An overview on polycystic ovary syndrome and its treatment

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INTRODUCTION

Polycystic ovary syndrome is a heterogeneous endocrine condition that affects approximately 5% to 10% of women in the reproductive age group (12–45 years old) [1]. PCOS was first identified by Stein and Leventhal in 1935 so that it can also be known as Stein – Leventhal Syndrome. Depending on the population being examined, however, prevalence rates as high as 26% have been reported that 70% of them were previously undiagnosed. The prevalence of PCOS depends on the choice of diagnostic criteria. Women with PCOS have difficulty becoming pregnant due to hormone imbalances that cause or result from altered development of ovarian follicles. One such imbalance is high blood levels of androgens, which can come from both the ovaries and adrenal gland. Other organ systems that are affected by PCOS include the pancreas, liver, muscle, blood vasculature, and fat. Women with PCOS often present with infertility, obesity, and clinical features of hyperandrogenism, such as hirsutism, acne, and alopecia. It is important to understand that PCOS is a syndrome, not a disease, reflecting multiple potential etiologies with variable clinical expression of these and other features in adolescents and adults with this syndrome. PCOS treatments must be directed at addressing the immediate goals of patients and preventing short- and long-term complications. By addressing these complications and making lifestyle changes that are supported by appropriate pharmacologic interventions with continuous surveillance, patients’ quality of life can be improved.

Common signs and symptoms of polycystic ovary syndrome

Common signs and symptoms of polycystic ovary syndrome include the following
- Irregular menstrual periods- menstrual bleeding may be absent, heavy, or unpredictable.

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Infertility—PCOS is one of the most common causes of female infertility.

- Obesity—up to 80% of women with PCOS are obese.
- Excess hair growth on the face, chest, abdomen, or upper thighs—this condition called hirsutism, affects more than 70% of women with PCOS.

**Fig 1. Multiple Cysts on ovary**

**Causes of PCOS**
Although the causes of PCOS are not known, it appears that PCOS may be related to many different factors together. These factors include insulin resistance, increased levels of androgens, and an irregular menstrual cycle.

a) **Insulin resistance**
Insulin resistance is a condition in which the body cells do not respond to the effects of insulin. When the body does not respond to insulin, the level of glucose in the blood increases. Higher than normal blood glucose levels may eventually lead to diabetes mellitus. Insulin resistance also may cause more insulin to be produced as the body tries to move glucose into cells. High insulin levels may cause the appetite to increase and leads to imbalances in other hormones. Insulin resistance is also associated with acanthosis nigricans.

b) **Higher than normal levels of androgens** are produced, the ovaries may be prevented from releasing an egg each month (a process called ovulation). High androgen levels also cause the unwanted hair growth and acne can seen in many women with PCOS.

c) **Irregular menstrual periods** can lead to infertility and in some women the development of numerous small cysts on the ovaries.

**Diagnostic Criteria**
Although debate on what constitutes PCOS continues, the Rotterdam Consensus on Diagnostic Criteria for PCOS published in 2003 is the most current definition. According to this consensus, a diagnosis of PCOS is based on at least 2 of the following 3 criteria.

- Oligo-ovulation or anovulation,
- Clinical or biochemical evidence of hyperandrogenism,
- Polycystic ovaries on ultrasound assessment (>12 small antral follicles in an ovary), with the exclusion of medical conditions such as genital adrenal hyperplasia, androgen-secreting tumours, or Cushing’s syndrome [3].

Patients who fulfill these criteria are often plagued by infertility secondary to both ovulatory dysfunction and the effects of hyperandrogenism. The following are the several methods that have been effective for ovulation induction and fertility treatment in women with PCOS:

- Weight loss, exercise, and lifestyle modifications
- Clomiphene citrate
- Metformin
- Gonadotropins
- Ovarian drilling
- IVF

**Complications and Recommendations Of Drugs For PCOD**
Women with PCOS may seek care from physicians in various medical specialties, including endocrinology, internal medicine, obstetrics and
gynecology, dermatology and family medicine. Therefore, physicians in these specialties must understand management of the short- and long-term complications associated with PCOS.

**Short term complications**

**Obesity**

Obesity in the PCOS patient tends to be central (android) or visceral in its distribution. The prevalence of obesity is 40% to 60% in this population. This epidemic exacerbates insulin resistance, ovulatory and menstrual dysfunction and pregnancy outcome. Obesity is associated with increased prevalence of metabolic syndrome, glucose intolerance, cardiovascular risk factors and sleep apnea [4].

**Recommendations**

Lifestyle modification is crucial. Modest amounts of weight loss have been shown to restore spontaneous ovulation and menstruation and to improve insulin sensitivity. No particular type of dietary modification has been shown to be superior. Anti-obesity medications, such as orlistat, sibutramine and rimonabant, and surgical weight loss have been found to be effective and even more sustainable in the long term for weight loss. Metformin has also appeared to have some benefit [5].

**Menstrual irregularities**

The prevalence of menstrual dysfunction in women with PCOS is 14.6% to 22.8%, and irregularities range from amenorrhea to menorrhagia with a classic peripubertal onset [6].

**Recommendations**

A modest weight reduction of 5% can return menses to normal. Combination oral contraceptives (COCs) or progestins are also effective at regulating the menstrual cycle in these patients. Metformin has been shown to have positive effects on ovulatory dysfunction and hyperandrogenism, ultimately restoring normal menstruation [7].

**Hyperandrogenisma**

Cutaneous hyperandrogenism manifests as hirsutism, acne androgenic alopecia. Its prevalence in the PCOS population in the form of acne is 15% to 25%; hirsutism, 65% to 75%; and alopecia, 5% to 50% [8].

**Recommendations**

COCs are beneficial for all forms of cutaneous hyperandrogenism; however, the selection of a low-androgenic progestin component is essential. Anti-androgens, such as spironolactone, flutamide or finasteride can then be added if acceptable results are not achieved, but these medications must be used in conjunction with COCs due to known risk of congenital anomalies. Efalornithine, a topical medication, has been shown to be effective in hirsute women, and waxing, shaving, depilatories, electrolysis and laser treatments are alternative options for hirsutism [9]. Topical retinoids and antimicrobials or oral antibiotics can be effective in the treatment of acne. Limited data support the use of topical minoxidil in the treatment of alopecia. Hyperandrogenism has also been shown to improve with dietary modification [10].

**Infertility**

Infertility due to anovulation affects 75% of women with PCOS [11].

**Recommendations**

Lifestyle modifications, including weight reduction, decreasing alcohol consumption, smoking cessation and limiting caffeine intake, are beneficial. Weight loss induces ovulation in overweight patients. Clomiphene citrate (CC) is a first-line pharmacologic treatment in anovulatory women with PCOS. Other agents used in ovulation induction include metformin and thiazolidinediones. Clomiphene citrate has been used as a first-line ovulation induction agent for over 40 years. It is a selective estrogen receptor modulator that stimulates endogenous FSH production and secretion by interrupting estrogen feedback to the hypothalamus and pituitary. PCOS patients can be sensitive to ovulation induction medications because of a large number of antral follicles. This places some women with PCOS at risk of overresponse with multiple follicular development and ovarian hyperstimulation; however, other women have a poor response without development of a dominant follicle, despite using higher doses of CC. The starting dose of clomiphene citrate is 50 mg per day for 5 days, commencing between day 2 and 5 of menses. Menses may be induced with a progestin if required. If this dose produces multiple follicular developments, the dose can be lowered to 25mg. If ovulation is not achieved using 50mg per day, the dose can be increased in increments of 50
mg. The manufacturer does not recommend exceeding 100 mg per day; however, many clinicians use doses up to 150 mg and some even up to 250 mg per day for 5 days, taking into account that alternatives treatments such as gonadotropins are more costly and have greater risk. Cycle monitoring should be considered in at least the first cycle and when the treatment dose has to be increased because of failure to ovulate. Although 60% to 85% of patients will ovulate on CC, only about one half will conceive. Approximately 50% of conceptions will occur on 50 mg, with another 20% to 25% and 10% occurring on 100 mg and 150 mg, respectively. Lack of conception despite evidence of ovulation may be due to anti-estrogenic effects of CC on the endometrium, which may manifest as a thin endometrium on ultrasound. In one study, no pregnancies occurred when the endometrium was < 6 mm at midcycle, but others have not found a similar association. Nevertheless, alternatives for ovulation induction should be considered if the periovulatory endometrium is persistently thin on CC therapy. Similarly, if pregnancy does not occur within 6 ovulatory cycles, another ovulation induction method should be considered.

Other drawbacks of CC include an increased rate of twin (7% to 9%) and triplet (0.3%) pregnancy, and side effects such as vasomotor hot flashes. Unusual visual symptoms (visual blurring or persistent after-images) are also noted in 1% to 2% of patients taking CC, which are likely due to anti-estrogenic effects of CC on the visual cortex. Although more studies are required, it is best to limit a patient’s lifetime exposure to CC to 12 treatment cycles, as additional cycles may place the patient at increased risk of borderline ovarian tumours.

**Insulin resistance and hyperinsulinemia**

Insulin resistance and compensatory hyperinsulinemia affect 40% to 70% of women with PCOS independent of obesity. The recognition of an association between PCOS and hyperinsulinemia has led to the use of insulin-sensitizing agents in ovulation induction. Metformin, the most widely studied agent used in PCOS, is a biguanide insulin-sensitizing agent that acts by inhibiting hepatic glucose production and increasing peripheral glucose uptake. It does not stimulate secretion of insulin or cause hypoglycemia. Many earlier studies examining the use of metformin alone or in conjunction with CC in ovulation induction showed promising results. The strongest predictors of insulin resistance in a patient with PCOS are body mass index, hyperandrogenemia, and hirsutism. Insulin resistance is also associated with obstructive sleep apnea, nonalcoholic steatohepatitis (nonalcoholic fatty liver disease) and metabolic abnormalities such as metabolic syndrome, dyslipidemia and Type 2 diabetes mellitus (T2DM), which are all more prevalent in these patients. Hyperinsulinemia also exacerbates cutaneous hyperandrogenism.

**Recommendations**

Weight reduction and medications such as metformin and thiazolidinediones have all been shown to decrease insulin resistance.

**Dyslipidemia**

Lipid abnormalities, including elevated low-density lipoprotein cholesterol levels, triglyceride levels, total cholesterol to high-density lipoprotein cholesterol ratios, and decreased high-density lipoprotein cholesterol levels are found in women with PCOS. The prevalence of abnormal lipid levels, according to National Cholesterol Education Program criteria, approaches 70% in these patients. PCOS patients have higher concentrations of smaller and higher-density LDL particles.

**Obstructive sleep apnea (OSA)**

Patients with PCOS have a higher risk for obstructive sleep apnea, even when compared with obese non-PCOS control subjects. Insulin resistance seems to be a better predictor of sleep-disordered breathing. Glucose tolerance is directly related to the severity of sleep apnea in these patients.

**Recommendations**

Weight loss, avoidance of alcohol, sleep position changes, avoidance of medications that inhibit the central nervous system and positive airway pressure have been shown to be effective.
Pregnancy loss
Pregnant women with PCOS have a 30% to 50% increased risk of early spontaneous abortion [20].

Recommendations
Weight reduction and medications such as metformin have been shown to reduce first trimester spontaneous abortion (SAB) rates. The optimum time to discontinue metformin has yet to be elucidated [21].

Pregnancy complications
Women with PCOS also have an increased risk of preterm delivery, hypertensive disorders, gestational diabetes and perinatal mortality. Maternal and neonatal risk are increased by iatrogenic multiple gestation from infertility treatment [22].

Recommendations
Metformin continued during pregnancy decreases rates of gestational diabetes [23].

Long-term complications
Following are long-term complications related to PCOS, as well as treatment options.

Endometrial hyperplasia and carcinoma
The chronic unopposed estrogen exposure in PCOS increases the risk of endometrial hyperplasia and endometrial carcinoma. An increased incidence of endometrial hyperplasia and atypia in the obese PCOS patient has been observed. Increased progression to carcinoma, however, has not been supported by epidemiologic evidence. PCOS patients have other risk factors for endometrial cancer including chronic hyperinsulinemia, increased concentrations of serum insulin-like growth factor, hyperandrogenemia and obesity.

Recommendations
To prevent endometrial hyperplasia, the use of COCs or the use of intermittent progestins is warranted. For women with oligomenorrhea or amenorrhea, menstruation is induced by the administration of medroxyprogesterone acetate prior to initiation of COCs. Progestins can be given every one month to three months to induce a withdrawal bleed. Endometrial biopsy should be performed for all women older than 35 years with abnormal bleeding and women younger than 35 years with risk factors for endometrial hyperplasia.

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Metabolic syndrome
Metabolic syndrome is associated with an increased risk of cardiovascular disease (CVD) and T2DM. Metabolic syndrome occurs in up to 43.6% of women with PCOS. Specifically for the PCOS patient, the presence of three of the following provides the diagnosis of metabolic syndrome:

- abdominal obesity (waist circumference, >35 inches) - triglycerides, >150 mg/dL
- high-density lipoprotein cholesterol, >50 mg/dL
- blood pressure, >130 systolic and/or >85 diastolic mm Hg
- fasting glucose level, 110 mg/dL to 126 mg/dL
- two-hour glucose tolerance test result, 140 mg/dL to 199 mg/dL

Recommendations
Treatment starts with lifestyle modification such as diet and exercise to reduce weight. Prevention of T2DM (pre diabetes) is achieved by administration of oral hypoglycemic metformin and thiazolidinediones. Use of lipid-lowering and antihypertensive therapies is effective in reducing cardiovascular risk [24].

Impaired glucose intolerance
Fifty percent to 75% of women with PCOS have T2DM or prediabetes. The conversion rate from impaired glucose tolerance to frank diabetes is fivefold to tenfold higher in women with PCOS.

Recommendations
Women should be screened with a fasting glucose test followed by a two-hour glucose test after ingesting a 75-gram glucose load. Management involving lifestyle modification, including diet, exercise and weight reduction, and an oral hypoglycemic and insulin should be initiated. Lifestyle modification has been shown to be the superior treatment for improving insulin sensitivity, reducing weight, decreasing the incidence of T2DM and metabolic syndrome and n improvising risk factors for CVD [25].

Cardiovascular disease
Insulin-resistant states are associated with a greater susceptibility to coronary artery disease. Women
with PCOS have increased CVD risk factors such as obesity, metabolic syndrome, hypertension, T2DM and dyslipidemia. These women exhibit greater endothelial dysfunction, arterial stiffness in the internal and external carotid arteries, presence of carotid and aortic plaque, increased thickness of intima media layers of the carotid artery and coronary artery and cerebrovascular artery calcification. Increased early left ventricular diastolic dysfunction, lower ejection fraction and a 7.1-times-higher risk than a non-PCOS patient for developing a myocardial infarction. Death from CVD is more common in women with PCOS. These risk factors could be the result of inflammation because C-reactive protein levels are elevated in PCOS patients.

Recommendations
Women with PCOS should be screened for cardiovascular risk by determination of body mass index, fasting lipid and lipoprotein levels, and metabolic syndrome risk factors. Management focuses on modifying the CVD risk factors [26].

Nonalcoholic steatohepatitis (NASH)
The prevalence of nonalcoholic steatohepatitis is increased in the PCOS patient and is associated with obesity, T2DM, and hyperlipidemia. Insulin resistance may be the key mechanism leading to hepatic steatosis.

Recommendations
There is no proven effective therapy for nonalcoholic steatohepatitis, although modification of risk factors is recommended [27].

Psychological disorders
The prevalence of depression in PCOS patients is reported to be as high as 40%. Depression has been associated with insulin resistance, impaired glucose intolerance and obesity. Patients with PCOS may have low self-esteem and poor selfimage. They can suffer from social withdrawal, eating disorders, and anxiety and may attempt suicide.

Recommendations
Treatment should include behavioral and psychological interventions adjunctive to standard medical care [28].

CONCLUSION
PCOS is a complex medical condition that requires a multidisciplinary team approach for optimal treatment. It is important to understand that PCOS is a syndrome, not a disease, reflecting multiple potential etiologies with variable clinical expression of these and other features in adolescents and adults with this syndrome. PCOS treatments must be directed at addressing the immediate goals of patients and preventing short- and long-term complications. By addressing these complications and making lifestyle changes that are supported by appropriate pharmacologic interventions with continuous surveillance, patients’ quality of life can be improved.

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