower the production of SHBG and so increase the free fraction of androgen. Elevated serum androgen concentrations stimulate peripheral androgen receptors, resulting in an increase in 5-alpha reductase activity directly increasing the conversion of testosterone to the more potent metabolite, dihydrotestosterone. Symptoms of hyperandrogenism include hirsutism and acne, which are both distressing conditions. Hirsutism is characterised by terminal hair growth in a male pattern of distribution, including chin, upper lip, chest, upper and lower back, upper and lower abdomen, upper arm, thigh and buttocks. A standardised scoring system, such as the modified Ferriman and Gallwey score, should be used to evaluate the degree of hirsutism before and during treatments.

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MANAGEMENT OF INFERTILITY IN PCOS

- PCOS accounts for approximately 80–90 per cent of women with anovulatory infertility, which in turn comprises about a third of those attending the infertility clinicA patient's weight correlates with both an increased rate of cycle disturbance and infertility secondaryto disturbances in insulin metabolism. National guidelines in the UK for managing overweight women with PCOS advise weight loss, preferably to a BMI of less than 30 kg/m2, before commencing drugs for ovarian stimulation.Hypersecretion of LH is found in 40 per cent of women with PCOS and is associated with a reduced chance of conception and an increased risk of miscarriage, possibly through an adverse effect of LH on oocyte maturation

MANAGEMENT OF INFERTILITY IN PCOS

- Strategies to induce ovulation include weight loss, oral anti-oestrogens (principally clomiphene citrate), parenteral gonadotrophin therapy and laparoscopic ovarian surgery.

Clomiphene citrate therapy

- The anti-oestrogen clomiphene citrate (CC) has traditionally been used as first-line therapy for anovulatory PCOS. CC
- therapy is usually commenced on day 2 of the cycle and given for 5 days. If the patient has oligo/amenorrhoea it is necessary to exclude pregnancy and then induce a withdrawal bleed with a short course of a progestogen, such as medroxyprogesterone acetate 20 mg/day for 5 to 10 days. The starting dose of CC is 50 mg/day, for 5 days beginning on days 3–5 of the menstrual cycle (the first day of bleeding is considered day1 of the cycle).

- The dose of CC may be increased to
- 100 mg if there is no response. Doses of 150 mg/day or more appear not to be of benefit. If there is an exuberant response to 50 mg/day, as in some women with PCOS, the dose can
- be decreased to 25 mg/day. Discontinuation of CC therapy should be considered if the patient is anovulatory after the dose has been increased up to 100 mg/day .CC induces ovulation in approximately 70–85 per cent of patients and approximately
- 60–70 per cent should be pregnant by six cycles of therap All women who are prescribed CC should be carefully monitored with a combination of endocrine and ultrasonographic assessment of follicular growth and ovulation because of the risk of multiple pregnancies, which is approximately 10 per cent

- If pregnancy has not occurred after 6–9 normal ovulatory cycles it is then reasonable to offer the couple assisted conception (i.e. IVF). Patients with anovulatory infertility who are resistant to antiestrogen they term ‘clomiphene resistance, strictly speaking refers to a failure to ovulate rather than failure to conceive despite ovulation, which should be termed ‘clomiphene failure

Gonadotrophin therapy

Gonadotrophin therapy is indicated for

- women with anovulatory PCOS who have been treated withanti-oestrogens if they have failed to ovulate or if they have a response to clomifene that is likely to reduce their chance of conception (e.g. persistent hypersecretion of LH, or anti-oestrogenic effect on cervical mucus

In order to prevent the risks of overstimulation and multiple pregnancy, a low-dose step-up regimen should be used

- with a daily starting dose of 25–50 IU of FSH or hMG. Ovulation is triggered with a single subcutaneous injection of hCG 5000 units, when there has been the development of 18mm mature follicle.

Insulin-sensitising agents

The biguanide metformin both inhibits the production of hepatic glucose, thereby decreasing insulin secretion,and also enhances insulin sensitivity at the cellular level. In the

reproductive effects of metformin in patients with PCOS. Initial studies appeared to be promising, suggesting that metformin could improve fertility in women with PCOS;

Surgical ovulation induction

- An alternative to gonadotrophin therapy for clomiphene resistant PCOS is laparoscopic ovarian diathermy involves burning four ‘holes’ into each ovary with a diathermy probe. This has replaced the more invasive and damaging technique of ovarian wedge resection. Laparoscopic ovarian diathermy is free of the risks of multiple pregnancy and ovarian hyperstimulation and does not require intensive ultrasound monitoring. Furthermore, ovarian diathermy appears to be as effective as routine gonadotrophin therapy in the treatment of clomiphene-insensitive PCOS, although it does take longer to conceive and often additional therapy with CC or gonadotrophins is required after surgery if ovulation is not occure.,

n addition, laparoscopic ovarian surgery is a useful therapy for anovulatory women with PCOS who fail to respond to clomiphene and who persistently hypersecrete LH, or who live too far away from the hospital to be able to attend for the intensive monitoring required in gonadotrophin therapy. Surgery does, of course, carry its own risks and must be performed only by fully trained laparoscopic surgeons.

IVF in women with polycystic ovaries

- IVF is not the first-line treatment for PCOS, but many patients with the syndrome may be referred for IVF, either because there is another reason for their infertility or because they fail to conceive despite ovulating (whether spontaneously or with assistance) – i.e. their infertility remains unexplained.