



PCOS TUTORIALS

*A Post Graduate
Certificate Course in
PCOS Management*

**Module 6
PCOS and Long-Term
Health Consequences**

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Module VI

PCOS and Long-Term Health Consequences

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Module Overview

- Polycystic ovary syndrome (PCOS) is a common disorder and in the previous modules we have seen how it can affect the adolescents and the younger women.
- Cosmetic issues related to PCOS have been discussed in module 3.
- Association of PCOS with chronic anovulatory infertility has been discussed in module 4.
- Complications associated with pregnancy in women with PCOS have been discussed in module 5.
- The effects of PCOS last for a lifetime and long-term consequences of this syndrome will be briefly discussed in this module.
- Many women with PCOS are obese and tend to have a higher prevalence of impaired glucose tolerance (IGT), type II diabetes (T2DM) and sleep apnoea than observed in the general population. Evidence of an adverse cardiovascular risk profile, characteristic of the cardiometabolic syndrome characterised by higher association with hypertension, dyslipidaemia, visceral obesity, insulin resistance and hyperinsulinaemia among women with PCOS is noted. Oligo- or amenorrhoea in women with PCOS predisposes them to a higher risk of endometrial hyperplasia and subsequent carcinoma.
- Most often, it is the gynaecologists who diagnose PCOS and it is, therefore, important that there is a good understanding of these long-term implications of the diagnosis to ensure a holistic approach to this disorder.
- This module will provide information, based on clinical evidence, regarding these long-term health consequences of PCOS.

Reference:

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Learning Objectives

At the completion of this module, the participant is expected to:

- Be aware of the various known long-term consequences associated with PCOS.
- Be competent to provide the information regarding these consequences to their patients.
- Provide health education to the patients to defer these long-term consequences of PCOS.
- Educate and arrange for the screening and monitoring of conditions such as postmenopausal bleeding, blood glucose levels, blood pressure, lipids, heart diseases, sleep apnoea, liver function tests and other associated conditions.
- Understand the management and be able to make a timely decision for the referral to the concerned experts for various long-term consequences of PCOS.

PCOS and Long-Term Health Consequences

PRE-TEST

State whether the following statements are True or False.

- 1. Endometrial hyperplasia is seen more often in women with PCOS.**
 - a) True
 - b) False
- 2. Breast cancer is more common among women with PCOS.**
 - a) True
 - b) False
- 3. Risk reduction of long-term consequences of PCOS is possible with lifestyle changes.**
 - a) True
 - b) False
- 4. Cardiovascular risk factors such as obesity, dyslipidaemia, diabetes and hypertension are seen more frequently among women with PCOS.**
 - a) True
 - b) False
- 5. Metformin decreases the risk of endometrial hyperplasia and hence endometrial cancer.**
 - a) True
 - b) False
- 6. Women with PCOS carry the same risk as general population for diabetes.**
 - a) True
 - b) False
- 7. Obese women with PCOS are at a greater risk of metabolic syndrome.**
 - a) True
 - b) False

- 8. Letrozole increases the risk of breast cancer.**
- a) True
 - b) False
- 9. Kidney and colon cancers have been found to have lower frequency among women with PCOS.**
- a) True
 - b) False
- 10. Haepatomegaly is the only way to screen for non-alcoholic fatty liver disease.**
- a) True
 - b) False

Answers: 1. True; 2. False; 3. True; 4. True; 5. True; 6. False; 7. False; 8. False; 9. False; 10. False

Introduction

PCOS is one of the most common endocrinopathies diagnosed in premenopausal women but it can continue to influence even the postmenopausal health of the women. PCOS has been redefined as a reproductive and metabolic disorder after the recognition of the important role of insulin resistance in the pathophysiology of the syndrome.¹

Long-term health consequences associated with PCOS

- Neoplastic
- Metabolic consequences
- Dyslipidaemia and vascular dysfunction
- Mental health disorders

- As mentioned above, PCOS has been related with significant adverse sequelae that affect overall long-term health and well-being.²
- These long-term morbidities of PCOS are grouped into:
 - o Neoplastic (primarily endometrial adenocarcinoma and other cancers)
 - o Metabolic consequences (IGT, T2DM, metabolic syndrome, and non-alcoholic fatty liver disease [NAFLD])
 - o Dyslipidaemia and vascular dysfunction (including hypertension, increased incidences of cerebrovascular accidents and thromboembolism on oral contraceptives)
 - o Mental health disorders (including greater incidences of depression, anxiety disturbances and psychosexual dysfunction)³

Prevalence of Long-Term Consequences in Women with PCOS

- High prevalence of endometrial and some borderline serous subtypes of ovarian cancer, kidney, colon and brain cancers are seen among women with PCOS.

Metabolic risk factors	Prevalence among PCOS women
Impaired glucose tolerance	20–35%
T2DM in young women with PCOS	2–8% (seems related to body weight and ethnic group)
T2DM among women with PCOS >40 years age and/or postmenopausal	10–16%

T2DM: Type 2 diabetes mellitus

- High prevalence of risk factors associated with vascular dysfunction e.g., obesity, IGT, diabetes, hypertension, mood disorders and metabolic syndrome are seen among women with PCOS
- High prevalence of depression and anxiety are seen among women with PCOS.

In women with PCOS, the prevalence of uterine pathology extending up to neoplasia, metabolic disequilibrium resulting in insulin resistance, T2DM and cardiovascular risk factors is significantly high.²

Higher prevalence of neoplasia

- A stronger association between PCOS and endometrial cancer particularly when restricted to type I (endometrioid) cancer has been noted.
- Evidence supports a link between PCOS and the borderline serous subtype of ovarian cancers, resulting in higher prevalence of the latter among women with PCOS.
- The current evidence points towards no increase/decrease in the risk of breast cancer among women with PCOS.
- A higher prevalence than expected of kidney, colon, and brain cancers has been seen among women with PCOS, as reported by the Danish study.⁴

High prevalence of metabolic syndrome and cardiovascular risk factors

- Young women with PCOS have been associated with higher prevalence of T2DM and cardiovascular diseases (CVD).
- The prevalence of IGT ranges between 20 and 35% in patients while the prevalence of T2DM ranges between 2 and 8% and seems related to body weight and ethnic group.
- Moving from the young fertile age to the 40s and the menopause the prevalence of T2DM continues to increase compared to the general female population and may reach to 10–16 % of women with PCOS.⁵
- Adolescents and reproductive age women with PCOS have an increased prevalence of cardiovascular risk factors. These include obesity, IGT, diabetes, hypertension, mood disorders and metabolic syndrome. There is sufficient evidence to confirm the presence of subclinical atherosclerosis in women with PCOS compared to age-matched controls.
- Further studies are needed to assess the prevalence of non-fatal and fatal cardiac events in women with well-defined PCOS.⁶

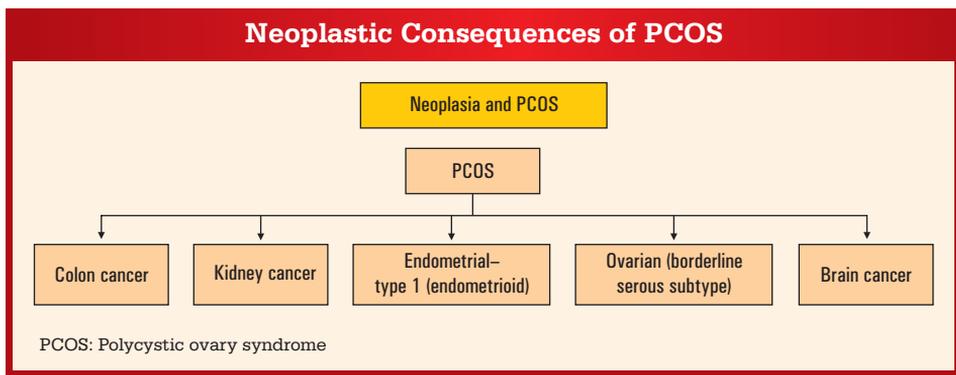
High prevalence of mental health disorders

- High prevalence of depression and anxiety are seen among women with PCOS.⁷

References:

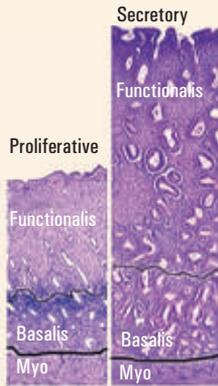
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- The altered metabolic and hormonal environment among women with PCOS may increase their risk for certain cancers:
 - Endometrial cancer have higher occurrence among women with PCOS.
 - Ovarian cancers have potentially increased risk among women with PCOS.
 - Breast cancer has no consistent association with PCOS risk.
 - Other cancers, e.g., kidney, colon, and brain cancers have increased frequency among women with PCOS.^{1,2}

PCOS and Endometrial Cancer



Risk factors

- Oestrogen
- Nulliparous
- Diabetes
- Hypertension
- Obesity
- PCOS
- Tamoxifen

Since endometrial hyperplasia is a precursor to cancer, all risk-factors of endometrial cancer are related to endometrial hyperplasia.

Prevalence	<ul style="list-style-type: none"> • 2.7% increased risk in women with PCOS • 9% lifetime risk of developing an endometrial cancer in women with PCOS
Pathogenesis	<ul style="list-style-type: none"> • Anovulation leads to prolonged exposure to unopposed oestrogen • Ovulation induction drugs and synthetic progestins act on secretory endometrium
Surveillance	<ul style="list-style-type: none"> • TVS for examining endometrial thickness • Endometrial biopsy
Management	<ul style="list-style-type: none"> • Surgeries include total abdominal hysterectomy with bilateral salpingo-oophorectomy + pelvic and para-aortic lymph node dissection • Chemotherapy • Radiotherapy • If patient desires fertility, medical treatment is an option.

PCOS: Polycystic ovary syndrome; TVS: Transvaginal ultrasound screening

- Endometrial hyperplasia, the precancerous stage of endometrial cancer, has demonstrated a strong association with PCOS.
- Multiple studies reported that women with PCOS were at a higher risk for endometrial cancer; however, several of these studies did not take into account the body mass index (BMI), a strong and well-established risk factor for endometrial cancer.^{3,4}
- Endometrial tumours display a variety of histologic features but the majority of cases are adenocarcinomas (>95%) and can be classified into two main subtypes, endometrioid (type I) and non-endometrioid (type II).
- A stronger association between PCOS and endometrial cancer is observed when limited to type I (endometrioid) cancer.¹

Prevalence

- Women with PCOS display nearly three times increased risk of developing endometrial cancer.
- Caucasian women with PCOS have 9% higher lifetime risk of developing endometrial cancer.⁴

Pathogenesis

- The main cause of increased malignancy risk is prolonged exposure of the endometrium to unopposed oestrogen that results from anovulation.

- Additionally, secretory endometrium of some women with PCOS undergoing ovulation induction or receiving exogenous progestin exhibits progesterone resistance accompanied by dysregulation of gene expression controlling steroid action and cell proliferation.

Surveillance and prevention

- Endometrial surveillance includes transvaginal ultrasound and/or endometrial biopsy to assess thickened endometrium, prolonged amenorrhoea, unopposed oestrogen exposure or abnormal vaginal bleeding.⁵

Management

- One-fourth of the patients are diagnosed in fertile age.
- Primary progesterone therapy, sometimes combined with local surgical excision, has been used as conservative treatment in early well-differentiated tumours.
- Using hormonal therapy ± hysteroscopic resection, a mean of 72% complete response was reported, with a 23% relapse rate.
- Endometrial hyperplasia is the premalignant stage for endometrial cancer which needs to be treated actively.⁶

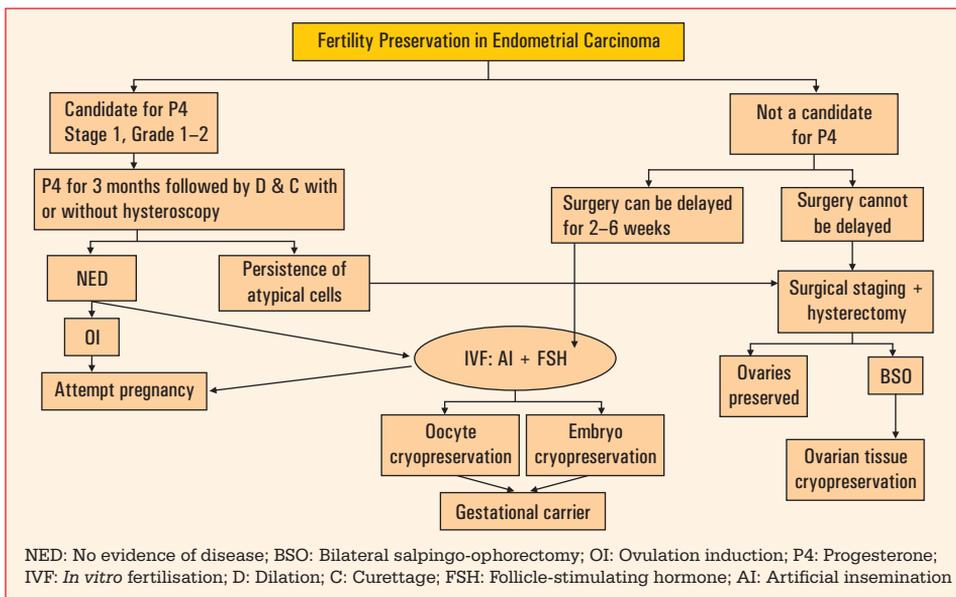
Therapeutic Options for Endometrial Hyperplasia			
Current therapies			Future targets
Progestin therapy	Surgical modalities	Other therapy	• Oestrogen receptor
• MPA	• Thermal balloon ablation	• GnRH therapy	• Hydroxy-steroid dehydrogenase
• Megestrol acetate	• Laser therapy	• Metformin	• Wnt signalling
• Levonorgestrel	• Hysterectomy	• Genistein	• Pro-inhibitory cytokines
• Norethindrone acetate	• Resectoscopic surgery	• Danazol	• Growth factors
			• Aromatase

MPA: Medroxyprogesterone acetate; GnRH: Gonadotropin-releasing hormone; Wnt: Wingless-int

- It is prudent to refer these patients to specialists early in the course of disease.
- For endometrial cancers, the management is preferably carried out by team of experts including onco-surgeons, oncologists, onco-pathologists and radiologists.

- Briefly, the management of endometrial cancers includes:
 - o Surgery
 - TAH+BSO (total abdominal hysterectomy with bilateral salpingo-oophorectomy), pelvic and para-aortic lymph node dissection (LND) or sampling.
 - For high-grade cancers such as papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma; omentectomy and peritoneum sampling is added to the above mentioned surgery.
 - For advanced stages (entire visible tumour is removed/debulked along with extended surgery) radical hysterectomy, LND or sampling, omentectomy and peritoneum sampling is carried out.
 - o Radiotherapy
 - Vaginal brachytherapy + pelvic radiation
 - Frail patients who cannot withstand surgery are only treated with radiation.
 - o Chemotherapy
 - Carboplatin+taxol, cisplatin, doxorubicin with other agents
 - For high-grade cancers such as uterine carcinosarcoma along with the above mentioned drugs ifosfamide may also be added in chemotherapy.
 - o Hormone therapy
 - Progestins and tamoxifen is used, while aromatase inhibitor are being explored.
 - o Fertility preservation
 - Medroxyprogesterone acetate is given orally 400–800 mg/day in three divided doses as an initial treatment for 3 months.
 - Megestrol acetate is given orally 160 mg daily and is a preferred treatment as associated with a better remission probability and a slower progression rate.
 - Instead of progesterone tablets one can also use a progesterone intrauterine device (IUD).
 - After 3 months, if regression occurs assisted reproductive treatment (ART) is performed.
 - If no regression occurs additional MPA or megestrol is given.
 - Twenty-eight percent of complete responders subsequently conceived with or without ART.
 - Prevalence ratios are 32% to 100% in patients attempting to conceive.

- In case, surgery cannot be avoided due to advanced disease the option for fertility preservation is to stimulate the patient preferably using mild forms of stimulation in an antagonist cycle along with aromatase inhibitors to keep the oestradiol levels low. Depending on whether the women have a partner or not one could either freeze the oocytes or embryos.
- After opinion with oncologist and pathologist, treatment with progestins in form of pill, injection or IUD can be carried out until childbearing is complete, followed by TAH+ BSO and LND/ sampling as soon as childbearing is completed. This is not a routine procedure and increases the risk of cancer progression.



o Recurrent endometrial cancer

- Spots can be treated by local surgery/radiation and hormone therapy. Extensive cases are treated as stage 4, chemotherapy may be necessary for widespread recurrences.⁷

PCOS and Ovarian Cancer	
Prevalence	Increased risk of borderline serous ovarian cancers
Pathogenesis	PCOS has been hypothesised to increase ovarian cancer risk through increased androgen exposure
Risk reduction	Use of oral contraceptive pills reduces the risk
	Reduction is directly proportional to the duration of use

There were confusing reports regarding the association of ovarian cancer and PCOS, but as it is well known, there are several histological types of ovarian cancer. Hence, only after the study of PCOS and particular histological types were pursued the picture became clearer.

Prevalence

- Olsen, *et al.* and North East Cerebrovascular Consortium (NECC) study reported an association between PCOS and the borderline serous subtype (odd ratio [OR]=2.5; 95% confidence interval [CI]=1.0–6.1) and noted this association was strongest among women with a BMI ≥ 25 (OR=3.0; 95% CI= 1.2–7.5).⁸

Pathogenesis

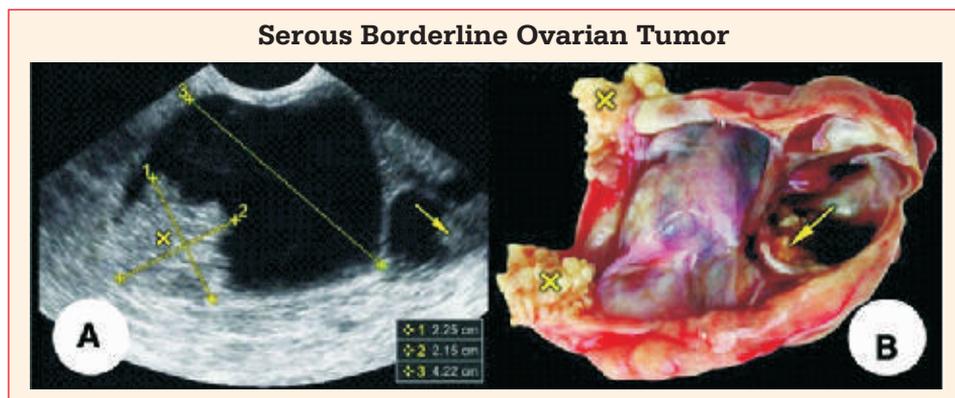
- PCOS has been hypothesised to increase ovarian cancer risk through increased androgen exposure.¹

Risk amelioration

- There is strong data to suggest that oral contraceptive use is protective against ovarian cancer and increases with the duration of therapy.
- The mechanism of this protection may be through suppression of gonadotropin secretion rather than the prevention of "incessant ovulation".

Surveillance

- Almost 30% of patients with borderline ovarian tumours (BOTs) are asymptomatic; approximately 50%–60% of patients complain about nonspecific symptoms (abdominal pain or abdominal distension) and 10% complain of bleeding abnormalities.⁹
- Most BOTs are detected by ultrasound.
- In line with the low performance of cancer antigen 125 (Ca125), the risk of malignancy index (RMI), developed by Jacobs *et al.* in 1990, did not perform well for patients with BOTs.¹⁰



Management

- These tumours are commonly found in reproductive age group. The therapeutic decisions that need to be considered are regarding fertility-sparing surgery, treatment of infertility or premature hormonal deprivation, intra- and postoperative morbidity, and adjuvant chemotherapeutic treatment.
- Fertility preserving surgery
 - o Conservative surgery for sparing fertility (i.e., involving the preservation of the uterus and at least part of one ovary, with comprehensive surgical staging) for borderline tumours of the ovary in all stages.¹¹
 - o Conservative approach is a standard management in early stage, which may increase the risk of recurrence without affecting the survival.
 - o Spontaneous fertility rate is about 60% after conservative surgery.
 - o The available data suggest that the rate of recurrence is higher after conservative surgery (10% to 20% vs. approximately 5% for radical surgery).¹²
 - o For women with advanced disease- frozen embryo and uterus can be preserved before bilateral oophorectomy.
 - o Cystectomy can be considered in serous borderline ovarian tumours, however must be weighed against the risk of high recurrence rate of 31%.
 - o Removal of the preserved ovary after patients complete their fertility plans depends on several factors such as histologic subtype, Federation of Gynaecology and Obstetrics (FIGO) stage of disease, type of conservative surgery, and the patient's own will.

Fertility Preservation in Ovarian Cancer		
Borderline ovarian tumours	Epithelial ovarian tumours	Germ cell tumours
Conservative surgery in stage IA	Stage IA, IC grade 1 and possibly grade 2 tumours of mucinous, endometrioid or serous types suitable for fertility sparing surgery	Sensitive to chemotherapy
Intra surgery oocyte and ovarian tissue cryopreservation		Majority will resume normal menstrual function following their chemotherapy
Post surgery COS with IVM or IVF		If oophorectomy required cryopreservation of ovarian tissue and IVM from aspirated follicles of the contralateral ovary
	Oophorectomy with cryopreservation of ovarian tissue from contralateral ovary and IVM from aspirated follicles	
	Oophorectomy with preservation of contralateral ovary followed by IVM or IVF	

Must monitor contralateral ovary by USG and tumour markers regularly
Risk of re-implanting cancer cells with OT transplant
Once fertility complete → oophorectomy

COS: Controlled ovarian stimulation; IVM: *In vitro* maturation; IVF: *In vitro* fertilization; USG: Ultrasound; OT: Ovulation tracking

- Intraoperative diagnosis and staging
 - BSO in combination with hysterectomy is recommended.
 - Lymphadenectomy is not indicated because the recurrence and survival rates for patients with positive or negative lymph nodes were similar.⁹
- Adjuvant treatment (chemotherapy, radiotherapy, hormone therapy, and targeted therapy)
 - More studies are required to establish the safety and effectiveness of all the adjuvant therapies mentioned above.
- Fertility
 - Spontaneous conception is reported after conservative surgery in 50% of patients without any deterioration in the survival rate.¹³
 - For patients who fail to conceive spontaneously, *in vitro* fertilisation (IVF) must be considered by the multidisciplinary team comprising of specialist from reproductive medicine, gynaecologists, oncologists, and others.
- Hormone replacement therapy (HRT)
 - HRT is carried out to prevent CVD, osteoporosis and improve quality of life (QoL). It is an important issue, as many patients with BOTs are relatively young women. HRT should be offered to these patients.
- Follow-up
 - Regular and intensive follow-up of the patients is essential for the early detection of recurrence in the form of borderline or invasive disease.
 - This must be conducted for a longer period of time than for patients with ovarian cancer.
 - Studies have reported cases in which relapse and death occurred after more than 10–15 years.^{10,13,14}

Other Cancers

Associated with PCOS	Not associated with PCOS
Kidney cancer	Breast cancer
Colon cancer	Vaginal cancer
Brain cancer	Vulvar cancer
	Cervical cancer/Uterine leiomyosarcoma

Cancers associated with PCOS

- Higher prevalence of kidney, colon, and brain cancers was observed among women with PCOS compared to expected rates in the general Danish population.¹

Cancers not associated with PCOS

- The association between PCOS and breast cancer has been complex as infertility resulting from anovulatory dysfunction decreases breast cancer risk.¹⁵ While, obesity which is a common occurrence with PCOS, increases the breast cancer risk among postmenopausal women.
- Several studies including the Danish registry and the Iowa Women's Health Study reported no elevation in risk for women with PCOS.^{3,2,16}
- There are insufficient data to evaluate any association between PCOS and vaginal, vulvar and cervical cancer or uterine leiomyosarcoma.⁵

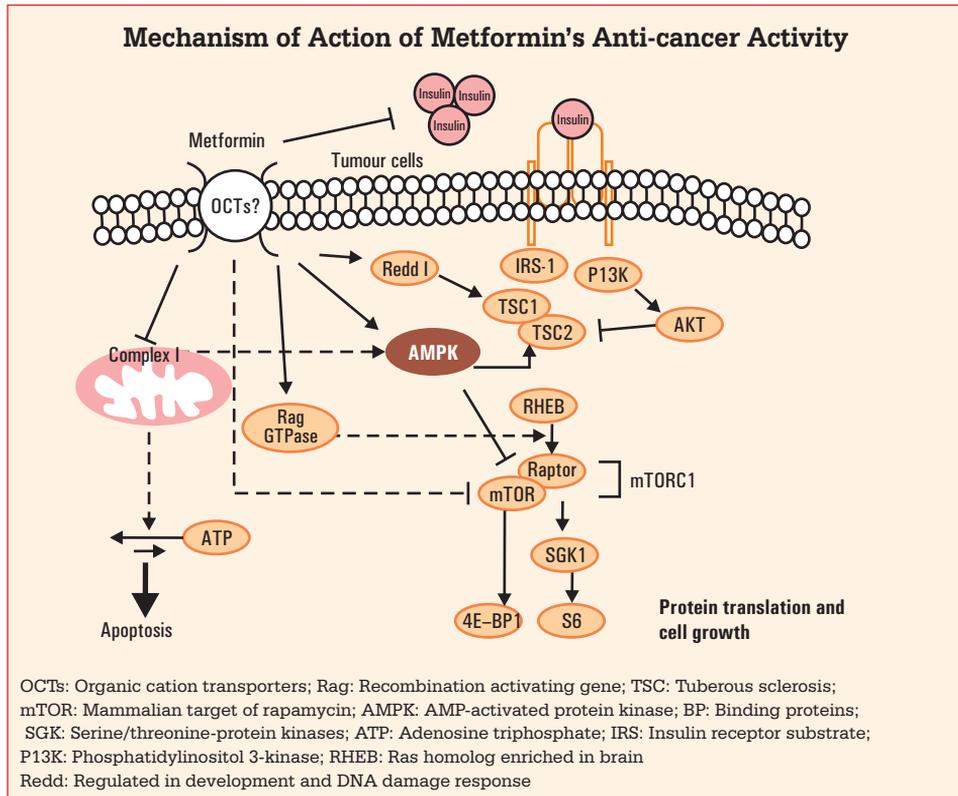
PCOS Medication That May Influence Cancer Risk		
Oral contraceptive pills	Metformin	Ovulation induction agents
<ul style="list-style-type: none">• Decrease risk of:<ul style="list-style-type: none">◦ Ovarian cancer◦ Endometrial cancer• Small short-term increase in:<ul style="list-style-type: none">◦ Breast cancer risk	<ul style="list-style-type: none">• Lab studies support its anti-cancer properties	<ul style="list-style-type: none">• Clomiphene<ul style="list-style-type: none">◦ Non significant increase in endometrial cancer, thyroid cancer◦ Significant increase in melanoma• Letrozole<ul style="list-style-type: none">◦ Decrease in breast cancer risk

Combined oral contraceptives pills

- Combined oral contraceptives are associated with decreased risk of ovarian¹⁷ and endometrial cancers.¹⁸
- The protective effect of oral contraceptives on ovarian cancer risk is likely explained by a decreased lifetime number of potentially damaging ovulations, while the protective effect in endometrial cancer may be the result of reducing exposure to unopposed oestrogen which limits the cell proliferation that is stimulated by oestrogens.
- In contrast, oral contraceptives may result in a very small short-term increase in breast cancer risk, while 10 years after cessation of use the risk among women who had used oral contraceptives was similar to those who had not used oral contraceptives.¹

Metformin

- Evidence has suggested that metformin use may be protective against various forms of cancer.
- This is supported by laboratory studies that demonstrate metformin's anti-cancer activities.¹⁹
- However, fewer studies have examined the impact of metformin on the incidence of endometrial, breast, and ovarian cancer.¹



- Metformin exerts its anti-tumour effects by insulin-dependent and insulin-independent mechanisms. Metformin can suppress cell growth by inactivation of AKT-mTOR pathway and/or may act on both AMPK and mitochondrial complex I, leading, respectively, to increase in apoptosis and downregulation of protein translation and inhibition of cell growth.

Ovulation induction drugs

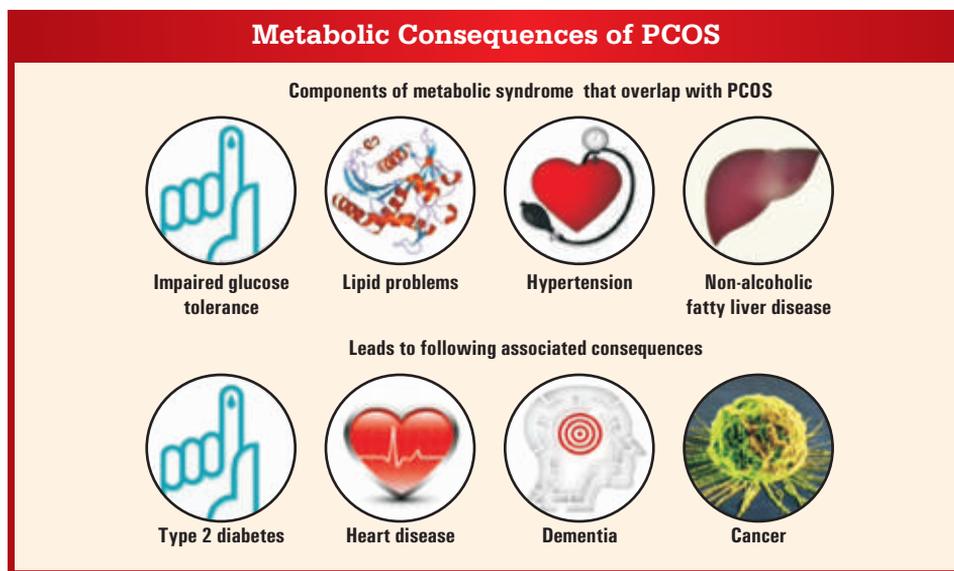
- Clomiphene
 - Breast cancer is generally not associated with increased risk, but a statistically non-significant increased risk was observed for those with over 12 cycles.²⁰

- o A non-significant increased risk was observed in ovarian cancer,
- o A non-significant increased risk was observed in endometrial cancer.²¹
- o A statistically significant increased risk of melanoma (hazard ratio [HR]=2.0; 95% CI=1.2–3.2), a non-significant increased risk of thyroid cancer (1.6; 95% CI=0.9–2.8), and non-significant increased risks of colorectal or lung cancer was observed.²²
- Letrozole
 - o Letrozole is currently used as an adjuvant treatment for hormone receptor-positive postmenopausal breast cancer^{1,23} thus it could be hypothesised that it would likely decrease hormonal related cancer risk.

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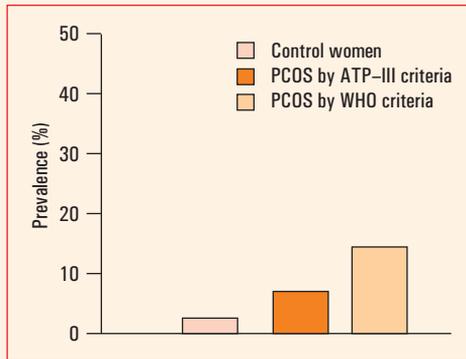


PCOS and metabolic disorders

- Metabolic syndrome is a constellation of metabolic disorders which include mainly abdominal obesity, insulin resistance, IGT, hypertension and dyslipidaemia.
- These associated disorders directly increase the risk of T2DM, coronary heart disease (CHD), CVD and endometrial cancer.

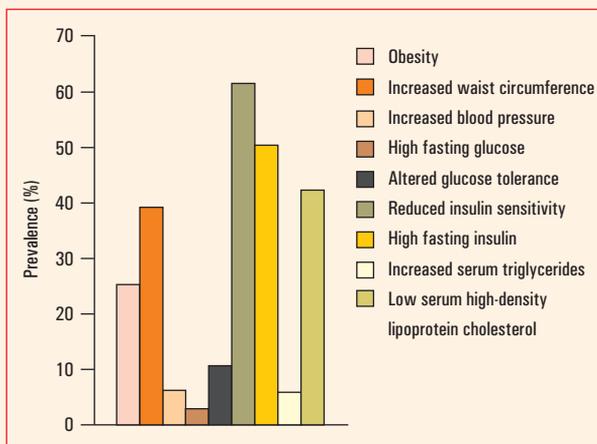
- Many patients with PCOS have features of metabolic syndrome such as visceral obesity, hyperinsulinaemia and insulin resistance.
- These place patients with PCOS under high risk of developing CVD, T2DM and gynaecological cancer, in particular, endometrial cancer.
- Metabolic syndrome is also increased in infertile women with PCOS.¹

Prevalence of Metabolic Syndrome in Women with PCOS based on ATP-III and WHO criteria.



The prevalence of metabolic syndrome in PCOS was 3.4–6.6 times higher than in the matched control population suggesting that PCOS *per se* results in a higher prevalence of metabolic syndrome

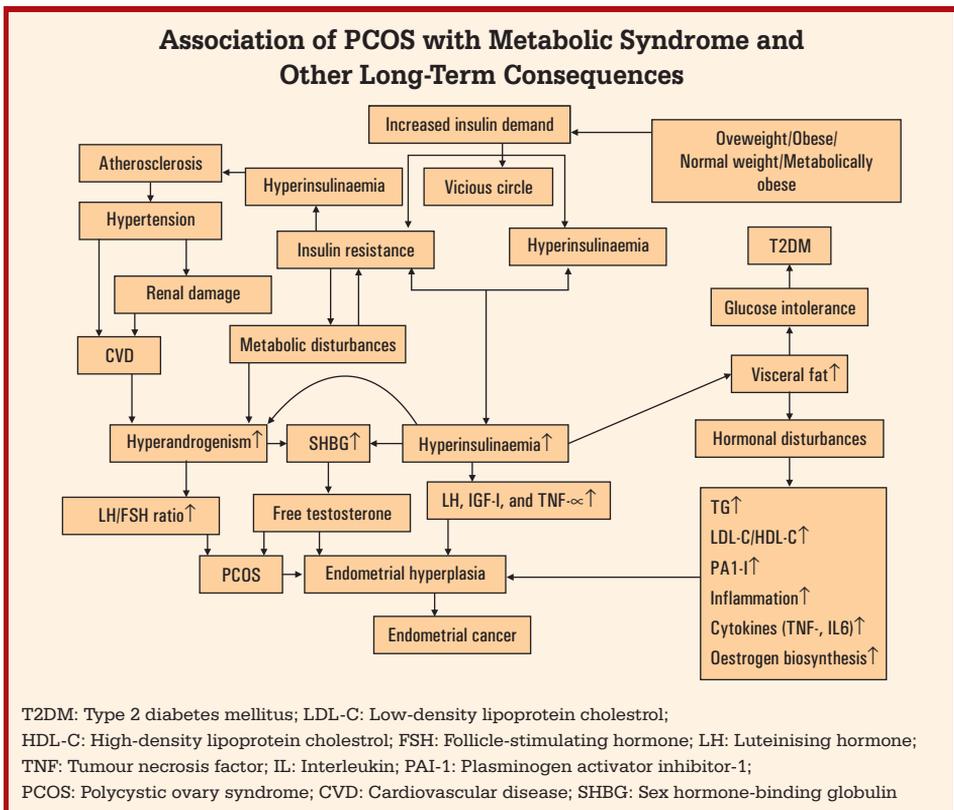
Prevalence of Different Elements of the Metabolic Syndrome in Women with PCOS



Prevalence of metabolic syndrome in women with PCOS

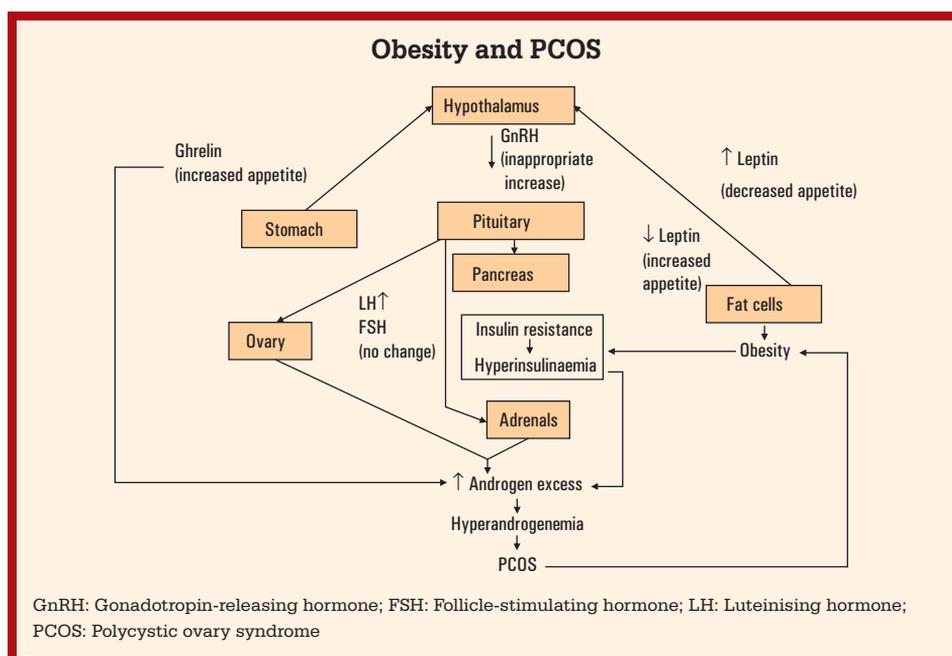
- Women with PCOS demonstrate the higher prevalence of being overweight (BMI > 25 kg/m²) and obese (BMI > 30 kg/m²) as compared to women without PCOS.

- Sixty-one percent of women with PCOS are obese and overweight.²
- The prevalence of metabolic syndrome in PCOS is strongly influenced by the criteria used to diagnose metabolic syndrome as well as the criteria used to diagnose PCOS.
- However, higher prevalence of metabolic syndrome is seen in women with PCOS than in the general population in women of similar age.³
- Further, the prevalence of each cardiac risk factor is approximately double for women with PCOS when compared with controls, while it is 1.5 times higher in BMI-matched studies beginning in adolescence and it is found in every decade.⁴
- Women with PCOS are twice as likely to suffer from hypertension when compared to women without PCOS.⁵



- Key pathogenetic link – Excessive weight and larger abdominal circumference are the key pathogenetic link between PCOS and metabolic syndrome.

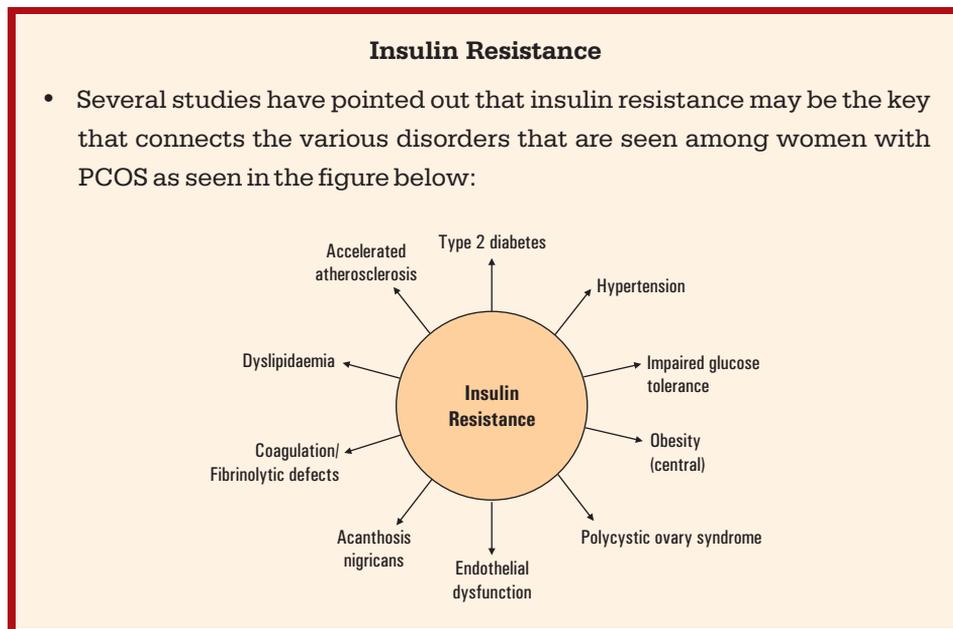
- PCOS and obesity – Obesity has a bidirectional relationship with PCOS, as women with PCOS are more inclined to weight gain and excessive weight gain increases PCOS prevalence.⁶
- Obesity and metabolic syndrome – Visceral obesity correlates with greater fasting insulin levels and greater insulin area under the curve.^{7,8}
- Excess central adiposity echoes a worsened dyslipidaemic profile, with higher triglyceride levels, increased levels of small dense low-density lipoprotein (LDLs) particles and low high-density lipoprotein (HDL) cholesterol levels, a lipid pattern similar to that seen in patients with T2DM.⁹



Dyslipidaemia

- Commonly represented by hypertriglyceridaemia and low HDL cholesterol levels and small dense LDL cholesterol particles (also called atherogenic lipoprotein phenotype), similar to that found in T2DM and typical for the states of insulin resistance.¹⁰
- Increased LDL cholesterol in PCOS is less dependent on body weight and may be partially related to the hyperandrogenism.¹¹
- Hypertriglyceridaemia
 - o Insulin resistance has been postulated to play a key role in causing hypertriglyceridaemia in PCOS.
 - o Obesity has been associated with high triglyceride levels.

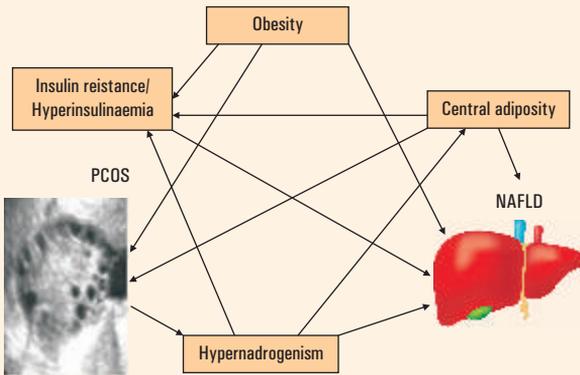
- o Lean women with PCOS had normal triglyceride levels.
- o Increased plasma triglyceride concentrations in obese women with PCOS are likely due, at least in part, to hyperandrogenaemia and relative progesterone deficiency.¹²



Type 2 Diabetes

- Level A evidence has been attributed by ESHRE/ASRM statement of the third PCOS Consensus Workshop Group, for PCOS is an independent risk factor for the development of glucose intolerance which may extend variably to T2DM.⁴
- Obesity and overweight increase the risk of developing T2DM in PCOS women.¹³
- PCOS is a significant risk factor for development of diabetes both in later life and in young overweight or obese women with PCOS.⁴
- Presence of PCOS, elevated the risk of developing T2DM by four fold when compared to their BMI matched controls, while the OR for IGT was 2.5.¹⁴
- The likelihood of developing T2DM significantly increased as BMI, fasting glucose, and glucose area under the curve (AUC) at baseline increased and significantly decreased as sex hormone-binding globulin (SHBG) levels at follow-up increased.¹⁵

PCOS and NAFLD



High prevalence of NAFLD is seen in:

- Obese individuals (90%)
- Women with diabetes (70%)
- Women with premenopausal NAFLD had been diagnosed with PCOS by Rotterdam criteria. (10 out of 14)

Link between NAFLD and PCOS:

- Obesity
- Insulin resistance
- Hyperandrogenism

Tests to screen NAFLD:

- Serum aminotransferase levels
- Haepatic steatosis by abdominal ultrasound

PCOS: Polycystic ovary syndrome; NAFLD: Non-alcoholic fatty liver disease

- NAFLD is the most common cause of chronic liver disease.
- It extends from liver damage from fatty infiltration to end-stage liver disease, in patients without significant alcohol consumption.

Prevalence

- Increased prevalence of NAFLD has been reported in patients with PCOS.
- Studies support high prevalence of NAFLD in obese individual reaching up to 90%.
- In morbidly obese individual and in people with diabetes up to 70%.
- Women with premenopausal NAFLD had been diagnosed with PCOS by Rotterdam criteria. (10 out of 14).¹⁶

Pathophysiology

- Main factors related to NAFLD in PCOS are:
 - Obesity, in particular central adiposity
 - Insulin resistance
- Androgen excess is the main feature of PCOS and is interrelated to insulin resistance, may be an additional contributing factor to the development of NAFLD.

Surveillance

- PCOS patients, particularly obese patients with features of the metabolic syndrome, should be submitted to screening for NAFLD comprising of:
 - Assessment of serum aminotransferase levels
 - Haepatic steatosis by abdominal ultrasound

Risk amelioration and management

- Lifestyle modifications including diet, weight loss and exercise are the initial therapeutic interventions for PCOS patients with NAFLD.
- Metformin may be considered, when above measures fail, although currently there is no medical therapy of proven benefit for NAFLD.¹⁷
- A trial of pioglitazone and vitamin E 800mg has been tried for the treatment of nonalcoholic steatohepatitis (NASH) in adults without diabetes with few benefits.¹⁸

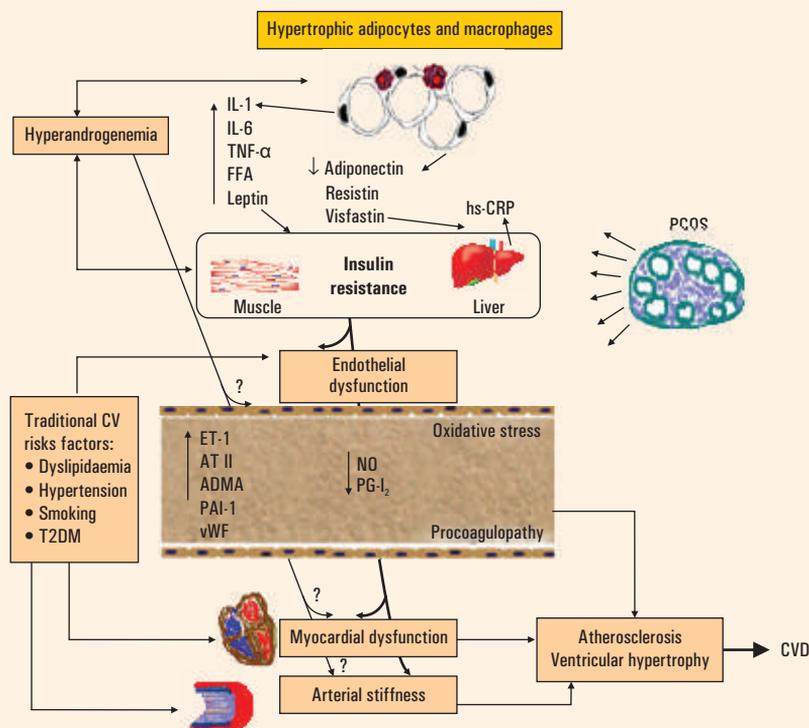
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Cardiometabolic Consequences of PCOS

Association between PCOS and cardiometabolic risk factors



IL: Interleukin; vWF: von Willebrand factor; PAI-1: Plasminogen activator inhibitor-1; AT-II: Antithrombin-II; ET-1: Endothelin-1; ADMA: Asymmetric dimethylarginine; MDA: Malondialdehyde; NO: Nitric oxide; FFA: Free fatty acids; hsCRP: high sensitivity C-reactive protein; PCOS: Polycystic ovary syndrome; T2DM: Type 2 diabetes mellitus; CVD: Cardiovascular disease

- Higher prevalence of classic risk factors for CVD such as hypertension, dyslipidaemia, diabetes, and obesity and non classic risk factors such as C-reactive protein (CRP), homocysteine, and tumour necrosis factor- α are seen in women with PCOS.¹
- PCOS at any age is characterised by greater odds for elevated CVD risk markers and these elevated markers can occur without obesity but are magnified with obesity.
- The cardiometabolic profile of women with PCOS appears to be dependent on PCOS reproductive phenotypes.
- Women with hyperandrogenic PCOS (classic NIH-criteria PCOS) have a worse cardiometabolic profile and higher prevalence of CVD risk factors compared with women with non-hyperandrogenic PCOS.^{2,3}
- More than 25% prevalence of metabolic syndrome is seen in women with hyperandrogenic PCOS.³
- Though metabolic and reproductive phenotypes mirror, different phenotypes of PCOS with same BMI were found to carry similar cardiometabolic risks. Thus obesity exacerbates the occurrence of metabolic syndrome.⁴
- A Swedish study found that even in the absence of a real hypertensive state, PCOS women presented a significantly higher daytime systolic blood pressure, mean arterial values of blood pressure, and an increased pulse rate, than healthy controls.
- This significant pre-hypertensive state remained even after adjusting for BMI, body fat distribution, and insulin resistance. Among the cardiovascular risk factors, T2DM represents one of the most important risk factor and PCOS is considered a major risk factor for developing IGT and T2DM.⁵
- Several non classic CVD risk factors, related to a systemic inflammatory state, such as CRP are reported at higher levels in women with PCOS.
- Plasma homocysteine levels are widely accepted as an independent CVD risk factor which several studies have reported are elevated in women with PCOS.⁶
- Other biochemical, inflammatory and thrombotic markers of cardiovascular risk have been reported in excess in women with PCOS compared with non-PCOS controls,^{7,8} such as tumour necrosis factor- α , interleukin-6 (IL-6), IL-18, IL-17, factor VIIc, tissue plasminogen activator (t-PA), fibrinogen, von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1), thrombo-modulin, D-dimers, antithrombin-II (AT-II), Sp (Selectin), endothelin-1 (ET-1), asymmetric dimethylarginine (ADMA), intercellular

adhesion molecule-1 (ICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), serum advanced glycation end-products (AGEs), membrane receptor for AGEs (RAGE), malondialdehyde (MDA), nitric oxide (NO), and latency-associated peptides (LAPs).²

- Typical features of PCOS, such as increased waist/hip ratio, hirsutism, or polycystic ovarian morphology (PCOM), are more commonly related to coronary artery disease in women undergoing coronary angiography.

Surveillance for metabolic syndrome

- Women with PCOS who are obese or overweight are at higher risk of developing metabolic syndrome. Hence it is recommended to screen these women for metabolic syndrome.²
- CVD surveillance
 - Invasive and non invasive tests may be applied to evaluate endothelial function, carotid intima-media thickness (CIMT), and coronary artery calcification (CAC) scores.⁹
 - Endothelial dysfunction, an early sign of atherosclerosis, can be assessed by examining artery's flow-mediated dilatation and, in a recent meta-analysis, this parameter, measured at brachial artery, was found to be lower in women with PCOS compared to controls, even after controlling for age, BMI, and smoking.^{10,11}

Risk amelioration

- The INTERHEART study found nine potentially modifiable risk factors which accounted for over 94% of the population-attributable risk of a first myocardial infarction in women.¹³
- The nine factors are:
 - Smoking, hypertension, dyslipidaemia, diabetes, visceral obesity, psychosocial factors, decreased consumption of fruits and vegetables, regular consumption of alcohol, and regular physical activity.
- The majority of these occur in the PCOS woman. Hence it is necessary to take these crucial steps for reducing the risk of development of metabolic syndrome/ CVD / T2DM.
 - Step- 1: Lifestyle modifications such as exercise and weight reduction, regular consumption of fruits and veggies (3–5 servings/ day) should be considered and smoking and alcohol intake should be avoided, to reduce insulin resistance, dyslipidaemia, T2DM and CVD risk factors.¹²

- o Step- 2: Metformin is an effective treatment for diabetes with favourable effects on lipid abnormalities to reduce cardiovascular risk. Metformin lowers triglycerides, increase HDL cholesterol, and favourably influences serum insulin levels.¹³

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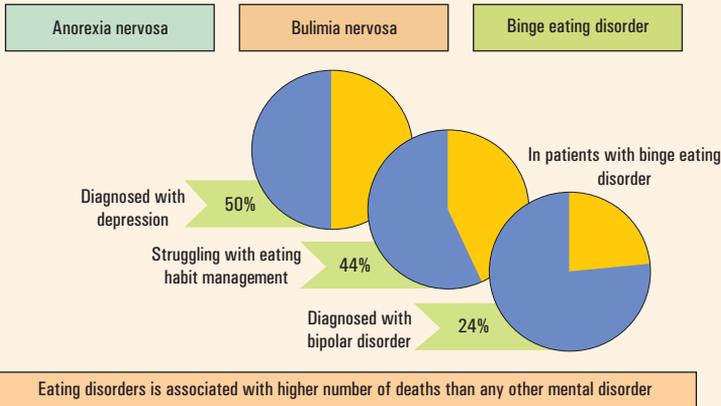
Other Consequences of PCOS



- The challenges to feminine identity and body image due to obesity, acne and excess hair, as well as infertility and long-term health-related concerns compromise the QoL and adversely impact on mood and psychological well-being.¹
- Women with PCOS carry a higher risk of developing depression, anxiety, low self-esteem, negative body image, and psychosexual dysfunction.²
- The other critical aspect of psychosocial impact in PCOS is the negative impact of mood disturbance, poor self-esteem and reduced psychological well-being on motivation and on the ability to implement and sustain successful lifestyle changes that are critical in this condition.^{1,3}
- High prevalence of depression and anxiety is seen among women with PCOS.⁴
- Women with PCOS with lower BMI tended to have slightly lower anxiety and depression scores, suggesting that having a lower BMI reduces anxiety and depression.
- Holistic management of PCOS warrants the need to look out and treat these conditions during PCOS assessment and management.
- Experts from the field must be involved in the care plan.

PCOS and Eating Disorders

PCOS is associated with higher prevalence of eating disorders



Prevalence among women with PCOS

- Prevalence of clinical and subclinical eating disorders particularly bulimia nervosa is increased among women with PCOS compared to healthy women.
- High prevalence of eating disorders is seen among women with PCOS:
 - Clinical bulimia nervosa: 5.3%,
 - Subclinical anorexia nervosa: 1.1%
 - Subclinical bulimia nervosa: 10.5%
 - Subclinical bulimia nervosa as detected in the hyperandrogenic group: 1.6%⁵
- PCOS women with anxiety and depression had higher odds of developing an eating disorder.⁶

Consequences

- Disordered eating attitudes and behaviours are associated with decreased QoL in women with PCOS.
- Eating disorders can have significant negative influence on the outcome of the treatment of PCOS.
- Eating disorders are associated with higher number of deaths than any other mental disorder.

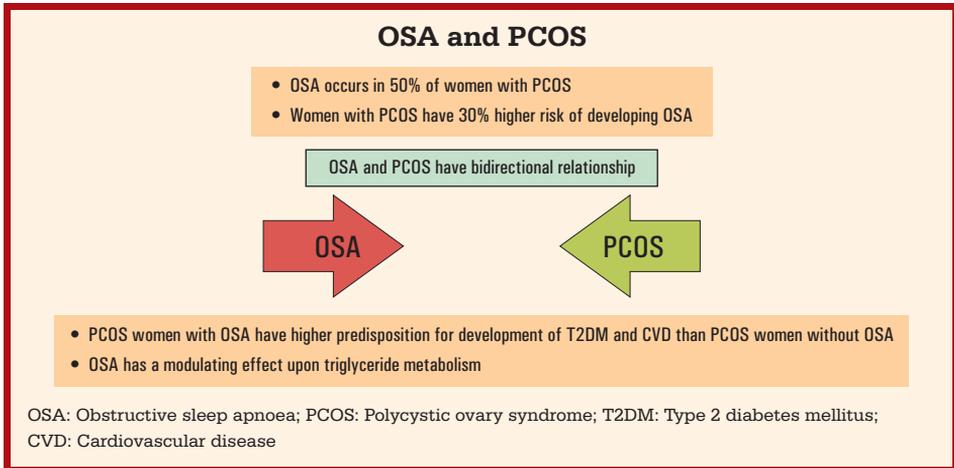
Surveillance

- It is necessary to screen women with PCOS for eating disorders especially those with co-existing anxiety or depressive symptoms.

- Eating disorder examination questionnaire (EDEQ) may be employed for screening.

Management

- Psychological treatment of eating disorders among women with PCOS is crucial.⁶



- Obstructive sleep apnoea (OSA) and excessive daytime sleepiness (EDS) are strongly associated with insulin resistance.
- BMI-independent OSA risk has been noted in the PCOS population.⁷
- Neither the degree of androgen elevation nor BMI fully account for the presence or severity of OSA in PCOS.

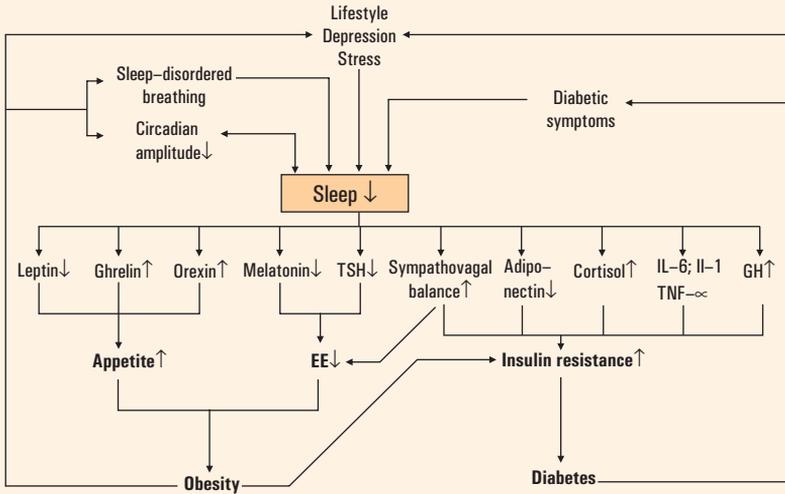
Prevalence

- PCOS patients were 30 times more likely to suffer from sleep disordered breathing (SDB) than the controls [OR = 30.6, 95% CI (7.2–139.4)].
- OSA is found in 50% of women with PCOS.⁸

Pathophysiology

- Bi-directional relationship exists between OSA and PCOS as shown in the figure above.
- Overweight and (visceral) obesity are exceptionally common in women with PCOS and contribute to the increased risk of OSA in this population.
- IGT and T2DM are present at an early age and in a disproportionate number of women with PCOS.
- The presence and severity of OSA may directly impact the mechanism of IGT in women with PCOS.

Disrupted Sleep Pattern – A Cause of Metabolic Disorder in Women with PCOS



IL: Interleukin; TSH: Thyroid-stimulating hormone; TNF: Tumour necrosis factor; GH: Growth hormone; EE: Ethinyloestradiol; OSA: Obstructive sleep apnoea

Consequences

- PCOS women with OSA may have a much greater predisposition for development of diabetes and CVD than PCOS women without OSA.
- Further, there is the potential that OSA has a modulating effect upon triglyceride metabolism.

Surveillance

- There is a significant increase in risk for OSA in PCOS. When present, OSA largely remains under-diagnosed and untreated.
- Patients need to be referred to sleep medicine for screening and management.

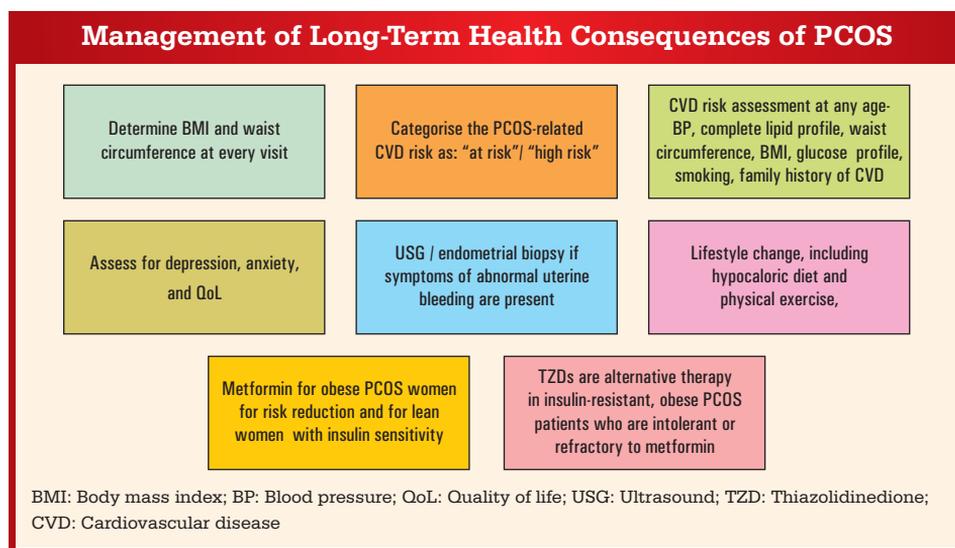
Management

- Treatment of OSA with continuous positive airway pressure (CPAP) in PCOS results in significant reductions in 24 hr secretory cortisol and norepinephrine profiles as well as improved insulin sensitivity.⁹

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- The long-term risks observed in women with PCOS are vary based on different phenotypes and are negatively influenced by obesity and lifestyle factors. It is recommended that BMI and waist circumference should be determined at every visit, considering the presence of abdominal obesity in women with a waist circumference of at least 80 cm.¹
- Categorise the PCOS-related CVD risk as:
 - “At risk” for PCOS women with any following risk factors: obesity, cigarette smoking, hypertension, dyslipidaemia, subclinical vascular disease, IGT, and/or family history of premature CVD (<55 years of age in male relative, <65 years of age in female relative).

- o “At high risk” for PCOS women with metabolic syndrome and/or T2DM and/or overt vascular or renal disease.
- CVD risk assessment at any age, for blood pressure, complete lipid profile (including total, LDL, HDL, non-HDL cholesterol, and triglycerides), waist circumference, BMI, glucose profile, cigarette smoking, and a family history of early CVD.
- Because cardiovascular risk increases with age and it can be exacerbated by obesity and worsened by environmental insults, periodic reassessment for CVD risk is suggested but there is no agreement how often the CVD risk assessment should be repeated.
- PCOS patients must be assessed also for depression, anxiety, and QoL.
- There is no agreement on the optimal method, whether ultrasound or endometrial biopsy and timing of screening for endometrial cancer. In line with American Cancer Society Guidelines, the decision to assess for the presence of endometrial cancer should be based essentially on the presence of abnormal uterine bleeding or spotting. Other relevant decision factors are amenorrhoea length, women’s age, and the ultrasound appearance of endometrium.²
- Lifestyle change, including hypocaloric diet and physical exercise, is considered a cornerstone of the management of women with PCOS presenting with obesity, particularly the abdominal phenotype; so it is generally recommended as a first-line approach for obese PCOS women. A 5%–10% weight loss is considered clinically significant and able to reduce IGT and metabolic syndrome prevalence in general population.³
- From a pharmacological standpoint, considering the metabolic and hormonal relevance of insulin resistance and associated compensatory hyperinsulinaemia, common features of the PCOS women, the treatment choices have been expanded to insulin-sensitising agents, in particular, metformin.⁴
- Moreover, metformin is not of benefit in improving weight loss, insulin sensitivity, or lipid profiles; hence a long-term prophylactic treatment with metformin is unlikely to prevent progression to diabetes. In line with these considerations, the main⁵ societies agree to consider metformin for prevention of diabetes in women with PCOS and IGT when lifestyle modification is not successful and/or as an adjuvant to general lifestyle modifications that remains the first-line therapy for PCOS women at increased metabolic risk.⁶

- Thiazolidinediones may be considered as an alternative therapy in insulin-resistant, obese PCOS patients who are intolerant or refractory to metformin, or in PCOS women with severe insulin resistance due to genetic disorder. At present, in overweight/obese PCOS women, we advice lifestyle changes (consisting of Mediterranean diet and physical activity) as preliminary approach, at any age, with the aim of weight loss. We suggest the association with metformin in obese/overweight PCOS patients, when lifestyle program alone is not enough to obtain metabolic improvements and we proposed metformin use in lean PCOS patients with impaired insulin sensitivity.⁷

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Conclusion

- PCOS is associated with serious long-term health consequences.
- The prevalence of certain neoplastic, cardiometabolic and mental health conditions is higher in women with PCOS when compared against those without PCOS.
- Obesity and insulin resistance are the major pathologic factors that lead to all these consequences.
- It is important to screen the patients with PCOS for identifying early signs and promptly treating these serious health conditions.
- Lifestyle modification particularly associated with weight loss is the first step to curtail the risk of endometrial cancer, cardiometabolic syndrome and mental disorders.
- Pharmacological treatment may be necessary when lifestyle measures are unable to meet the expectations of risk reduction.
- Several studies support the benefits of the use of metformin.
- Involvement of respective experts is necessary for the care of patients with long-term health consequence of PCOS.

Key points

Key recommendations for clinical assessment and treatment of long-term PCOS complications

	Clinical assessment	Therapeutic approaches
Metabolic risk	<p>Screening for IGT and T2DM with 75 g OGTT in PCOS women with:</p> <ul style="list-style-type: none"> • Age >40 years • BMI >30 • Classic phenotype • Presence of acanthosis nigricans • Personal and/or family history of T2DM <p>BMI and waist circumference at every visit:</p> <ul style="list-style-type: none"> • Waist circumference >80 cm 	<p>Lifestyle change programmes (hypocaloric diet and physical exercise) represent the first-line approach for treating obese PCOS women</p> <p>Metformin use for prevention of diabetes in PCOS women with IGT when lifestyle modification is not successful and/or as an adjuvant to general lifestyle modifications</p>

Key points (Table cont...)

	Clinical assessment	Therapeutic approaches
	<ul style="list-style-type: none"> • Abdominal obesity Periodic reassessment with OGTT	Thiazolidinediones as alternative therapy in insulin-resistant, obese PCOS patients who are intolerant or refractory to metformin, or with severe insulin resistance due to genetic disorder
Cardiovascular risk	CVD risk assessment at any age with: <ul style="list-style-type: none"> • Blood pressure • Lipid profile • Waist circumference • BMI • Glucose profile • Cigarette smoking • Family history of early CVD • Evaluation for depression, anxiety, and quality-of-life Categorise PCOS patients as “at risk” for CVD if present: <ul style="list-style-type: none"> • Obesity • Hypertension • Dyslipidaemia • Cigarette smoking • Subclinical vascular disease • IGT • Family history of premature CVD Categorise PCOS patients as “at high risk” for CVD if present: <ul style="list-style-type: none"> • Metabolic syndrome 	Lifestyle modification: <ul style="list-style-type: none"> • Diet • Physical exercise • Smoking cessation Metformin use for prevention of T2DM in PCOS women with IGT when lifestyle modification is not successful and/or as an adjuvant to general lifestyle modifications Statins to lower LDL-C levels Antihypertensive drugs

Key points (Table cont...)

	Clinical assessment	Therapeutic approaches
	<ul style="list-style-type: none"> • T2DM • Vascular and/or renal disease Periodic clinical reassessment	
Cardiovascular risk	In presence of amenorrhea or abnormal uterine bleeding, assessment for the presence of endometrial cancer with ultrasound and/or endometrial biopsy	Periodic progestogen withdrawal (at least four episodes per year) should be indicated in anovulatory PCOS women

CVD: Cardiovascular disease; OGTT: Oral glucose tolerance test; PCOS: Polycystic ovary syndrome; LDL-C: Low-density lipoprotein cholesterol; BMI: Body mass index; T2DM: Type-2 diabetes mellitus; IGT: Impaired glucose tolerance

Reference

1. Palomba S, Santagni S and Falbo A. Complications and challenges associated with polycystic ovary syndrome: current perspectives. *Int J Womens Health*. 2015;7:745–763.

Suggested Readings

1. Harris HR and Terry KL. Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review. *Fertil Res Pract*. 2016;2:14.
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PCOS and Long-Term Health Consequences

POST-TEST

- 
- 1. PCOS has been associated with:**
 - a) Endometrial cancers
 - b) Orthopaedic cancers
 - c) Lung cancers
 - d) All of the above
 - 2. Adolescents and reproductive age women with PCOS have an increased prevalence of cardiovascular risk factors. Is this truth or myth?**
 - a) Truth
 - b) Myth
 - 3. Which of the following is not associated with PCOS ?**
 - a) Depression
 - b) Anxiety
 - c) Both a and b
 - d) Schizophrenia
 - 4. Which are the different modes of treating endometrial cancer? Select the most appropriate answer.**
 - a) Surgery only
 - b) Surgery and radio therapy
 - c) Surgery, radio and chemo therapy
 - d) Surgery, hormonal, radio and chemo therapy
 - 5. For patients with conservative surgery for borderline ovarian serous tumours , which of the following is true?**
 - a) Most of them turn infertile
 - b) Spontaneous conception occurs in less than 20% patients
 - c) Spontaneous conception occurs in nearly 50% patients
 - d) All of the above are untrue
 - 6. Clomiphene citrate increases the risk of and endometrial cancer.**
 - a) Ovarian cancer
 - b) Breast cancer
 - c) Colorectal cancer
 - d) Melanoma
- 

7. **Metabolic syndrome leads to increase in all, except:**
- a) Triglycerides
 - b) HDL
 - c) LDL
 - d) V-LDL
8. **Which of the following is associated with PCOS?**
- a) Obstructive sleep apnoea
 - b) NAFLD
 - c) Coronary heart disease
 - d) All of the above
 - e) None of the above
9. **All patients with PCOS must have endometrial biopsy at every visit to screen for endometrial cancer.**
- a) True
 - b) False
10. **How much weight loss is considered clinically significant and able to reduce IGT and metabolic syndrome prevalence?**
- a) $\geq 50\%$
 - b) 30–40 %
 - c) 20–25%
 - d) 5–10%

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