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Polycystic Ovary Syndrome: More Than Just Anovulation

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Abstract
Since its description by American gynaecologists, Irving Stein and Michael Leventhal in 1935, considerable information has accumulated about the pathology, pathogenesis and manifestations of what is currently known as polycystic ovary disease. Although there is a lack of unanimity in nomenclature, this condition continues to afflict women, usually manifesting with menstrual disturbances and infertility. Recent advances in understanding of its pathophysiology and pathogenesis have unfolded a number of long term health risks to the syndrome. This makes specific treatment or prevention by way of screening for these risks an imperative in patients with the syndrome.
Key Words: PCOD, Polycystic Ovaries, Anovulation

Introduction

Since its description by American gynaecologists, Irving Stein and Michael Leventhal in 1935 [1, 2], considerable information has accumulated about the pathology, pathogenesis and manifestations of the Polycystic Ovary Syndrome (PCOS). It has also been described as polycystic ovary disease, functional ovarian hyperandrogenism, hyperandrogenic chronic anovulation, ovarian dysmetabolic syndrome and ovarian androgen excess .This probably highlights a lack of unanimity in nomenclature. Recent advances in understanding of its pathophysiology and pathogenesis have unfolded a number of long term health risks to the syndrome. This enables specific treatment or prevention by way of screening for these risks in patients with the syndrome[3,4]. PCOS is the commonest endocrine abnormality in gynaecological practice affecting 5-20% of women of reproductive age[4,5] of all races and nationalities.

Aetiology

Debate continues as to the exact cause of PCOS. A widely accepted hypothesis proposes androgen overproduction by the adrenal gland at puberty or at times of stress resulting in disturbance in the cyclical production of GnRH release by the hypothalamus.[6]

An autosomal dominant transmission with incomplete penetrance has been shown with differential inheritance of the various aspects of the syndrome[7, 8] Furthermore, a sub-clinical PCOS may exist which may then become expressed over time. [9]

Pathophysiology

Basically a disturbance in the hypothalamic-pituitary-ovarian axis hormonal regulatory pathway is triggered by abnormal adrenal androgen production. The result is elevated LH and normal or low FSH. There is also increased levels of estrogens primarily oestrone and oestradiol. These results in suppression of pituitary FSH secretion and increase release of LH. This results in increased production of androgen precursors by ovarian theca cells. The peripheral conversion of androgens to oestrogens primarily oestrogens strengthen the feedback effect on the pituitary gland.

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High serum androgens inhibit the production of sex hormone binding globulin in the liver indirectly increasing the levels of free estrogens in the blood. Elevated androgen levels in the ovary exerts inhibitory effect in the follicular maturation, this in conjunction with the continuous but diminished FSH levels encourage growth of follicles but not their maturation thus the finding of numerous small sized follicles in various phases of development and atresia.

Obesity may play a pathogenic role in the development of the syndrome in susceptible individuals [7].It also worsens the symptomatology and endocrine profile as well as contributing to insulin resistance and associated hyperinsulinemia thereby increasing the risk of type 2 diabetes.

Presentation

PCOS can be diagnosed at any age from menarche to the menopause but typically presents in patients in their late teens or early twenties with acne, hirsutism or difficulty to conceive respectively. Although uncommon, patients could present with primary amenorrhoea between the ages of 10 and 20 years due to PCOS[3].

Patients are obese in a third of cases with oligomenorrhoea and amenorrhea typically punctuated by occasional heavy bleeding due to absence of progesterone. Infertility due to chronic anovulation and features of androgen excess including male pattern baldness androgenic alopecia) acne, oily skin, seborrhoea, acanthosis nigricans (dark patches of skin tan to dark brown), acrochordons (skin tags) which are tiny flaps of skin over areas of the skin being rubbed by clothes like behind the neck, under the arm , and under the breast.

Other features include PMS-like symptoms (bloating, mood swings pelvic pain, backaches) Depressions and anxiety which may be due to the hormonal imbalance or by self-esteem problems often experienced by these women. A number of patients are identified only when they present with unrelated symptoms.[10]

Diagnosis is made by TVS or TAS in a patient with clinical and biochemical features of PCOS. The ovaries are generally enlarged 1.5 to 3 times the normal size with thickened smooth, pearl-white outer surface. The stroma is echogenic and small peripherally arranged follicles give it a string of pearl appearance. There are no dominant follicles. However about 30% of patients with endorinological findings of PCOS have normal sized ovaries on sonograms[11]. Doppler analysis can be a valuable additional tool for the diagnosis of polycystic ovary syndrome. Studies have shown significantly elevated uterine artery pulsatility index values associated with a typical low resistance index of stroma ovary vascularization. The plasticity index show positive correlation with the Luteinizing hormone/follicle-stimulating hormone ratio, and the resistance index show negative correlation. The elevated uterine artery resistance are correlated with androstenedione levels.[12]

Magnetic Resonance Imaging [MRI] is useful as an adjunct. It is more sensitive than sonography, its findings however is less specific. It is expensive and not available in every unit.

Biochemical features of PCOS include elevated LH with normal or low FSH. LH: FSH of two or more is common. Elevated androgens androstenedione, low sex hormone binding globulin, high oestradiol, oestrone and elevated serum prolactin are associated features. There is associated insulin resistance i.e. high fasting insulin with normal or hypoglycaemia. Dyslipideamia, raised triglycerides and total and low density lipoprotein, cholesterol are

additional biochemical features.

PCOS is an important metabolic disease and is associated with long term health consequences[13, 14]. Insulin resistance has been linked to later development of

Table 1
The Spectrum of clinical manifestation of Polycystic Ovary Syndrome

Clinical Features	Serum Endocrinology	Late Sequel
Obesity Menstrual abnormality Infertility Acne Hirsutism Seborrhoea, Acanthosis nigricans Acrochordons Asymptomatic with polycystic ovaries on ultrasound.	↑Fasting insulin (not routinely measured, insulin resistance assessed by GTT ↑Androgens (testosterone androstenedione) ↑Luteinizing hormone (LH) Normal Follicle stimulating hormone ↓Sex hormone binding globulin (SHBG) ↑free androgen index ↑Oestrodiol, Oestrone ↑Prolactin	Diabetes Mellitus Dyslipidaemia Hypertension Cardiovascular disease Endometrial carcinoma

impaired glucose tolerance (IGT) and type 11 diabetes. Evidence from long-term cohort studies and case series points to a 10-20% risk of diabetes which usually sets in at around the middle age [15, 16]. Beta cell dysfunction and hyperinsulinemia have been found in both lean and obese patients alike.[16]

PCOS is also associated with increased risk of cardiovascular disease including atherosclerotic condition and myocardial infarction [12, 17, 18].Obesity hypertension, hyperandrogenism further increase the risk of cardiovascular disease. This is frequently associated with abnormal lipid profile in form of raised triglycerides and total and low density lipoprotein cholesterol [16, 17, 18].**Risk of Cancer**

The risk of endometrial cancer in PCOS is caused by a coupling of the effects of infertility, chronic estrogen exposure, obesity and diabetes mellitus. It has been demonstrated in *numerous* studies that women who have not achieved a pregnancy have two to three times the risk of developing endometrial cancer compared to women who have [19].

Women with PCOS experience severe oligomenorrhoea and amenorrhoea in the presence of premenopausal levels of oestrogens. Anovulatory cycles result in chronic exposure of the endometrial lining to estrogen with out progestogenic protection. This results in an increased risk of developing endometrial hyperplasia and endometrial cancer before the age of 45 years[20, 21]. The lesions tend to be well-differentiated cancers, suggesting the influence of estrogen exposure[21]

Obesity is an important risk factor, as women

who are 21 to 50 pounds (9.5-22.7 kg) overweight have a three fold increase in the risk of endometrial cancer. Women who weigh more than 50 pounds over their recommended weight have a 10 fold increase in risk [22]. This is due the an increased peripheral conversion of androstenedione to estrone in adipose tissue resulting in chronic exposure of the endometrium to increased circulating estrogen, thus increasing the risk of endometrial cancer.

Diabetes mellitus increases a woman's risk of developing endometrial cancer by greater than two fold [23].The effect may be mediated through elevated oestrogen levels in diabetic women, hyperinsulinemia or insulin-like growth factor-I (IGF-I). The association between diabetes and risk of endometrial cancer was considered in a large case-control study involving 752 women conducted in Italy which results confirm that non-insulin-dependent diabetes increases the risk of endometrial cancer [24]

The associated increased risk of breast cancer in PCOS is however disputed by the result of a large prospective cohort study which showed no significant increase in the risk of breast cancer in association with PCOS compared with controls (RR 1.2 95% CI 0.7-2.0) [25]

PCOS and Pregnancy

Not only are patients sub fertile due to chronic an ovulation, the high levels of Luteinizing hormone (LH) predisposes them to recurrent miscarriages. Prepregnancy suppression of LH however neither reduces the risk of miscarriage nor improves the live birth rate [26].It is therefore not an appropriate treatment option for PCOS patients with recurrent miscarriage.

Ovulation induction in patients with PCOS is associated with increased risk of ovarian hyper stimulation syndrome (OHSS) and multiple pregnancies due to their increased sensitivity to ovulation inducing agents. Gestational diabetes and abnormal glucose tolerance in pregnancy are common medical problems in obese women with PCOS [27]

Management of PCOS

The heterogeneity of the syndrome makes it necessary to individualise treatment. Obese patients should have fasting blood sugar and urinalysis and abnormal results investigated with a 75g OGTT because of the high incidence of type II Diabetes. Measurement of fasting cholesterol, lipids and triglycerides if abnormal, will require further surveillance or treatment with cholesterol lowering agents.

Obesity

Weight loss should be encouraged through diet and exercise. Studies have shown weight loss to improve both the endocrine and metabolic profile as well as the likelihood of spontaneous ovulation and a healthy pregnancy [28]. Others have shown reduction of ovarian volume and micro follicles with improvement in the anthropometric indices [29]. The 'correct' diet is one that is acceptable to the individual but diets low in carbohydrates and fats are sensible. A target BMI of around 27kg/m is ideal[2] and the help of a dietician may be invaluable. The role of anti-obesity drugs such as orlistat and sibutramine is inconclusive although some early reports show effective weight loss with. Their use should however be monitored as there are no long term studies on their safety.

Exercise is a useful adjunct in improving end-organ sensitivity to insulin and should be encouraged. Modifying lifestyle factors including alcohol and tobacco consumption and psychosocial stressors are useful in the long term management.

Use of Insulin Sensitizing Agents (ISA)

The recent understanding of the long term consequences of PCOS has been accompanied by renewed interest in the use of pharmacological agents such as metformin and triglitazone in order to

reduce insulin resistance, risk of diabetes and hyperandrogenism.

Metformin is preferred to triglitazone due to the latter's adverse effect on hepatic function. Metformin is a biguanide which reduces insulin resistance by inhibiting the hepatic glucose production and increasing peripheral tissue sensitivity to insulin. It is safe and effective and its benefits include improving obesity, hyperandrogenism, fertility, insulin sensitivity as well as lipid profile. It may have a direct effect on ovarian function [30, 31]. It is especially indicated in obese patients with PCOS. Started at a dose 750mg twice daily, it has no specific licence for this use and patients hepatic and renal functions must be assured before commencing therapy. Side effects include anorexia, nausea flatulence and diarrhoea. This may be reduced by taking metformin just before food and gradually increasing the dose from 750mg at night to 750mg twice daily after one week. The dose may need to be titrated to individual need.

Metformin does not cause lactic acidosis in non-diabetic women with normal hepatic and renal functions. It is usually discontinued in pregnancy though it has no teratogenic effect. . Most women require 4-6 months of metformin therapy before achieving ovulatory menses.

It could be used long term although its benefits in reducing the incidence of IGT, type II diabetes and dyslipideamia are yet to be proven by RCTs.It has however been proven to be effective and early reports indicate that it may reduce the risk of gestational diabetes [32,33,34]. It interacts with iodine and must be discontinued for three days after use of iodine containing contrast medium. Newer ISA like Rosiglitazone, proglitazone are currently being evaluated. D-chiro-inositol, a phosphoglycan has also been effective in patients with PCOS [35].

Use of Ovulation Induction Agents

Ovulation induction often requires careful progression through various treatment options to reduce the risk of multiple pregnancy and OHSS. Anti-oestrogens such as clomiphene citrate (50-100mg) or tamoxifen (20-40mg) are commonly used. Patients with PCOS generally do well with anti- oestrogens due to their high oestrogen levels.

Clomiphene citrate achieves a 60-80% ovulation rate but the pregnancy rate is only about 40%. Clomiphene acts at the level of the hypothalamus, pituitary and ovary. It is started at a dose of 50mg for five days of spontaneous menstruation or progesterone induced bleed, when ovulation occurs at this dosage there is no advantage to increasing the dose in subsequent cycles. Otherwise, a second course of 100mg (in single dose) for five days should be given. Increase in dose beyond 100mg rarely confers any benefit and can be associated with thickening of cervical mucus and a negative effect on the endometrium with consequent decrease in fertility rate. Women on clomiphene citrate should be monitored with ultrasound, to tract ovulation and also reduce the 10% risk of multiple pregnancy. Majority of patients will ovulate after three courses. Once ovulatory dose has been reached the cumulative pregnancy rate continues to increase up to ten to twelve cycles [36].However use of the drug should be limited to six cycles only. This is because its safety beyond six months has not been demonstrated.

There have been reports of ovarian cancer associated with use of fertility drugs however infertility itself is a primary risk factor. [37] Epidemiological data however does suggest that the prolonged use of clomid may increase the risk of ovarian cancer which emphasizes the need for caution. Tamoxifen is useful in selected patients but its effects on endometrium make it a second

line drug.

Clomiphene Resistance

Twenty percent of patients are resistant to Clomiphene citrate for which a number of other agents are used alone or in combination. Metformin in addition to clomiphene citrate is more effective than Clomiphene alone. This is supported by evidence from meta-analysis of 15 RCT involving over 500 women which showed that metformin is effective in achieving ovulation in women with polycystic ovary syndrome, with odds ratios of 3.88 (95% confidence interval 2.25 to 6.69) for metformin compared with placebo and 4.41 (2.37 to 8.22) for metformin and clomiphene compared with clomiphene alone. An analysis of pregnancy rates shows a significant treatment effect for metformin and clomiphene (Odds ratio 4.40, 1.96 to 9.85) [38]. This evidence supports the addition of metformin to clomiphene resistant patients

Gonadotropins in form of dose FSH, recombinant FSH, or urinary FSH are reasonable efficient strategy for inducing ovulation in clomiphene resistant patients. The use of gonadotropins must be closely monitored with ultrasound scan and serum oestradiol levels to minimise risk of OHSS and higher multiple pregnancy.

OHSS occurs if too many follicles are stimulated (>10mm) and presents with abdominal distension, nausea, vomiting and sometimes difficulty in breathing. The mechanism of OHSS may be activation of ovarian renin angiotension pathway and excessive stimulation of vascular epidermal growth factor (VEGF). Ascites, pleural and pericardial effusion aggravate this already serious condition and the resultant haemoconcentration could result in thromboembolism. The condition worsens if pregnancy has resulted from the treatment as the placental human chorionic gonadotropin further stimulates the ovaries. Moderate to severe conditions are treated in hospital with intravenous fluids and heparin to prevent dehydration and thromboembolism. Although rare, OHSS is potentially fatal and must be prevented by appropriate monitoring of gonadotropin therapy.

The advent of transvaginal ultrasonography has enabled multiple pregnancies to be reduced to approximately 7% because of its higher resolution and clearer view of the developing follicles. The cumulative conception and live birth rate after 6 months is about 62% and 54% respectively and after 12 months 73 and 62% respectively. [39] It is reasonable to suspend treatment if three or more follicles develop in order to reduce risk of multiple pregnancy.

GnRH though effective is expensive, stressful and time consuming requiring intensive monitoring.

Laparoscopic Ovarian Diathermy (LOD)

LOD is now the surgical option of choice, avoiding peritubal adhesions and follicular wastage of wedge ovarian resection, (WOR). It is also minimally invasive and has a high success rate in achieving unifollicular ovulation and singleton pregnancy with comparative efficacy to parenteral gonadotropins. . [34] There is no risk of OHSS or problems with high order multiple pregnancy. It is especially suitable for patients in who USS monitoring is not available.

There is currently an uncertainty about the optimum number of punctures to be applied at LOD and the amount of energy to use. Retrospective analysis has however shown that more than 2 punctures per ovary are required to achieve an effect. Application of seven or more punctures results in excessive destruction of the ovary without improvement of results and should be

avoided. . [35]

The procedure can be done as an outpatient and has less risks of trauma and fewer postoperative adhesions compared to WOR. Repeat LOD has been shown to be effective in some selected patients.

Regarding technique, similar results have been obtained using biopsy, cauterisation micro coagulation or laser therapy which is > 50% ovulation and a mean pregnancy rate of 50%. Use of transvaginal hydro laparoscopic ovarian drilling has been shown to be an effective alternative option with equivalent ovulation and pregnancy rate and avoids the inherent risks of laparoscopy. [36] The risks of LOD include premature ovarian failure and ovarian atrophy.

IVF and PCOS

A proportion of patients will ultimately require some form of assisted reproduction but caution must be exercised during super ovulation because of higher risk of OHSS. These patients have a higher average number of oocytes per stimulation than controls but because of the higher rate of immature oocytes, they tend to have a slightly lower rate of fertilisation than control (52 vs. 61%).. [38] However both IVF and ICSI are efficient for PCOS patients.

Management of Acne and Hirsutism

Acne and excessive body hair growth in a male pattern distribution are cutaneous responses to excessive androgen stimulation and may be the main concern of especially young women at presentation. A standardised scoring system such as the Ferriman and Galloway score should be used to evaluate the degree of hirsutism before and during treatment.

Treatment depends on severity and can be either local or systemic. Physical methods using shaving, waxing, bleaching, electrolysis or indeed laser and photothermolysis achieve quick but temporary relief. Each has its unique side effects and inconveniences. [39]. They however are useful pending the effect of drug therapy. Drug therapies take at least six to nine months to be effective because of the length of the hair cycle. The best pharmacological method of proven effectiveness is a combination of the synthetic progesterone cyproterone acetate (CPA 50mg-100mg) and ethinyl oestradiol 35 mcg. The cyproterone is used for the first 10 days of the cycle the "reversed sequential" method while the oestrogen for the first 21 days .After a gap of 7days during which menstruation occurs, the regime is repeated again. Dianette is combination of CPA and Ethinyl oestradiol (CPA/EE 2mg/35mcg). Though in a lower dose, is convenient, easier to use and equally effective. Cyproterone can rarely cause liver damage therefore liver function test should be checked every six months.

Third generation combined oral contraceptives are very useful in control of acne and hirsutism. Yasmin, the new drosperinone containing contraceptive has shown promise.

Spironolactone has an anti androgenic effect and may be used in a dose of 25-100mg in women in who the combined oral contraceptive pills are contraindicated.

Anti- androgens like finesteride, flutamide and ketoconazole are also effective but must be used with effective contraception as they interfere with genital development of a male foetus. [40].

In conclusion PCOS is a heterogeneous disorder with associated long term metabolic risks and endometrial cancer. Treatment is individualised according to patient needs. Effective surveillance could prevent or enable early diagnosis of dyslipideamia and type 2 diabetes while endometrial protection with progesterone will reduce the risk of cancer

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