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POLYCYSTIC OVARY SYNDROME WITH METABOLIC SYNDROME

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Abstract

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder, where the main clinical features include menstrual irregularities, sub-fertility, obesity, acne, and hirsuitism. The Rotterdam criteria are used for diagnosis. Metabolic syndrome (MS) is a constellation of metabolic disorders that include abdominal obesity, insulin resistance, impaired glucose metabolism, hypertension and dyslipidaemia. PCOS has high potential to develop metabolic syndrome and it's consequences. Prevalence of MS is as high as 33% in women with PCOS, and is associated with consequences of cardiovascular disease (CVD), diabetes type II, cancers, sleep apnoea and psychological problems. Although PCOS may not present with MS rather present with chronic anovulation, hyprerandrogenism & infertility. But this could be the opportunity to intervene with lifestyle modification, medications to alter the risk profile for development of MS & cardiovascular disease. Despite the prevalence of MS in PCOS, it is a neglected entity. So it is prudent approach to emphasis on screening of MS in all PCOS. For that clinician's need to be aware in-depth of MS. Accurate identification and timed intervention may prevent long-term complication.

Lifestyle modification is the only universally accepted intervention. Metformin is widely used drug, it improves insulin sensitivity. The use of newer drugs such as myoinositol and liraglutide require further validation, while the use of statins should be limited only to women with dyslipidaemia. Bariatric surgery can be considered as a last resort.

Timely intervention and screening of metabolic syndrome in PCOS women improve the quality of life. The aim of this review is to provide clear and up to date information about PCOS and its relationship with metabolic syndrome.

Search done from AJOG, BJOG, Cochrane database, Pubmed, Webmed, UpToDate, Scholar Articles etc.

No conflict of interest.

Key words: PCOS, Metabolic syndrome, Hyperandronism, Metformin, Hirsuitism..

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder, where the main clinical features include menstrual irregularities, sub-fertility, obesity, acne, and hirsuitism.

The prevalence of PCOS depends on ethnicity, environmental and genetic factors, as well as the Rotterdam criteria used to define it. On the other hand, metabolic syndrome is a constellation of metabolic disorders, which include abdominal obesity, insulin resistance, impaired glucose metabolism, hypertension and atherogenic dyslipidaemia. Understanding metabolic syndrome involves two concepts- cardiovascular factors and endocrine factors, with emphasis on insulin resistance and its squeals. Many of the features of the metabolic syndrome, including insulin resistance, obesity, and dyslipidemias, are also present in PCOS. Is PCOS an early manifestation of the metabolic syndrome?

PCOS affects 10-18% of women of reproductive age1. Metabolic syndrome is increased in infertile women with PCOS.

Insulin resistance is believed to play an intrinsic role in the pathogenesis of PCOS.

Hyperinsulinemic-euglycemic clamp studies have shown that both obese and lean women with PCOS have some degree of insulin resistance. Insulin resistance is implicated in the ovulatory dysfunction of PCOS by disrupting the hypothalamic-pituitary-ovarian axis. Given the association with insulin resistance, all women with PCOS require evaluation for the risk of metabolic syndrome (MS) and its components, including type 2 diabetes, hypertension, hyperlipidaemia, and the possible risk of clinical events, including acute myocardial infarction and stroke. Obese women with PCOS are at increased risk for metabolic syndrome with impaired glucose tolerance (IGT; 31 to 35%) and type 2 diabetes mellitus (7.5 to 10%) 2. It is shown that the prevalence of metabolic syndrome is as high as 33% in women with PCOS, and is associated with long-term consequences such as cardiovascular disease (CVD), diabetes type II, cancers, sleep apnoea and psychological problems.

PCOS with hyperandronism & MS alter the physical appearance with loss of femininity. So it has been described poetically as “the thief of womanhood3.

Table 1.

Features of Polycystic Ovary Syndrome.

By definition:

- Oligomenorrhea
- Hyperandrogenism: acne or hirsutism, or
- Hyperandrogenemia: elevated total or free testosterone or DHEA-S

Also frequently seen:

- Insulin resistance
- Hyperinsulinemia
- Elevated LH:FSH ratio
- Abdominal obesity
- Polycystic ovaries by ultrasound*
- Infertility

DHEA-S, dihydroepiandrosterone-sulfate; LH, luteinizing hormone; FSH, follicle-stimulating hormone.
*Polycystic ovaries are not part of the definition of PCOS because they are also found in 24% of normal cycling, nonhyperandrogenic women.[84]

Julie L. Sharpless Clin Diabetes 2003;21:154-161

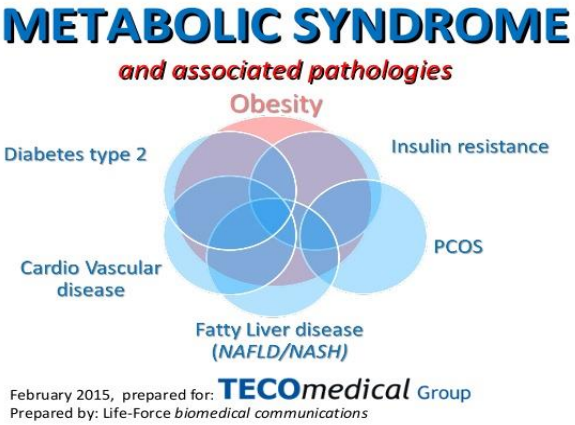
Women with PCOS seek medical attention for irregular menstruation, features of hyperandrogenism like obesity, acne, hirsuitism and infertility (table 1).

Pathogenesis

Insulin resistance and its consequent hyperinsulinemia, is central to the pathogenesis of PCOS. Women with PCOS have a higher prevalence and a greater degree of hyperinsulinemia 4,5 and insulin resistance 6, 7 than weight-matched control subjects. The mechanism by which insulin resistance gives rise to oligomenorrhea and hyperandrogenemia, however, is unclear. Obesity likely results from the combined effect of genetic predisposition, poor diet and a sedentary lifestyle, thus compounding pre-existing metabolic derangements predisposes PCOS.

Women who have PCOS, as many as 30% have impaired glucose tolerance (IGT) and an additional 7.5% have diabetes8. Even among non-obese women with PCOS, 10.3% has IGT, and 1.5% has diabetes 8. In long-term follow-up, 16% of women who had been treated for PCOS 20–30 years earlier had developed diabetes by the age of menopause 9. Interestingly suppression of the excess androgens does not alter the insulin resistance10,11.

Fig 1.



Insulin resistance is worsened by the coexistence of obesity, which is also increased in the PCOS population12. More than 40% of PCOS patients are obese. The insulin resistance is disproportionate to the obesity, however obese women with PCOS have greater chance of metabolic syndrome13,14.

Hyperandrogenaemia increases a person's predilection for central adiposity (Fig 1) and worsens insulin resistance and dyslipidaemia_15. In obese individuals, hypertension is linked to the potentiation of sympathetic outflow and the renin–angiotensin–aldosterone system, resulting from increased levels of insulin and free fatty acids. Concomitant vascular endothelial dysfunction also contributes to the development of hypertension16. Where metabolic syndrome coexists with PCOS, the risks are significantly higher. Despite adjusting for body mass index (BMI), there was a 55% increase in risk17._Subjects with metabolic syndrome are three to six times more likely to develop CHD, with a 12% increase in mortality 18,19. PCOS is associated with an increased likelihood of endometrial cancer 20. There is no strong association between PCOS and ovarian or breast cancer21. Metabolic syndrome has been associated with an increased risk of endometrial cancer (OR 1.6), poorer cancer outcomes, increased recurrences and overall mortality 22,23._PCOS is associated with 30-fold higher risk of obstructive sleep apnoea (OSA), independent of elevated testosterone levels and obesity 24. The prevalence of depression is higher in women with PCOS (OR 4.03) than the general population 25. Although inflammation has been linked to the development of depressive symptoms, the precise mechanisms have yet to be elucidated 26.

Diagnosis

Diagnosis of PCOS is guided by Rotterdam criteria. These criteria require that patients have at least two of the following conditions: hyperandrogenism, ovulatory dysfunction, and polycystic ovaries in USG. The diagnosis of PCOS also requires exclusion of other potential aetiologies of hyperandrogenism and ovulatory dysfunction.

Detailed History taking is most important to find out the symptoms of irregular menstruation, presence of hyperandrogenism like acne, hirsuitism, acanthosis nigricans, male type baldness, excessive weight gain and infertility.

Clinical examination includes, measurement of weight, BMI, waist circumference, BP estimation & heart- lungs auscultation. Presence of hirsuitism is examined by Ferry Galman's score. Abdominal examination needs to be done; vaginal exam is carried out when necessary.

There is no single diagnostic test for PCOS. Key investigations include prolactin, TSH, FSH, LH, 17 alpha OH progesterone, androstenedione, testosterone, DHEA, Cortisol, SHBG to exclude other disorders. An oral glucose tolerance test (rather than fasting glucose) and lipid profiles are appropriate in all women at diagnosis. Insulin levels should not be measured in clinical practice because variability and inaccuracy of assay. AMH is not recommended for routine test.

Pelvic ultrasound is done to look for ovarian morphology (Necklace pattern) and endometrial thickness.

The criteria used in diagnosing metabolic syndrome is depicted in Table 1 .

Table 1. Diagnostic criteria for metabolic syndrome

Measure	Categorical cut-off points
1. Elevated waist circumference	≥88 cm 24, 25 ≥80 cm 26, 27
2. Elevated triglycerides	≥150 mg/dl (1.7 mmol/l), or receiving drug treatment
3. Reduced HDL-C levels	<50 mg/dl (1.3 mmol/l), or receiving drug treatment
4. Elevated BP	Systolic BP ≥130 or diastolic BP ≥85 mm Hg, or treatment of previously diagnosed hypertension
5. Elevated fasting glucose levels	≥100 mg/dl (5.6 mmol/l) 25-27 ≥110 mg/dl (6.1 mmol/l)24 or receiving drug treatment

Data analysed by the IDF (International diabetes federation) supports a waist circumference of 80 cm and higher in women across different ethnicities. The Joint Interim Statement (JIS) 28 however, highlighted the importance of ethnicity-specific waist measurements, with equal emphasis placed on the individual risk-predicting factors. By unifying the diagnostic criteria of metabolic syndrome, the JIS simplifies its utility as a clinical tool and has emerged as one of the most commonly used definitions.

Screening of metabolic syndrome

The clustering of insulin resistance, obesity, hypertension, and dyslipidaemia has been termed "the metabolic syndrome."

Early detection and management of metabolic syndrome, especially in women of reproductive age with PCOS are very important to the healthcare system as the are at high risk of death from CVD. The study of JIS (joint interim statement) detected a very high prevalence of metabolic syndrome (nearly half of the adults), but the AHA defined better predictor of risk factors for cardiovascular events 28.

Anyway incidence of metabolic syndrome for PCOS is increasing. A comprehensive evaluation of the risk factors for metabolic syndrome, adapted from evidence-based guidelines from Australia and the UK's Royal College of Obstetricians and Gynaecologists 29 is shown in Table 2. This assessment can be applied in the clinical setting.

Table 2. Recommendations for metabolic syndrome risk factor screening in women with polycystic ovary syndrome

Screening parameters	Frequency of assessment
Cigarette smoking	At every visit, obtain history of recent smoking habits, if any, or cessation
Obesity (weight, BMI, waist circumference)	At every visit
Blood pressure	For women with a BMI <25 kg/m2: annually For women with a BMI ≥25 kg/m2: at every visit
Complete lipid profile	For women with a normal profile: every 2 years For women with an abnormal profile or excess weight: annually
Oral glucose tolerance test (75 g)	All women: every 2 years Women with risk factors (age >40 years, ethnicity, physical inactivity, smoking, waist circumference (>80 cm), BMI ≥25 kg/m2, hypertension, previous gestational diabetes mellitus, family history of diabetes mellitus): annually

• Key: BMI = body mass index

Management

Increased overlapping of PCOD and MS advocate's therapies that improve insulin resistance and ameliorate PCOS symptoms.

Though there is no established cure for PCOS, lifestyle changes have demonstrated substantial improvements in symptoms. Primary intervention for PCOS with metabolic syndrome requires adopting lifestyle changes that may prevent or slow progression to adverse events. Weight reduction through dietary changes and exercise are key in this process. Who does not respond adequately to lifestyle modifications, secondary interventions can be considered, including drug therapy and bariatric surgery.

Healthy lifestyle

It includes exercise and dietary regulation, women with PCOS should lose 5–10% of their body weight in the first year after diagnosis for improved clinical outcomes 30 . The lifestyle arm of the DPP included dietary education, weight loss counseling, and 150 minutes of exercise per week, resulted in a net loss of 7% body weight and a 58% reduction in the progression to diabetes. .79 The metformin arm, while effective, only reduced the progression to diabetes by 21% 79.

Weight loss decreases insulin resistance, optimises lipid profile, and may have psychological benefits such as reduced anxiety and depression. But for weigh reduction they deserve special consideration & high motivation.

Exercise

As a lifestyle modification, physical exercise helps sustain weight loss, but it also has benefits independent of weight loss. Exercise can increase glucose disposal and muscle sensitivity to insulin. PCOS, women who did 8 hours of sports activities per week, had improvement in acne and menstrual

irregularities 31. Exercise with weight loss (< 5%) improved insulin sensitivity and free testosterone index and induced ovulation in 9 of 18 obese PCOS patients 32.

Diet

Diet plan should be given to the all-obese PCOS patients irrespective of metabolic syndrome. PCOS women should intake carbohydrates with a low glycaemic index (GI), which improves insulin sensitivity 33. Diet should contain many fibres,that causes satiety, lowers cholesterol and slows absorption of carbohydrates. Proteins take longer to digest than carbohydrates; hence they can improve the insulin profile. Monounsaturated fatty acids improve cholesterol and glucose levels, as well as insulin response. Adequate omega-3 fat intake is important in PCOS as it benefits by lowering levels of inflammatory markers, cholesterol and triglycerides and increased insulin sensitivity 34,35. To maximise the benefits of a healthy diet, it is important to adopt healthy eating patterns, taking small portions of calorie-appropriate meals at frequent intervals36.

Medical therapies for PCOS

The treatment of the polycystic ovary syndrome is primarily directed at the major clinical manifestations, which are anovulation, cutaneous hyperandrogenism.

Combined hormonal contraceptive (CHC), Progesterone, Metformin. Inisitol, Orlistat, Satin are being used.

Abnormal uterine bleeding (AUB) can be managed either by a low-dose oral contraceptive or by cyclical/continuous administration of progestin.

CHC reduces LH, 5 alpha reductase, ovarian androgen and increases SHBG. So free androgens are reduced which results improvement of hirsuitism, acne and endometrial hyperplasia.

Choice of Progestin is crucial. Progestin that have intrinsic androgenic activity (such as norgestrel or norethindrone) should be avoided. OCP should be the 1st line therapy for adolescents especially who are contemplating sexual activity and alsowho are not willing to get pregnancy. Drospirenone, Microgest, cypreteterone acetate, could be the choice of progestin. Progesterone IUCD can be used which also reduce endometrial hyperplasia.

Hirsutism may be treated simply by the removal of hair or by cosmetic treatment, electrolysis, shaving, threading and with laser. Antiandrogen therapy can be offered. The most widely used antiandrogen is cyproterone acetate (2mg, 12.5, 100mg), and when combined with ethinyl estradiol, it provides effective control of menses and contraception. It prevents further hair growth.

Spironolactone — a mineralocorticoid and androgen receptors antagonist is used to treat hirsuitism. There is occasional incidence of vaginal bleeding and hyperkalemia. So administration needs monitoring of serum potassium.

Metformin improves insulin sensitivity in women with PCOS 37. It has also been shown to decrease fasting insulin levels, but this benefit was restricted to non-obese women with PCOS (BMI <30 kg/m2) 38. Metformin increases peripheral glucose uptake and decreases hepatic glucose production. The major advantage in PCOS is that metformin do not cause weight gain 39. Metformin has been used in incremental doses ranging from 500 to 1500 mg/day. There is no consensus on the duration of treatment required.

Lean women with PCOS also improve insulin resistance and hyperandrogenism without changing BMI on metformin. Metformin is a useful adjunct to lifestyle changes for women with complaints of menstrual irregularity or infertility, but not for those complaining of hirsutism.

Metformin is commonly associated with adverse gastrointestinal effects, including nausea, abdominal pain and diarrhoea. A few trials have demonstrated that use of metformin can lead to significant

weight loss, especially when combined with lifestyle modifications, but there is insufficient evidence to recommend its use for weight loss purposes 40. It improves the

Inisitol

Various studies have demonstrated that administration of Myo-inisitol (DCI) 1-4gm/day leads to decrease basal insulin levels, an improved lipid profile and reduced systolic blood pressure 41,42. No appreciable adverse effects have ever been recorded 43,44. Preliminary data suggest that supplementing with inositol can be considered for improving a patient's metabolic profile, but more studies are required before its use can be standardised.

Orlistat

Based on available evidence, orlistat can be considered for the treatment of overweight and obese women with PCOS for whom lifestyle modifications are insufficient 45. Patients take 60–360 mg of orlistat per day. Its use is associated with mild gastrointestinal side effects including steatorrhoea. A randomised study of orlistat on obese women with metabolic syndrome demonstrated reversal of metabolic syndrome in 43.5% of participants, with associated significant improvements in insulin resistance, lipid profile and blood pressure 46. The risk of progression of IGT to diabetes type II was also significantly reduced (by 37.3%)47. However, further studies are required to assess the use of orlistat in women with PCOS and metabolic syndrome before it can be recommend for therapeutic indications.

Liraglutide

Glucagon like receptor antagonist used for PCOS. No significantly positive effect has been shown on fasting insulin levels and insulin resistance 48. The use of liraglutide is limited by the need for parenteral administration

Statin

Statin improves lipid profiles. Furthermore, it reduces levels of markers of endothelial dysfunction and systemic inflammation suggests a decrease in cardiovascular risk factors49. Long-term use can cause liver dysfunction and, teratogenicity, which is of critical concern among women of reproductive age. So routine clinical use of statins cannot be recommended for women with PCOS. Though lot of medical treatments are available with apparent benefits but it must be weighed against the risk of potential adverse effects of prolong treatment.

Insulin does not improve chronic insulin resistance. Therefore, there is no apparent benefit to this therapy for women with PCOS who do not have diabetes, although the use of insulin specifically in PCOS has not been studied. Its use should be limited to women with diabetes and PCOS whose diabetes does not respond to the above oral agents (or who cannot tolerate them). As in any diabetic patient with extremely high blood glucose levels, in women with PCOS and diabetes, the short-term use of insulin may be necessary for immediate safety concerns to avoid dehydration and related complications. Insulin use also causes weight gain and therefore is not the best therapy for such women with early diabetes who are still producing excess insulin.

As with insulin, sulfonylureas act by augmenting insulin secretion rather than treating the primary pathology of insulin resistance. Therefore, they are not an appropriate therapy for women with both diabetes and PCOS.

Surgical treatment

Bariatric surgery have demonstrated reduced cardio metabolic risk, by an improved lipid profile and reduced insulin resistance 50,51. Common bariatric procedures include laparoscopic adjustable gastric banding, vertical banded gastroplasty and Roux-en-Y gastric bypass. This surgery reduces cardiovascular events, cures diabetes type II, hypertension, obstructive sleep apnoea and metabolic syndrome 52, 53. A meta-analysis of women with PCOS showed a significant reduction in the incidence of PCOS after bariatric surgery (from 45.6% to 6.8% at 12 months) 54. Bariatric surgery may also reduce the incidence of obesity-related cancers 55. But studies involving women with PCOS are

limited, though the results are encouraging. Further well-designed studies are required before bariatric surgery can form part of the mainstream management of metabolic syndrome in women with PCOS.

As national attention is focused on the emerging epidemic of type 2 diabetes and obesity, more energy is being directed toward earlier detection, improved therapies, and potential prevention

Pregnancy concerns.

The risks of these therapies in relation to their benefits for PCOS must be considered, especially in pregnancy. Because or PCOS patients pregnancy is a significant issue, as in many cases, infertility is the chief complaint. Metformin increases ovulation rapidly (as early as 3 months), modestly (increasing from one to two ovulations per 5 months), without weight loss56. Contraception is recommended for women who do not wish to become pregnant.

There is no evidence of animal or human teratogenicity for metformin (pregnancy category B). In mothers with diabetes, metformin has been used in the second and third trimesters without conclusive evidence of increased perinatal morbidity, although Coetzee et al 57 reported an increase in neonatal jaundice. Troglitazone is contraindicated in pregnancy. The study showed despite the controlled setting of a major study of troglitazone, 5.9% of subjects had unexpected pregnancies in the treatment arms, highlighting the need for counselling and contraception 58. Most insulin is safe for use and is the preferred therapy for diabetes in pregnancy. Having said this, most women with PCOS can have successful pregnancies without a dramatic increase in health risk, and the risks of pregnancy from diabetes and obesity can be minimized with good pre-pregnancy counselling and care.

The lifestyle arm of the DPP included dietary education, weight loss counselling, and 150 minutes of exercise per week, resulting in a net loss of 7% body weight and a 58% reduction in the progression to diabetes59. The metformin arm, while effective, only reduced the progression to diabetes by 21%. Metformin modestly increases menstrual regularity and ovulation and decreases weight without improving hirsuitism. Lean women with PCOS also improve insulin resistance and hyperandrogenism without changing BMI on metformin 60. Because of these benefits and its relative safety before pregnancy, metformin is a useful adjunct to lifestyle changes for women with complaints of menstrual irregularity or infertility, but not for those complaining of hirsuitism.

Pcos Women Without Diabetes

The metabolic syndrome by definition is associated with an increased risk of CVD. Treatment of the individual components of the syndrome, including dyslipidaemia, obesity, and hypertension, clearly decrease CVD. Data from the DPP have demonstrated the powerful effects of treating insulin resistance in patients at high risk of developing diabetes 61. Should women with PCOS be treated for insulin resistance alone (when infertility, oligomenorrhea, and hirsutism do not require treatment)? In this situation, the risks must be balanced with potential side effects and the need for monitoring in this young population. PCOS patients have distinct worsening with obesity and should be especially counselled not to gain excess weight. Lifestyle alterations and weight loss when indicated reduce insulin resistance and offer multiple benefits. Medical therapies are not only less effective, but also carry risks.

Future treatment options

Dual GLP-1/GIP receptor agonist (Twincretins).

Twicertins studies has shown a promising effect in reducing A1c and weight in T2DM patients compared with placebo62.

Conclusion:

Metabolic syndrome affects 33% of women with PCOS. Despite its high prevalence, it is a neglected entity in PCOS women. Unlike the metabolic syndrome PCOS presents with overt symptoms of infertility, hirsuitism, and acne. Although these are the problems that bring women to health care ,It

may afford providers the opportunity to intervene early with counselling and medications to alter the risk profile for later development of the metabolic syndrome or CVD.

It is imperative to screen MS, in PCOD to enable early diagnosis and institute aggressive measures for secondary prevention.

Lifestyle modification is the only universally accepted intervention. Metformin may be considered .The use of newer drugs such as inositol, Dual GLP-1/GIP receptor agonist and liraglutide require further validation & the use of statins should be limited only to women with dyslipidaemia. Bariatric surgery can be considered as a last resort. PCOS is complex heterogeneous disorder, which begins from childhood and may persist through life with complications. So, if we take proper care from adolescence, the complications of this progressive metabolic disease “PCOS” can be prevented in later ages and improve quality of life.

Disclosure of Interest; There is no conflicts of interest.