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Is PCOS An Early Manifestation of the Metabolic Syndrome? A Review Article with Latest Updates in the Laboratory Diagnosis, Prevention and Management

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Abstract: ***Background: Metabolic syndrome is a heterogeneous group of metabolic disorders which include mainly abdominal obesity, insulin resistance, impaired glucose metabolism, hypertension and dyslipidaemia. Main clinical manifestations of PCOS are irregular menstruation, infertility hyperandrog-enismand hirsutism. Discussion: Many patients with PCOS also have features of metabolic syndrome, and are at increased risk of Type 2 DM, CAD, CVD and endometrial cancer. Increased awareness of this overlap advocates therapies that improve insulin resistance and often ameliorate PCOS symptoms. 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. Summary: The aim of this review is to provide clear and up to date information about PCOS and its relationship with metabolic syndrome, and the possible interaction between different metabolic disorders.***

Keywords: Hypertension, insulin resistance; metabolic syndrome; polycystic ovary syndrome

1. Impact Statement

Obesity, Metabolic syndrome with increased risk of CAD, CVD, Type 2DM and PCOS are major health problems and more than 60% of the population is affected. With change in life style, exercise, and proper nutrition can prevent the progression of this associated metabolic disorders. Evidence based recent classification of these syndromes helps in better characterization and early detection. This study includes recent updates of cut off values of DM, IGT and HTN and newest drugs available in the market which will definitely improve the outcome of the disease.

NCEP	WHO	WHO modified*
Any three of the following criteria:		
Fasting plasma glucose ≥110 mg/dl	Insulin resistance (under hyperinsulinemic, euglycemic conditions)	Hyperinsulinemia: upper quartile of population **or** fasting plasma glucose ≥ 110 mg/dl
	Plus any two of the following criteria:	**Plus any two of the following criteria:**
Hypertension ≥ 130 mmHg systolic or ≥ 85 mmHg diastolic blood pressure	Hypertension > 160/90 mmHg or controlled with drug treatment	Hypertension ≥ 140/90 mmHg or controlled with drug treatment
Obesity Waist circumference > 40 inches for males, > 35 inches for females	Obesity BMI > 30 kg/m² **or** waist-to-hip ratio > 0.9 for males, > 0.85 for females	Obesity BMI ≥ 30 kg/m² **or** waist-to-hip ratio > 0.9 for males, > 0.85 for females
Elevated triglycerides ≥ 150 mg/dl	Elevated triglycerides ≥ 150 mg/dl	Dislipidemia with either or both: Elevated triglycerides ≥ 150 mg/dl
Low HDL cholesterol < 40 mg/dl for males, < 50 mg/dl for females	Low HDL cholesterol < 35 mg/dl for males, < 40 mg/dl for females	Low HDL cholesterol < 35 mg/dl for males, < 40 mg/dl for females
	Microalbuminuria > 20 µg/min or albumin-to-creatinine ratio ≥ 20 mg/g	

(Julie L. SharplessClin Diabetes 2003; 21:154-161)

2. Recent Updates - Metabolic Syndrome

PCOS and Metabolic syndrome have many features in common abdominal obesity, insulin resistance, impaired glucose metabolism, hypertension and dyslipidaemia. These associated disorders are at increased risk of Type 2 DM (Diabetes Mellitus), CAD (Coronary Artery Disease), CVD (Cardiovascular disease) and endometrial cancer The metabolic syndrome was recently codified in the National

Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) guidelines and has been differently defined by NCEP, WHO[1, 2]

Thus, major epidemiological studies such as the European Group for the Study of Insulin Resistance and the Botnia study in Finland and Sweden used widely applicable surrogate markers of insulin resistance, such as fasting glucose and insulin levels, or glucose tolerance tests.[3, 4, 5]

Recently the defining cut-off criteria of type2 DM & Hypertension has been lowered based on outcomes of research studies. The waist circumference has replaced BMI as a marker of obesity because of its better correlation within traabdominal visceral adipose tissue and worsened cardiovascular outcomes[6, 7, 8]

Using data from the Kuopio Finnish cohort, the NCEP ATP-III and the WHO modified definitions of the metabolic syndrome were both validated in a large epidemiological study that found up to four times CHD mortality in patients with the metabolic syndrome.[9]

PCOS– Defining criteria[10]
It has been described poetically as "the thief of womanhood

SOGC- Criteria for PCOD (any 2)
1) Menstrual dysfunction (Oligo/ Amenorrhoea, an ovulation, infertility)
2) Clinical / Biochemical evidence of of hyperandrogenism (Hirsuitism, testosterone,)
3) USG - >12 small antral follicles in an ovary

Other features are -
Obesity and metabolic syndrome & Diabetes (Acanthosisnigricans, HTN)
Insulin Resistance/or Hyperinsulinemia
Elevated LH/FSH ratio
Abdominal obesity
Infertility

Laboratory tests
1) TFT (TSH, free T4)
2) Serum Prolactin, FSH, LH, HCG
3) Total & free Testosterone
4) Fasting Blood glucose, HBA1c, Insulin level/ C peptide
5) Lipid – Total cholesterol, LDL, HDL, serum tryglycerides.

Women with PCOS have a higher prevalence and a greater degree of hyperinsulinemia[11, 12]and insulin resistance than weight-matched control subjects[13-15]. Among all PCOS cases, as many as 30% have impaired glucose tolerance (IGT) and 7.5% have diabetes.[16]Even among non obese women with PCOS, 10.3% have IGT, and 1.5% has diabetes. 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. [16, 17] The etiology of the insulin resistance is unclear, but suppression of the excess androgens does not alter the insulin resistance. More than 40% of PCOS patients are obese.[18, 19]

Increased risk	
Insulin Resistance Dyslipidemia HTN CAD CVD Type 2- DM	Obese PCOS are at greater risk as compared to Non obese PCOS

In classically defined PCOS, many risk factors, such as dyslipidemia and hypertension, and markers of CVD have been found. Models based on the combined risk factors of the metabolic syndrome in PCOS, such as obesity, diabetes, dyslipidemia, and hypertension; predict a sevenfold increased risk of myocardial infarction in women with PCOS compared to age-matched control subjects.

Therapeutic Overlap
It important to identify women with PCOS and the metabolic syndrome in order to target early intervention?

Classical PCOS + Type 2 DM → Treat DM & PCOS
Classical PCOS + other features of Metabolic syndrome → Broader range of therapeutic modalities

A) Diagnostic criteria for Type 2-Diabetes mellitus (DM): (ADA)
1) Glycatedhaemoglobin **(HbA_{1c}) value ≥6.5%** - (NSGP standards)
2) **FPG ≥126 mg/dl (7.0 mmol/L) (8 hours fasting) &2hPG ≥200 mg/dl (11.1 mmol/L)** (WHO :- OGTT using 75g Glucose)
3) **Random PG >200 mg/dl (11.1 mmol/L**).

Any one of the above Criteria+Typical Symptoms= DM

If patient is Asymptomatic, then repeat the test

Examination
Abdominal Circumference (AC) > 10% above Upper limit or AC >80 cms.
BMI > 27 Kg/m2, For Comorbities- Treatment required

Medical Management
1) **Work out - plan /strategy (Physical Activity + Aerobics / Gym) & Healthy eating**

a) Eating Habits:
Low-calorie diet for weight reduction.
Diet rich in fibers (25 to 40 g/day).-Whole grains, cereals, pulses, vegetables & fruits
Fats < 30% of total energy/day, low refined carbohydrate, transfats & saturated fats;
Increased omega-3 PUFA (reduce liver fat) - Fish, Cooking oil = Canola + Olive
Free sugars should be less than 5 % of total calories/day.

The (FDA) has approved 5 artificial sweeteners;
saccharin (Sweet 'N' Low, Sweet Twin, Necta Sweet), aspartame (Equal, Sweetex, Sugar free, Sugar free gold) acesulfame-K, neotame and sucralose (Splenda, Zero, natura)

b) Weight Reduction
1) Increase physical activity (severe), House work, Aerobics *, Gym,

2) Drugs for weight reduction :- (> 5% in 3 months)
- **PCOD + IGT + Risk factors – Metformin alone (preferred here) or**
- in combination with Orlistat (60 mg to 120 mg OD). GI symptoms
- PCOD + Type 2 DM – Metformin with standard regime (ADA+ ESD)
- GLP -1 agonists – Liraglutide** (3 mg/d).
- Bariatric surgery if BMI> 40 with comorbidities.

Increase physical activity (moderate to severe)
Daily 40 minutes of brisk walking or moderate running.
Both Aerobics + resistance exercise are essential to reduce HbA1C
(If you are obese then start weight management strategies & Healthy eating habits

Metabolic syndrome

Metformin (DOC)- makes menstrual cycles more regular, promotes ovulation and increase fertility, modest Wt reduction, Insulin sensitivity incr Prediabetes / IGT– Metformin can be given

Formulations: Immediate release - 500 mg, 850 mg, 1000 mg.
Extended release - - 500 mg, 750 mg, 1000 mg
Oral solution 100mg/mL
Taken Orally, along with food, plenty of water, avoid dehydration

MISSED DOSE: take it as soon as you remember. If it is near the time of the next dose, skip the missed dose and resume your usual dosing schedule. Do not double the dose to catch up.

Immediate-release tablet or solution
- Initial: 500 mg BD orally **or 850 mg OD** (prevention Type 2 DM), taken with meals; increase for every 2Weeks
- Maintenance: 1500-2550 mg/day PO divided for 8-12hr with meal
- Not to exceed 2550 mg/day

Extended-release
- **Glucophage XR**: 500 mg OD with dinner; titrate by 500 mg/day for every Week; not to exceed 2000 mg/day
- **Fortamet**: 500-1000 mg OD ; titrate by 500 mg/day For every Week; not to exceed 2500 mg/day
- **Glumetza**: 1000 mg OD; titrate by 500 mg/day for every Week; not to exceed 2000 mg/day

Caution: Hepatic impairment: Avoid use; risk of lactic acidosis,
Renal impairment
eGFR<30 mL/min/1.73 m²: - Contraindicated..

Adverse Effects: GI – Nausea, vomiting, dyspepsia, Diarrhea, Flatulence, constipation,

Weakness, Myalgia, Low serum vitamin B-12, Hypoglycemia

Hypertension
Systolic BP = 140 -159, Diastolic = 90-99 is HTN. Any 1 (ACE inhibitor/ ARB/ Thazide).

If Systolic> 150 mm/hg start dual therapy. Any 1 Drug (ACE inhibitor/ ARB) + Any 1 from (thiazide/ Ca Channel blocker/? B blocker)

If Type 2 DM – Start conventional therapy.

Dyslipidemia.
Aerobic physical activity raises HDL and lowers triglyceride levels

Protocols of Rx of Hypercholesterolemia
First target **is LDL** reduction & next **is TGs** & then **HDL & Non HDL-C**
a) First target LDL<100 mg/dl or 40% less than basal value
LDL < 70 mg/dl in CAD
If TGs - > 500 mg/dl then first target TGs

b) 2nd target – Triglycerides < 150 mg/dl,
HDL > 40 mg/dl (M) &> 50 mg/dl (F)
Non- HDL C < 130 mg/dl).

Step 1) Life style modification + Statins (if Goal not achieved)

Step 2) Statin + fenofibrate (If elderly & RF then fenofibrate is CI). Step 3) Combo of (Statin + PUFA) or High dose statins as single drug or PUFA only (if statins & fenofibrate not tolerated)

Statins: Rosuvastatin :-20 to 40 mg/day. more potent (lower TGs &Incr HDL)
Atorvastatin: - 40–80 mg/day
Statins provides long term safety. Myopathy rare

Caution: Statins can cause hyperglycemia (negated by intensification of therapeutic lifestyle changes)

If TGs> 200 & HDL < 35 better to start a dual therapy (statin and fenofibrate).
Combination very potent for Lowering TGs & increased HDL
Myopathy risk in elderly & with CRF
If statin or fenofibrate therapy - not tolerated then Omega-3 PUFA – as fish oil capsules at a dose of 2–4 g/day is an alternative strategy for lowering of TGs levels.

Niacin is the only drug that can cause significant elevation of HDL level.

But main adverse effect is flushing and can exacerbate hyperglycaemia

Frank Hypothyroidism
Full replacement dose is 1.6 µg L-thyroxine /kg /body wt.
Type 2 DM + CAD – start with initial low dose 25 µg daily,
Normal cases -?
L-thyroxine is increased by 25 µg monthly
The dose can be titrated by measuring TSH every 4–6 weeks initially.

On achieving TSH goal then a stable dose of L-thyroxine is used.

1) First-line treatment for ovulation induction & fertility - clomiphene citrate given singly or in combination of Metformin[20, 21, 22]

a) Clomiphene citrate (Clomid, Serophene):
Treatment of Ovulatory Failure 50 mg OD/day initially for 5 days, if no ovulation, treatment can be repeated as early as 30 days after previous therapy. Dosage can be increased to 100 mg only in patients who do not respond to first course

Monitor: Reassess diagnosis after 3 courses, if ovulation has not occurred or if menses does not occur following ovulatory response

b) Clomiphene citrate–resistant PCOS
Metformin/letrozole and bilateral ovarian drilling Ovulation induction with clomiphene citrate, metformin, or both does not alter hirsutism in infertile hirsute women with PCOS.

c) Metformin/ letrozole orLetrozole alone - more Effective than Clomiphene
(Legro et al 28% Letrvs 19% Clomp)
FSH, LH and ratio of LH to FSH - Reduces
Testosterone, FBG & FBG / Fasting Insulin - reduces

2) Oral Contraceptive Pills (OCP)
Ethinyl estradiol and a progestin with minimal androgenic activity such as norgestimate, norethindrone, or desogestrel, should be selected.
Ethinyl estradiol combined with drospirenone (Yasmin) has antiandrogenic effects.
Norgestrel and levonorgestrel should be avoided because of their androgenic activity.

OCP (estrogen and progestin)-Increase SHBG levels - reduce the free testosterone level.

LH & FSH are suppressed& this restores cyclic exposure of the endometrium to estrogen- progestin, with the resumption of menstrual periods and decreased hirsutism.

Withdrawal bleeding can be induced with medroxyprogesterone (Provera) given for 5-10 days before the start of OCP. Pregnancy must be ruled out before OCP is started. OCP – increases thromosis risk

3) Hirsutism

First line agents
OCP alone or in combination with Spironolacton (feminine effect ofetus)

Initiate OCP first, just to avoid worsening of menstrual irregularities and to prevent pregnancy, Spironolactone is periodically assess for adverse effects (e.g., fluid and electrolyte abnormalities). Spironolactone is also used a. (Antiandrogens) 50 – 100 mg BD are effective for hirsutism

Finasteride (Proscar, Propecia)- resistant Hirsutism (Off-label) 5 mg OD.
Avoid- teratogenic.
Depilatories and/or bleaching cream.
Plucking or waxing unwanted hair can result in folliculitis and ingrown hairs.
Permenant cure electrolysis and laser treatment.
Adjunctive eflornithine with laser treatment is superior to laser therapy.

Eflornithine (Veniqa)
- Does not have a depilatory action; but, it appears to retard hair growth.
- Improvement may be seen in 4-8 wks, but Rx is required for at least 6 mo
- hirsutism may return following discontinuation of eflornithine).
- Only on facial & chin hairs, not on genital area

4) Hirsutism (Off-label) or Hormonal Acne - 50-200 mg OD or divided for every 12hr. **Vit D supplements reduces - Metabolic syndrome**

5) Acne Agents, Topical
Benzoyl peroxide:
Topical gel: 2.5% (Proactive Repairing), 4% & 8% (BPO Gel), 5% & (Benzac AC Gel,)
Topical lotion: 2.5% (Proactive Repairing), 3.5% (Neutrogena Benzoyl Peroxide Lotion)
7% (Proactiv), 10% (PanOxyl Acne Cleansing Bar)

Topical cream: 2.5% (Neutrogena On-The-Spot Acne Treatment, Proactiv)
5.5% (NeoBenz Micro, NeoBenz Micro SD), 6% (Proactiv Advanced Blemish Treatment) 10% (Clearasil Vanishing Acne
Treatment Cream, Neutrogena Clear Pore Acne Treatment)
Topical foam: 5.3% (BenzEFoam), 9.5% (Riax)
Topical wash
5% (Benzac AC Wash, Clean and Clear Advantage 3-in-1 Exfoliating Cleanser)
7% (NeoBenz Micro Wash)

Topical gel cleanser
2.6% (Benzac Acne Eliminating Cleanser)

Instructions: Check for Allergy

1. **BenzEFoam Ultra (9.3%)**

Treatment goals in T2DM	
Fasting Glucose	80-130 mg/dl
Postprandial Glucose	<180 mg/dl
HbA1c	<7.0 %
Blood Pressure	<130 mg/dl
LDL	<100 mg/dl
HDL-C	>40 mg/dl
Triglycerides	<150 mg/dl

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