



Metabolic Syndrome and PCOS



Dr Alpesh Gandhi
President FOGSI



DR Anita Singh
Vice President
FOGSI



Dr Rakhi Singh
Chairperson
Endocrinology
Committee FOGSI
EDITOR



Editor :Dr Meenu Handa
Senior IVF specialist ,
Fortis Bloom IVF center
Gurugram.



Author
Dr.Chandrika Anand
Senior Gynecologist and
Director PCOS consultant

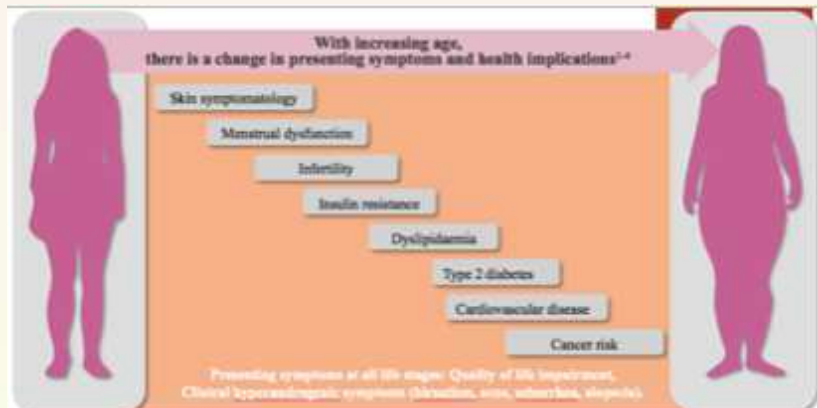
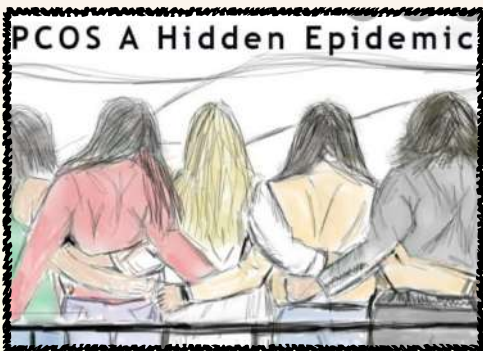
Introduction

Cardiovascular Diseases have emerged as the leading cause of death in all parts of India, including poorer states and rural areas and is a significant cause of morbidity and mortality in women.

Overall, cardiovascular diseases contributed 28.1% (95% UI 26.5–29.1) of the total deaths and 14.1% (12.9–15.3) of the total DALYs (disability adjusted life years) in India in 2016. Its prevalence has doubled in the last 25 years and is very high in Kerala, Punjab, and Tamil Nadu.

The prevalence of Metabolic syndrome in the Indian PCOS is reported to be 37.5%, with central obesity as one of its significant

**BECOME A PARTNER FOR
PCOS AWARENESS MONTH**



CVD in women

- Increasing trend now in women.
- Presents 10 year later compared to men
- Increase after menopause
- More severe disease compared to men
- More first time mortalities in women
- Under diagnosed and under treated in women.
- Need specific pharmacologic intervention in child bearing age.

Metabolic risk factors, such as those clustered in metabolic syndrome, have been identified and are targeted in efforts to reduce the risk of developing CVD. Consequently, clinicians face the challenge of being able to not only recognize but also intervene appropriately in these different settings to reduce CVD risk among women. Although lifestyle interventions should benefit all, clinicians need to be aware of pharmacologic treatment concerns for women of childbearing age.

By the age of 30 years, 30-50% of obese women with PCOS develop IGT or overt T2 DM. This is a 3-7 fold greater risk than an age-comparable population.

UNIQUE RISK FACTORS FOR WOMEN

- Pregnancy related weight gain
- Hormonal contraceptive use
- PCOS
- Gestational diabetes
- Pre-eclampsia
- Menopause



Gender differences in metabolic disease

Central adiposity

- Prevalence of extreme obesity is increased in women compared with men
- Increased waist circumference in women increases risk of metabolic syndrome to a greater degree than in men

Dyslipidemia

- Associated with a greater risk for coronary artery disease in women than in men
- Elevated triglyceride levels have a greater impact on coronary artery disease risk in women than in men, especially when combined with low HDL levels

Hypertension

- Congestive heart failure is more commonly seen as a consequence of hypertension in women than in men
- 'White coat hypertension' is more commonly reported in women than in men

Hyperglycemia

- Glucose levels after a glucose load are more commonly elevated than fasting blood glucose in women; the opposite is found in men

(2)

Cardiometabolic Complications In PCOS

- ❑ Insulin resistance- glucose intolerance and diabetes
- ❑ Dyslipidemia
- ❑ Inflammation
- ❑ Hypertension
- ❑ NAFLD
- ❑ Depression
- ❑ Obstructive sleep apnea
- ❑ Cancers



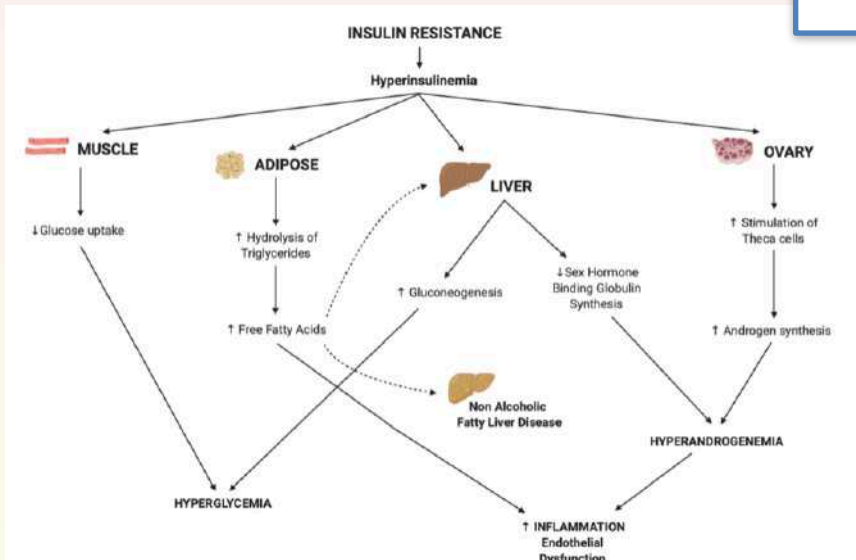
CONDITION	PREVALENCE IN PCOS	CLINICAL FEATURES	DIAGNOSIS	COMPLICATIONS	TREATMENT
Insulin resistance	50-75%	Acanthosis Central obesity Skin tags	FBS, fasting insulin OGCT and insulin	IGT Diabetes NAFLD GDM Miscarriage	Lifestyle modifications Metformin Thiazolidinediones Incretins Insulin (if diabetic)
Dyslipidemia	Up to 70%	Obesity	Fasting lipid profile	CVD Stroke	Lifestyle modifications Statins
Inflammation			CRP IL6 TLC CIMT FMD in brachial artery	Atherogenesis Endothelial dysfunction	Lifestyle modifications Metformin Statins Low dose aspirin
Hypertension	10-40%	High BP on examination	BP check	CVD Stroke Pregnancy complications	ACE inhibitors ACE Receptor blockers
Metabolic Syndrome	37-47% (doubled in PCOS)	Abdominal obesity Acanthosis	AC >36inches BP >130/85 FBS >110 HDL <50 TG >150	Increased CVD (doubled) Diabetes risk (5 times more) Overall mortality increased Cancer risk- colorectal cancer Cognition impairment Depressive disorders	Lifestyle modifications Metformin Statins Anti-hypertensives
Depression anxiety	28-60%	Depression Low mood Loss of interest	PHQ 9 questionnaire	Suicide medical emergency CVD	Lifestyle modifications Anti-depressants
NAFLD	27-60%	Non specific	LFT – AST/ALT Fatty liver – USG/ CT	Cirrhosis HCC	Lifestyle modifications Metformin
OSA	50%	Disturbed sleep Day time sleeping snoring	Nocturnal polysomnography Home sleep tests.	High risk of Hypertension Metabolic syndrome CVD Day time fatigue	Lifestyle modifications CPAP Oral appliances
Cancers-endometrial hyperplasia	3 times more risk	AUB Intermenstrual bleeding	TVS for ET Endometrial biopsy	Endometrial cancer	For hyperplasia: Cyclical or continuous progesterone & LNG IUD Hysterectomy

1. **INSULIN RESISTANCE IN PCOS** 2,3

- The importance of insulin resistance, hyperinsulinemia and role of insulin in pathogenesis of PCOS was first suggested in 1980.
- Insulin resistance is the condition where progressively higher doses of insulin is required to maintain glucose control.

Insulin Resistance in PCOS

- Prevalence of IR in PCOS 50-70%
- Obese PCOS 70-80%
- Lean PCOS 20-25%
- Glucose intolerance 35%
- Type 2 Diabetes 7-10%



2. DYSLIPIDEMIA

It is the commonest metabolic abnormality caused by Hyperandrogenemia.

70% have one abnormal lipid level:

- Decreased HDL
- Increased TG
- Increased total cholesterol and LDL

Diagnosis-

Fasting Serum lipid profile.

Complications –

Increased risk of CVD and Stroke

Management of dyslipidemia

1. Lifestyle modifications

Severe cases

2. Low dose aspirin
3. Lipid lowering drugs- STATINS-

For managing dyslipidemia in PCOS.

Simvastatin 20 mg – reduced lipids, serum testosterone, inflammation.

Improved endothelial function.

Atorvastatin also had similar effects, reduced insulin resistance

Promising drugs to prevent metabolic consequences of PCOS

Teratogenic, not given in woman trying for pregnancy.

3. INFLAMMATION

PCOS is a proinflammatory state.(5)

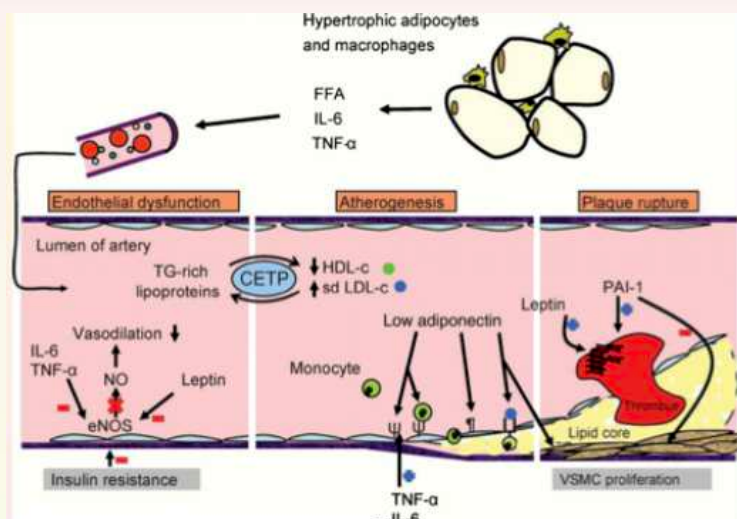
The term low-grade inflammation identifies a condition characterized by the increase in the circulation of several inflammatory mediators in response to a noxious stimulus.

Causes of Inflammation

Hyperinsulinemia

Obesity

Hyperandrogenemia



Complications -

- Atherogenesis
- Endothelial dysfunction: an alteration in endothelial function resulting in an increased state of vasoconstriction and impaired vasodilatation, pro-coagulation, platelet activation and adhesion, anti-fibrinolysis, and increased vascular stiffness and oxidative stress – all increasing CVD risk.

Markers of inflammation in PCOS-

1. Raised blood levels of
 - CRP
 - IL 6
 - Total leucocyte counts (lymphocyte and monocyte increase)

2. Measurement of endothelial dysfunction

Ultra-sound measurement of FMD (flow mediated dilatation) of the brachial artery after vascular transient occlusion.

3. Measurement of atherosclerosis-
CIMT- carotid intima media thickness (USG)

Management of inflammation

- Metformin – given for 6 months effectively reduces inflammation (7)
- Lifestyle modifications
- Lipid lowering drugs- Statins.
- Low dose aspirin

4. HYPERTENSION –

The prevalence of hypertension in PCOS ranges from 10 to 40%.

Pregnant women with PCOS have a greater risk of pregnancy-induced hypertension and preeclampsia

Every visit, BP has to be checked in all PCOS patients.

Complications of Hypertension - CVD, stroke.(4)

Antihypertensives are indicated when BP is of at least 140 mm Hg systolic or 90 mm Hg diastolic.

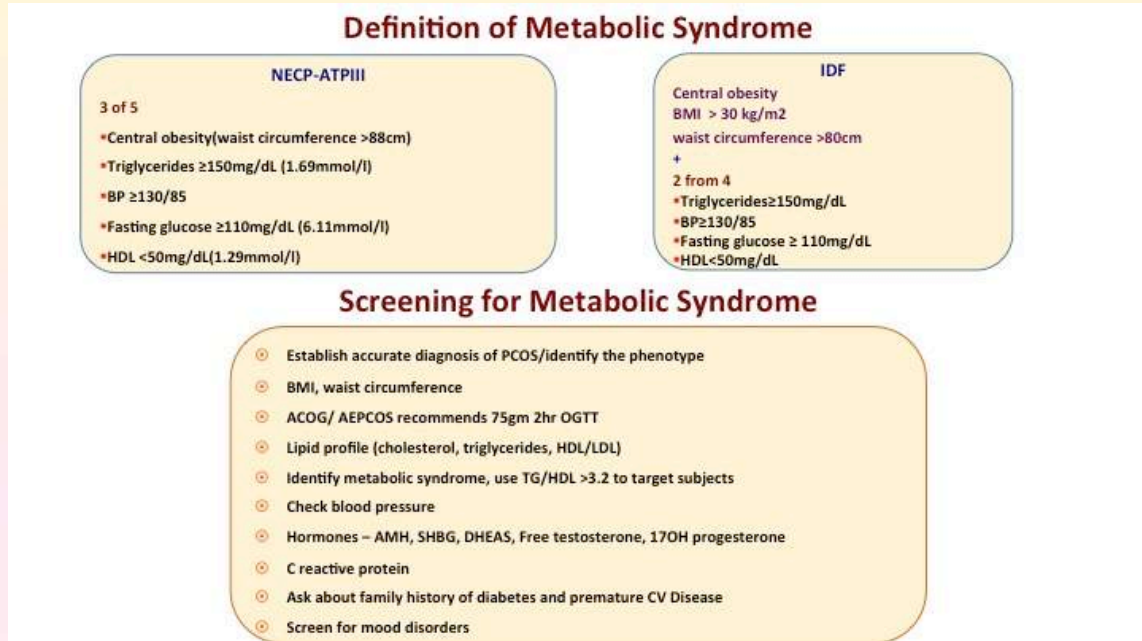
- Angiotensin-converting enzyme inhibitors and Angiotensin receptor blockers are preferred over diuretics and beta-blockers.
- These drugs are teratogenic, so in women planning pregnancy, the medicines have to be changed.

5. Metabolic syndrome and PCOS(7)

The metabolic syndrome is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure.

The prevalence of MetS in the Indian PCOS populations is reported to be 37.5%, with central obesity as one of its significant predictors.





Complications of metabolic syndrome (7)

- Increased CVD (doubled)
- Diabetes risk (5 times more)
- Overall mortality increased
- Cancer risk- colorectal cancer
- Cognition impairment
- Depressive disorders

Management of metabolic syndrome

- Lifestyle modifications
- Insulin sensitizers –Metformin
- Metformin with antiandrogens like flutamide very effective
- Anti Hypertensive drugs
- Lipid lowering drugs
- COC do not correct metabolic abnormalities in PCOS (except drospirinone limited effect).
 - Deficiency of Vit D3 is often observed in PCOS (<30ng/dl), supplementation improves insulin sensitivity, lipid profiles, reduces inflammation and androgen levels.



6. Depression, Anxiety, and Reduced quality of life

Prevalent in women with PCOS 28-60%

There is growing evidence that mood disturbances, mostly severe depression, are independent CVD risk factors, causing exaggerated ACTH and cortisol stress responses, impaired IL-6 up-regulation after stress and heightened sympathetic nerve activity. Hence, all women with PCOS should have screening for depression, anxiety (PHQ9 questionnaire).

Treatment

- Lifestyle modification
- Anti depressants (psychiatrist referral)

7. NON ALCOHOLIC FATTY LIVER DISEASE (6)

- Chronic disorder characterized by fat accumulation in the liver, histologically identical to alcoholic liver disease, in patients with nil or minimal alcohol consumption.
- Incidence- 27-60% of PCOS
- Can lead to severe steatohepatitis with lobular necroinflammation and variable degrees of fibrosis and can further progress to advanced fibrosis and cirrhosis in some cases.

Causes –

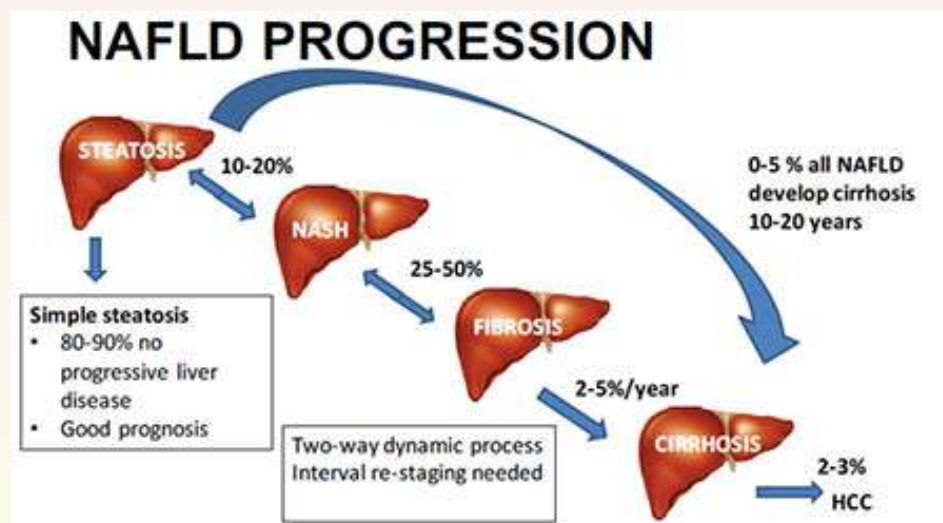
- Insulin resistance
- Hyperandrogenemia
- Obesity

All 3 are independent factors

Most patients with NAFLD are asymptomatic. Non-specific symptoms, such as fatigue, malaise and right upper quadrant discomfort. Hepatomegaly may be the only physical finding

Investigations –

- LFT - Elevated serum aminotransferase levels
- Imaging modalities -ultrasonography (sensitivity 80% in the presence of > 30% of fatty infiltration)
- CT, MRI, liver biopsy.



Complications of NAFLD- cirrhosis, HCC.

Management of NAFLD –

Lifestyle modifications

Metformin

8. OBSTRUCTIVE SLEEP APNEA (OSA)

50% of obese PCOS (twice as non pcos women)

Causes -Obesity, hyperandrogenemia, altered progesterone levels.

Associated IR.

Symptoms s/o OSA

- Excessive daytime sleepiness
- Loud snoring
- Observed episodes of stopped breathing during sleep
- Abrupt awakenings accompanied by gasping or choking
- Awakening with a dry mouth or sore throat
- Morning headache
- Difficulty concentrating during the day
- Experiencing mood changes, such as depression or irritability
- Nighttime sweating



Evaluation for OSA

- All overweight/obese women with PCOS should be screened for OSA.
- **Nocturnal polysomnography.**
- **Home sleep tests.**
-

Management –

Lifestyle modifications

CPAP

Oral appliances

9. **CANCERS (8)**

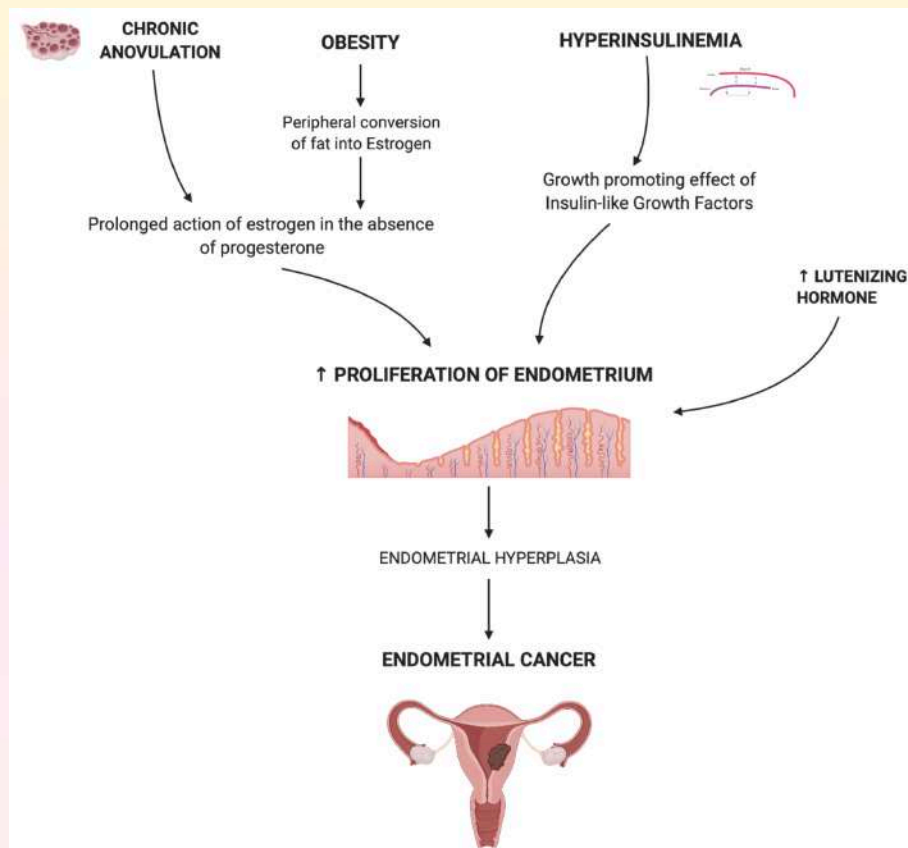
Endometrial cancer – 3 times increased risk

Clinical features –

AUB

Intermenstrual bleeding





Investigations

- Endometrial surveillance by transvaginal ultrasound (>8mm)
- Endometrial biopsy indications– in women with PCOS
 - Thickened endometrium
 - Prolonged amenorrhea
 - Abnormal vaginal bleeding.

Management of endometrial hyperplasia

Progestogens induce synchronous growth, development and shedding of a structurally stable endometrium, antagonize the mitotic actions of estrogen on endometrial development

- OCP
- Cyclic progestogen administration should induce at least four episodes of withdrawal bleeding annually, every three months
- Continuous progestogens. – 6 months

MPA 5–10 mg/day, norethindrone acetate 2.5–10 mg/day, micronized progesterone 200 mg/2–3 times daily

- levonorgestrel-releasing (Mirena) IUD

Hysterectomy – if atypical hyperplasia and family completed.

b. Ovarian cancer –

2.5 times increased risk of developing epithelial cancer, especially in women with high LH levels. This increased further if the women have never used COC pills.



SCREENING PCOS WOMEN FOR METABOLIC COMPLICATIONS

- **FIRST VISIT-**
 - Waist Circumference
 - BMI
 - Blood Pressure
 - Acanthosis Nigricans
 - CBC
 - FBS
 - OGCT
 - OG Insulin
 - Fasting Serum Lipid Profile
 - Hba1c
 - LFT (amino transferase levels)
 - USG abdomen pelvis – diagnose PCOS , fatty liver
 - OSA symptoms screening (if overweight /obese)
 - Mental health assessment (phq9)
- Advanced tests**
- Total Vit D3
 - CRP
 - CIMT
 - TVS for ET (longstanding PCOS or if AUB) and biopsy if >8 mm.

YEARLY SURVEILLANCE IN PCOS

- BMI
- Abdomen circumference
- BP
- CBC
- Serum lipids
- FBS
- OGCT
- TVS for endometrial thickness and biopsy in long standing PCOS, or if AUB.

LIFESTYLE MODIFICATIONS IN PCOS (2)**First Line Approach**

- Diet
- Exercise
- Stopping smoking
- Establishing a daily routine of eating, sleeping and physical activities.

Successful lifestyle management requires self-esteem and motivation Validated tools for screening, treating, and monitoring depression, abnormal eating patterns, and reduced life quality may be necessary for improving psychological symptoms and lifestyle management.

LIFESTYLE MODIFICATIONS

- 5% weight loss causes significant favourable metabolic changes.
- Decreased Insulin and LH levels
- Increased SHBG
- Decreased free E2
- Lowered Testosterone levels
- Improved menstrual function
- Reduced hirsutism and acne
- Improved cardiovascular risk factors including blood pressure, glucose intolerance



Weight loss :

- Initial attempt 5–10% weight loss.
- Long-term goals of achieving and maintaining reduced weight of 10 to 20%
- Abdominal fat has to be lost. Waist circumference of less than 88–80 cm

Diet

- Hypocaloric (500-1000k cal reduction)
- Low saturated fat, increased mono- and polyunsaturated fat diet
- Increased consumption of fiber, whole-grain breads, cereals, fruits and vegetables.

Drugs

- Antiobesity drugs

Phenteramine, sibutramine, and orlistat are not recommended in PCOS, the clinical experience is limited and significant side effects can occur.

- Bariatric surgery (2)

Bariatric surgery may induce a significant weight loss (up to 60%) and improve diabetes, hypertension, and dyslipidemia, reducing mortality from CVD and cancer when compared with lifestyle modifications.

Performed only after standard weight loss strategies have failed in PCOS women with a BMI greater than 40 kg/m² or greater than 35 kg/m² with a high-risk obesity-related condition.

Exercise

- 30-40 min, five times a week (10000 steps a day).
- Aerobic
- Strength training
- Interval training
- Moderate increase in physical activity -Brisk walking, Taking stairs, not elevators, parking far away from entrance

An individualized exercise program assures optimal compliance

YOGA and PCOS (9)

- The science of yoga works at root cause of PCOS i.e. Stress and Obesity. Asanas and pranayama promotes hormonal balance and deep relaxation, helping to bring the adrenal and cortisol levels.
- It is said to stabilize the hypothalamic–pituitary–adrenal axis and promote autonomic balance in girls with PCOS.
- Yoga was found to be more effective than conventional physical exercises in improving glucose, lipid, and insulin values, including insulin resistance values, in adolescent girls with PCOS independent of anthropometric changes (1).
- Holding weight-bearing asanas builds muscle, improving IR.
- Yoga increases cardiovascular workout and leading to weight loss.

BARIATRIC SURGERY IN OBESE PCOS

- A total of 2130 female patients were identified
- Mean age was 30.8 years and mean follow-up was 23.8 months. Overall sample weighted preoperative mean BMI was found to be 46.3 kg/m², which improved to 34.2 kg/m² postoperatively.

	Pre operative	Post operative
PCOS	45%	7.1%
Menstrual Irregularities	56%	7.1%
Hirsutism	67%	32%
Infertility	18%	4.3%

Skubleny et al. The Impact of Bariatric Surgery on Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis. *Obes Surg* (2015) October



Yoga Exercises to Improve PCOS, Recommended Asanas for PCOS are:

1. Badhakonasana (Butterfly pose)
2. Suptabdhakonasana (Reclined bound angle)
3. Bharadvajasana (Bharadvajasana twist's)
4. Chakki Chalanasana (Mill churning pose)
5. Shavasana (Corpse pose)
6. Padma Sadhana
7. A few rounds of Surya namskar (Sun Salutation).

CONCLUSION

- PCOS is a common, complex endocrine disorder which is increasing steadily, having long term health implications like CVD and cancers, apart from transgenerational impact of diabetes.
- PCOS can be controlled and complications can be prevented or postponed by sustainable lifestyle modifications and simple medications like metformin, COC etc.
- Gynaecologist being the primary physician in treating PCOS, has to be aware of serious cardiometabolic complications and screen, treat the same.

REFERENCES

1. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990–2016
India State-Level Disease Burden Initiative CVD Collaborators.
2. Assessment of Cardiovascular Risk and Prevention of Cardiovascular Disease in Women with the Polycystic Ovary Syndrome: A Consensus Statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. *J Clin Endocrinol Metab.* May 2010, 95(5):2038–204
3. Polycystic Ovary Syndrome. Novel Insights into Causes and Therapy. Macut D, Pfeifer M, Yildiz BO, Diamanti-Kandarakis E: *Frontiers of Hormone Research.* 2013, Vol 40:64–82.
4. Cardiovascular Risk and Subclinical Cardiovascular Disease in Polycystic Ovary Syndrome. Katica Bajuk Studen Mojca Jensterle Sever Marija. *Endocrine connections.* 2018. R238-R251.
5. The role of low-grade inflammation in the polycystic ovary syndrome. Andrea Repaci, Alessandra Gambineri, Renato Pasquali. *Molecular and Cellular Endocrinology* 335 (2011) 30–41
6. Nonalcoholic fatty liver disease and polycystic ovary syndrome. Evangeline Vassilatou. *World J Gastroenterol* 2014 July 14; 20(26): 8351-8363 ISSN 1007-9327 (print) ISSN 2219-2840 (online)
7. Metabolic syndrome associated complications. Danmini Nerkar, Aniruddha Mukherjee et al. *International Journal of Pharmacy and Pharmaceutical Sciences.* July 2015. ISSN- 0975-1491 Vol 7, Issue 7:22-25.
8. Cancer risk and PCOS
Daniel A. Dumesic, Rogerio A. Lobo. *Steroids* 78 (2013): 782–785
9. Effect of a yoga program on glucose metabolism and blood lipid levels in adolescent girls with polycystic ovary syndrome Ram Nidhi, Venkatram Padmalatha et al. *International Journal of Gynecology and Obstetrics* 118 (2012) 37–41



