**REVIEW ARTICLE**

# Polycystic ovary syndrome and metabolic disorders: A review of the literature

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## Abstract

Polycystic ovarian syndrome (PCOS) is one of the most common female endocrinopathies and is a leading cause of infertility. The syndrome derives its name from the pathological appearance of the ovary in women with menstrual irregularities and hyperandrogenism. Its symptoms appear as early as adolescence in the form of amenorrhea, hirsutism and obesity. The majority of patients are overweight, obese or of normal weight, but metabolically obese. The prevalence of PCOS is on the increase and is associated with a significantly higher risk of various metabolic disorders including cardiovascular disease (CVD), Type2 diabetes (T2DM), gestational diabetes, hypercholesterolemia and different types of cancer, including endometrial and possibly ovarian cancer, especially if associated with hyperinsulinaemia. In contrast, in women with PCOS who have normal insulin levels, it is likely that genetics, inflammation, oxidative stress and possible interaction with environmental factors are present that link these women to metabolic disorders. The mechanism of PCOS is not well understood and this review aims to provide a detailed description of the mechanism underlying the development of PCOS and associated metabolic disorders with a full description of all possible scenarios associating PCOS to metabolic disorders, as well as an epidemiological overview regarding the relationship between these metabolic disorders and PCOS. *(Afr J Reprod Health 2022; 26[8]: 89-99).*

**Keywords:** Polycystic ovary syndrome, insulin resistance, type2 diabetes, cardiovascular disease, endometrial cancer

## Résumé

Le syndrome des ovaires polykystiques (SOPK) est l'une des endocrinopathies féminines les plus courantes et l'une des principales causes d'infertilité. Le syndrome tire son nom de l'aspect pathologique de l'ovaire chez les femmes souffrant d'irrégularités menstruelles et d'hyperandrogénie. Ses symptômes apparaissent dès l'adolescence sous forme d'aménorrhée, d'hirsutisme et d'obésité. La majorité des patients sont en surpoids, obèses ou de poids normal, mais métaboliquement obèses. La prévalence du SOPK est en augmentation et est associée à un risque significativement plus élevé de divers troubles métaboliques, notamment les maladies cardiovasculaires (MCV), le diabète de type 2 (DT2), le diabète gestationnel, l'hypercholestérolémie et différents types de cancer, notamment le cancer de l'endomètre et éventuellement de l'ovaire, surtout s'il est associé à une hyperinsulinémie. En revanche, chez les femmes atteintes du SOPK qui ont des niveaux d'insuline normaux, il est probable que la génétique, l'inflammation, le stress oxydatif et une interaction possible avec des facteurs environnementaux soient présents et lient ces femmes à des troubles métaboliques. Le mécanisme du SOPK n'est pas bien compris et cette revue vise à fournir une description détaillée du mécanisme sous-jacent au développement du SOPK et des troubles métaboliques associés avec une description complète de tous les scénarios possibles associant le SOPK aux troubles métaboliques, ainsi qu'un aperçu épidémiologique concernant la relation entre ces troubles métaboliques et le SOPK. *(Afr J Reprod Health 2022; 26[8]: 89-99).*

**Mots-clés:** Syndrome des ovaires polykystiques, résistance à l'insuline, diabète de type 2, maladie cardiovasculaire, cancer de l'endomètre

## Introduction

Polycystic ovarian syndrome (PCOS), first described in 1935, is one of the most common hormonal disorders in women of reproductive age[1]. It derives its name from the pathological appearance of the ovary on transvaginal ultrasound, typically showing 7-10 cysts within the ovary, each measuring 3-7 mm in size, classically in the periphery of the ovary constituting the so-called "pearl string sign", in women with associated oligo-amenorrhea or amenorrhea and hyperandrogenism. Commonly have associated acne, blackheads and hirsutism, although the

clinical features may vary from one woman to another[2]. In developed and developing countries, PCOS is considered to be a leading cause of infertility, affecting millions of women.

The prevalence of PCOS critically depends on ethnicity, race, phenotype, environmental factors and genetic variation[3], as well as the criteria used to define PCOS[4]. Using different criteria to diagnose PCOS, different study methodologies and age of the group recruited in the study may produce different prevalence rates. The more recently determined prevalence of PCOS have increased with the use of different diagnostic criteria as opposed to the majority of past studies which defined PCOS by relying on a restricted number of features, namely morphological confirmation of polycystic ovaries only. The increase could also be due to public awareness of the condition through education and socio-economic related factors leading to more women with PCOS having been diagnosed. Depending on PCOS's definition, it has been estimated that this syndrome affects 4 to 20% of women of reproductive age worldwide[2].

Insulin resistance seemingly plays an important central role is the manifestations of the syndrome with the vast majority of women with PCOS being overweight or obese and usually presenting with features similar to the Metabolic Syndrome. Insulin resistance also controls fat distribution and is believed to be responsible of visceral fat accumulation[5]. Even small abdominal fat increases in women with PCOS with normal weight may be critical in the initiation and progression of obesity-related metabolic risk factors such as insulin resistance, atherogenic dyslipidaemia, and elevated blood pressure[6-7]. Compared to control groups, most studies of women with PCOS show that they are at higher risk of developing metabolic disorders such as Type 2 diabetes (T2DM) or impaired glucose tolerance test[6,8], hypertension[6,8-9], cardiovascular disease (CVD)[10], gynaecological cancers[11-13] and dyslipidaemias[14]. Other studies have found no differences in female mortality rates, metabolic markers, or risk factors contributing to metabolic disorders between women with PCOS and healthy controls[15-16]. This review provides detailed descriptions of the mechanisms underlying the development of PCOS and the metabolic disorders associated with PCOS and an epidemiological overview of previous studies aimed at PCOS is also included.

## *Mechanism of developing PCOS*

Although the precise mechanism of PCOS development is not clearly defined, it is believed that many factors are involved in the pathophysiology of PCOS (Figure 1). In normal women, ovarian function relies on the selection of a follicle which responds to the signal of a small increase in Follicle Stimulating Hormone (FSH) secretion at the appropriate time.This allows the development of a dominant and ultimately ovulatory follicle during that cycle. FSH stimulates the inner layer of the follicles (granulosa cells) to produce estradiol, while luteinising hormone (LH) stimulates the outer layer of the follicles (theca cells) to produce androgens. These androgens are converted to estrogen in the granulosa cells under the influence of FSH. Final maturation of the ovum and subsequent ovulation occurs only after initiation of LH secretion. There is a mid-cycle surge of FSH that is responsible for ovulation about 30-36 hours later.

In women with PCOS, this fine tuned and dynamic mechanism is disrupted. There is loss of FSH and LH pulsatile secretion resulting in persistently raised LH levels while that of FSH remains unchanged or is muted, and commonly, is in the low range level[17]. As a consequence, LH values increase and the LH: FSH ratio may reach 2:1 or even 3:1 in ovulatory cycles. Due to the increase in the ratio of LH:FSH, the ovarian granulosa cells are no longer able to aromatize the androgens to estrogens, leading to diminished estradiol levels, although estrone levels may be elevated. Furthermore, increased androgen levels result in multiple small cysts which may contain potentially viable oocytes within these dysfunctional follicles[18-19]. Consequently, women with PCOS are unable to produce and release a dominant ovulatory ovum. When androgen levels increase (under various environmental factors e.g. abdominal obesity), hormonal imbalance occurs which impairs follicular growth and survival, inhibits later follicular development, and directly causes a polycystic ovarian morphology (Figure 1).

Results from human and animal studies have shown that exogenous androgen causes PCOS-like morphological and functional changes.

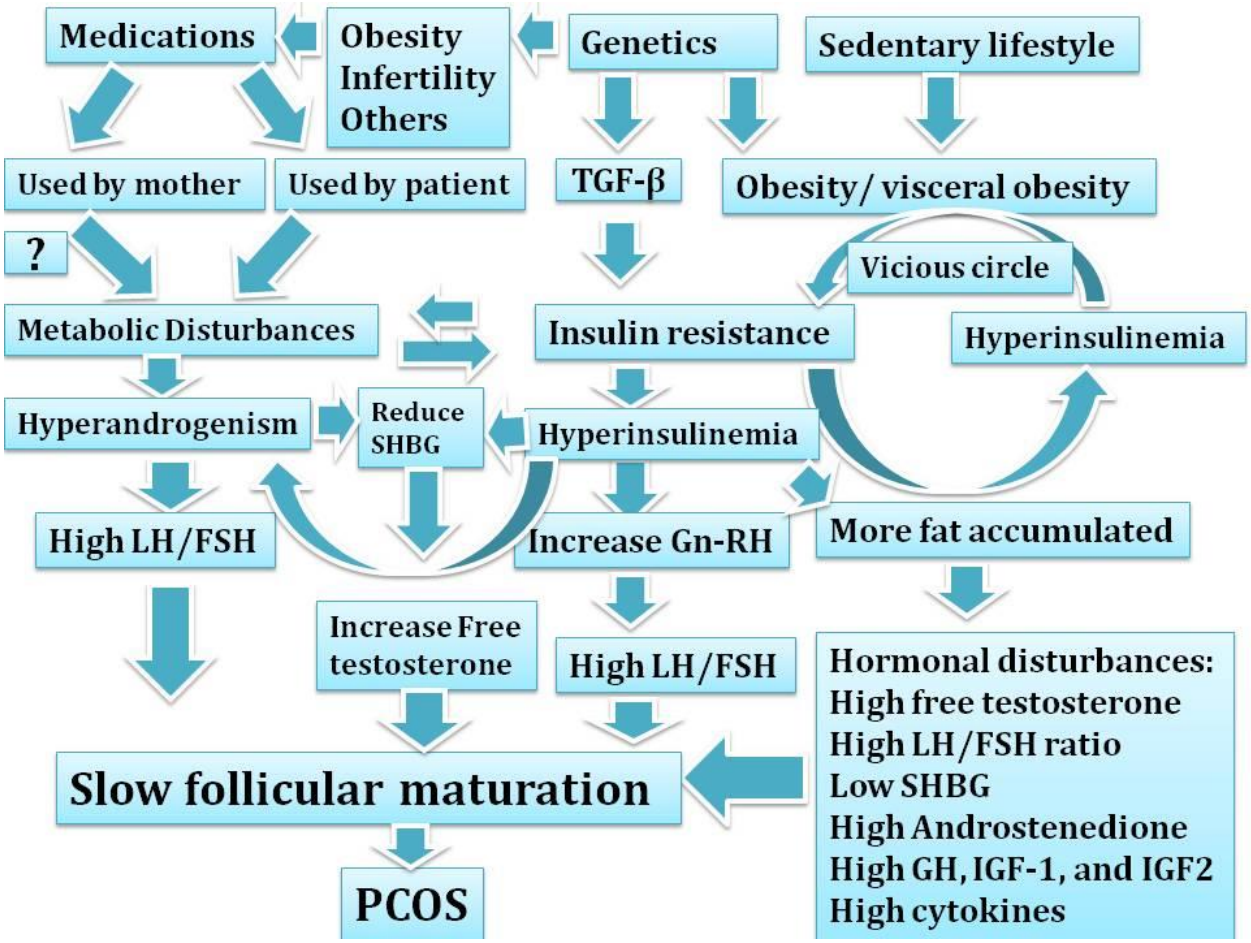


**Figure 1:** Pathophysiology of PCOS

Many factors are involved in the pathophysiology of PCOS, including increased obesity due sedentary lifestyle, age progression and decreased resting metabolic rate. PCOS can be also due to genetic predisposition especially hyperandrogenism and metabolic disturbances such as insulin resistance and daughters of mothers with PCOS may develop PCOS at certain point of their life.

Administration of high-dose testosterone to women will suppress gonadotropins release resulting in enlargement of the ovaries with increased numbers of "cystic" follicles and theca-interstitial hyperplasia which mirrors the morphological criteria for PCOS[18]. Furthermore, androgen-producing tumours and congenital adrenal hyperplasia both express PCOS-like morphological and functional changes as a result of the exposure to extra-ovarian androgens[19]. Previous animal studies have shown that treating healthy female rhesus monkeys (*Macacca mulatta*) with exogenous androgen for ten days resulted in a polycystic ovarian-like morphology[20]. In other words, it may be that PCOS does not develop unless there is an inappropriate increase in androgen. Findings from animal studies have supported the possibility of developing PCOS during the foetal period if the foetus is exposed to high levels of androgen[21]. Thus, diseases that express high level of androgens (i.e. androgen-secreting tumours), or diseases that encourage hyperandrogenism at some stage (i.e. obesity) can be considered as a risk factor for PCOS development. This applies to both adult females and developing foetuses. Obesity, especially visceral obesity, is associated with insulin resistance resulting in hyperinsulinaemia which directly or indirectly reduces sex hormone binding globulin (SHBG) and encourages hyperandrogenism (Figure 1).

### *Fat distribution, insulin resistance and the development of PCOS*

A comperhensive understanding of the mechanism of PCOS development requires a detailed description of the realtionship between fat disribution and insulin resistance.

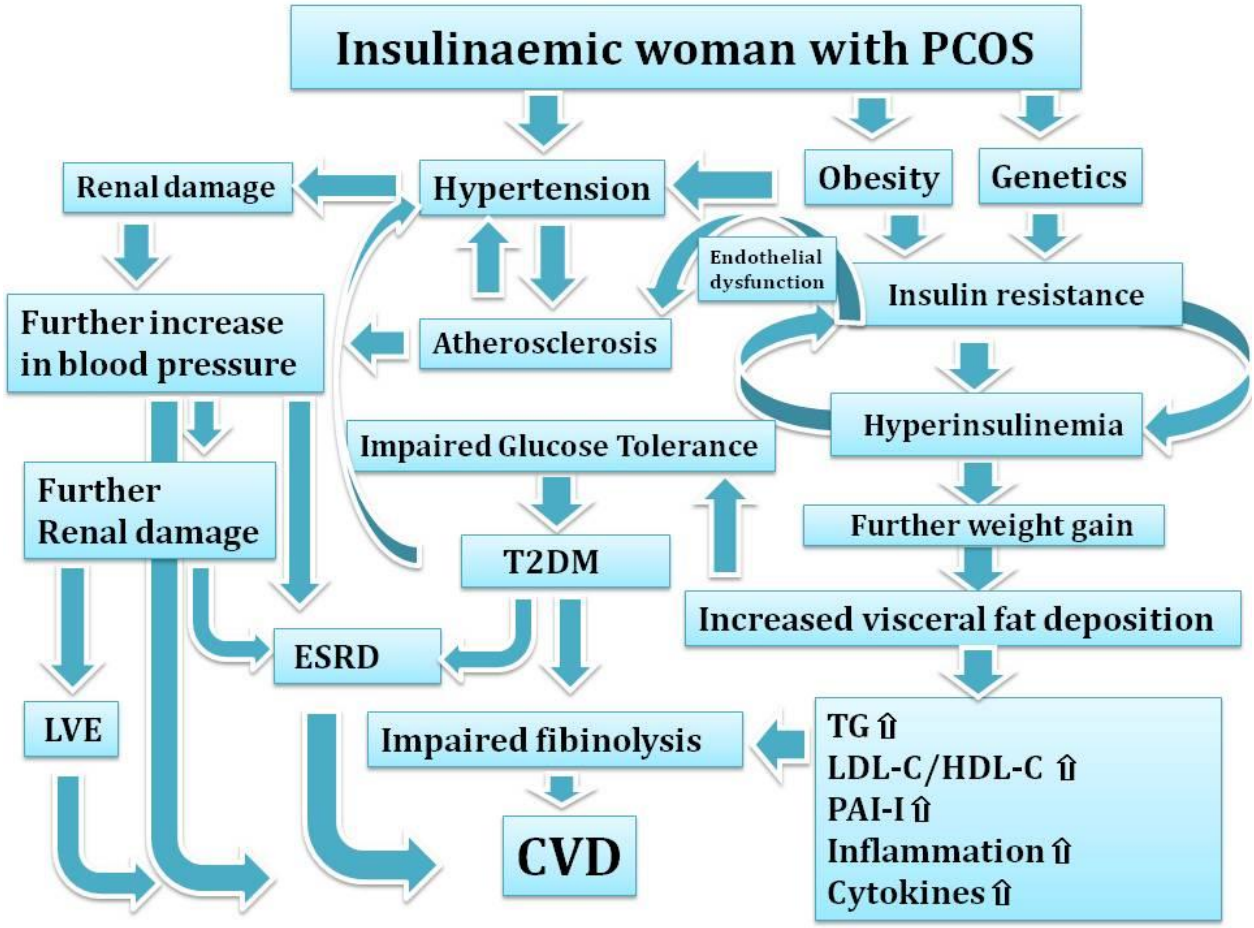


**Figure 2:** Mechanism of CVD in woman with PCOS and raised insulin levels

PCOS women with insulin resistance are usually obese, hypertensive and high insulin level in such patient could be due to obesity and/or genetic predisposition. Persistence insulin resistance may lead to endothelial dysfunction and atherosclerosis ending with Hypertension. Untreated hypertension may lead to renal damage and further increase in blood pressure will cause further renal damage (vicious cycle). Ultimately, this will lead to Left ventricle enlargement (LVE) and End Stage Renal Disease (ESRD), causing Cardiovascular Disease (CVD). On the other hand, obesity and especially abdominal obesity is associated with T2DM which also leads to ESDR and CVD if not well controlled. Abbreviation: LVE; left ventricle enlargement, ESRD; end stage renal disease, CVD; cardiovascular disease, TG; triglycerides, T2DM; type 2 diabetes, LDL-C/HDL-C; the ratio of low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, PAI-I; Plasminogen activator inhibitor-I.

Increased triglyceride and free fatty acid levels in blood encourages subcutaneous fat deposition , and when subcutaneous fat is seemingly saturated , the body directs deposition to the liver or the abdominal cavity as visceral fat. Eventually, this may lead to features associated with the Metabolic Syndrome, namely abdominal girth > 85 cm, obesity, increased visceral fat, insulin resistance and hyperinsulinaemia, features very common in patients with PCOS[22]. High levels of insulin in women precipitate the expression of PCOS. Evidence to support this includes a dramatic improvement in endocrine and ovarian function in response to weight reduction[23-25]. Weight reduction corrects hormonal imbalance, decreases inflammation, decreases insulin resistance, and causes a significant reduction in androgens, particularly testosterone and androstenedione[23-25]. The aim would ideally be about 10% body weight loss, but even modest weight loss (5%) has been shown to restore the menstrual regularity in women with PCOS[26].

Elevation of serum concentrations of insulin is significantly higher in obese and lean subjects with PCOS than in weight matched controls. The high level of insulin in these patients

is a direct consequence of insulin resistance, decreased insulin clearance and uninterrupted insulin secretion. Although insulin resistance/sensitivity varies according to the menstrual pattern, women with regular cycles have less insulin resistance compared with women with irregular cycles[27]. As insulin is an anabolic hormone, it is much easier for patients with hyperinsulinaemia to gain weight rather than lose weight. More weight gain causes a further increase in insulin secretion creating a vicious cycle that maintains the increased level of insulin in circulation, promoting hyperandrogenism (Figure 1). Hepatic synthesis of sex hormone–binding globulin, the key circulating protein that binds testosterone, is decreased in the presence of hyperinsulinaemia, leading to an increase in serum free testosterone and at the same time stimulating ovarian androgen secretion[28]. Studies using insulin sensitizers provided concrete evidence supporting the vital role of insulin resistance and hyperinsulinaemia in PCOS development. Pioglitazone treatment increases cellular insulin sensitivity, reduces circulating insulin levels, diminishes insulin resistance, normalizes menstrual cycle and diminishes ovarian hyperandrogenism in women[29] and most prenatally androgenized female monkeys[30].

Ovarian androgen secretion increases because hyperinsulinaemia inhibits the hepatic secretion of insulin-like growth factor binding protein-1 (IGFBP-1) leading to an increase in insulin-like growth factor-I (IGF-1), and insulin-like growth factor-2 (IGF-2), important regulators of ovarian follicular maturation and steroidogenesis. Together with IGF-2 secretion from theca cells, liver IGF-1 and IGF-2 further amplify ovarian androgen production and secretion by acting on IGF-1 receptors[31-32]. Hyperinsulinaemia provides another non-ovarian component of hyperandrogenism. Ovarian androgen secretion is also positively associated with increased LH secretion and weight gain. Excess local ovarian androgen increased by hyperinsulinaemia causes premature follicular atresia and anovulation.

The epidemiology of PCOS has shown that the syndrome may run in families, suggesting a genetic link. The rates of PCOS in mothers and sisters of patients with PCOS were 24% and 32%, respectively[33], associated with increased insulin resistance in the mother and sisters of patients with PCOS[34] suggesting that PCOS may be pre-programmed through either a genetic link or due to increased hormonal imbalance effects during pregnancy (fetal exposure to excess androgen before birth). Two genomic regions linked to PCOS have been identified. The first is close to the follistatin gene and the second is the dinucleotide repeat microsatellite marker D19S884, which is located in intron 55 of the fibrillin 3 gene. Both of these genes share common transforming growth factor--β (TGF-β) binding site and both of them regulate the activity members of TGF-β superfamily. However, the microsatellite D19S884 polymorphism located on the fibrillin 3 gene [41,42-NHMRC], involved in extra-cellular matrix regulation, also demonstrates a clear association with PCOS. Dysregulation of TGF-β has been shown to contribute to cardiovascular and reproductive abnormalities in patients with PCOS and related to foetal origins of PCOS[35].

## *Pathophysiology of metabolic disorders in women with PCOS*

Women with PCOS are more susceptible to specific health risks later in life compared to women of general population. Previous epidemiological and clinical studies have observed correlation between PCOS and T2DM[6,8,9,36], CVD[10] and endometrial cancer[11-13]. This section is discussing in details the possible mechanism linking women with PCOS to each one of these diseases.

### *1. Type 2 diabetes*

Compared with normal controls, T2DM is more often seen in obese women with PCOS[9,36] and is characterised by abnormalities in insulin secretion and action resulting in hyperglycaemia, elevated levels of triglyceride, total cholesterol, low dense lipoprotein (LDL) and decreased high density lipoprotein (HDL). Regardless of the criteria used to define the metabolic syndrome, women with PCOS have a significant increase in the risk of developing the metabolic syndrome even after controlling for age and BMI [7] leading to abdominal obesity, increased triglycerides, decreased HDL/LDL ratio, increased blood pressure and elevated plasma glucose and elevated apolipoprotein B and small LDL particles[37].

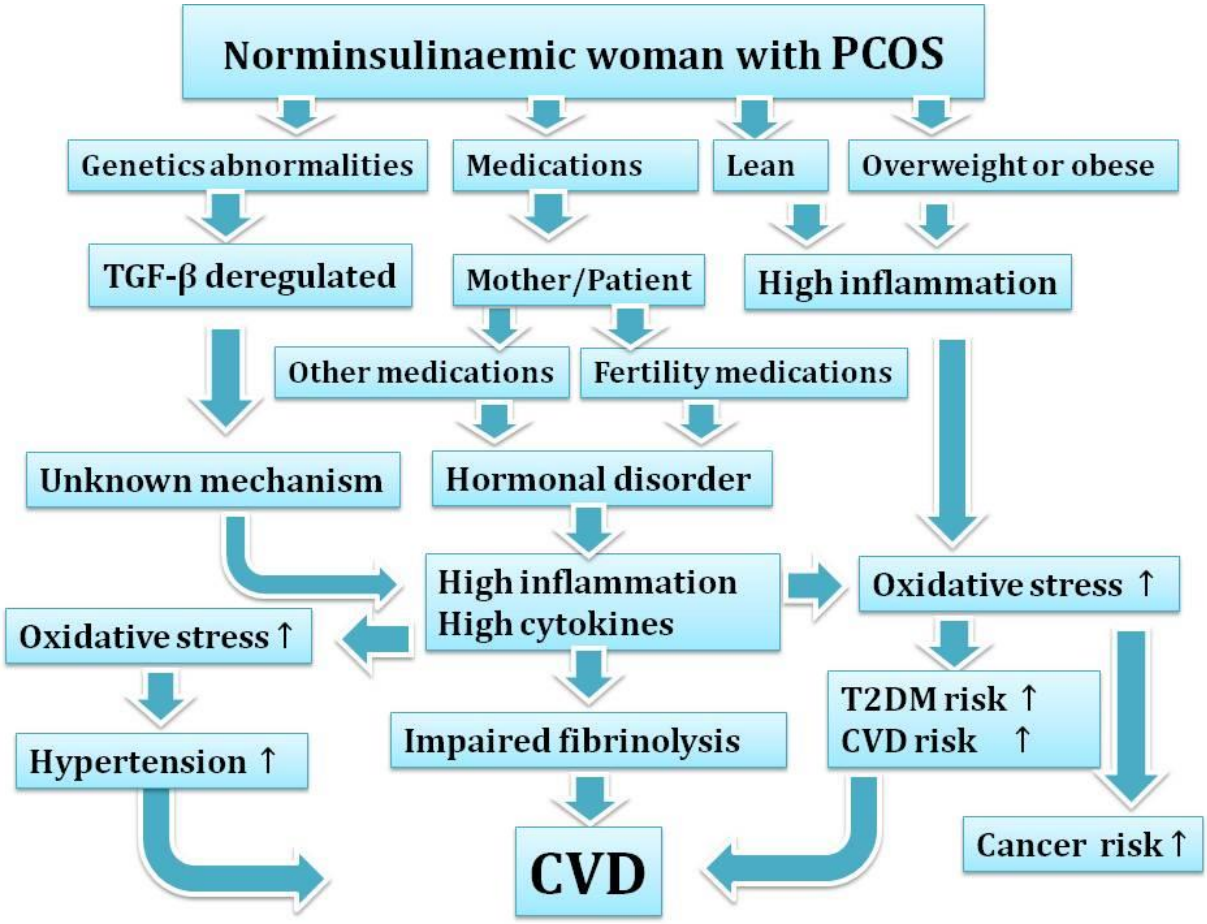


**Figure 3:** Mechanism of CVD in woman with PCOS and normal insulin levels

PCOS women with normal insulin level, they usually present with genetic predisposition that may associate with increased CVD risk. PCOS and metabolic distrurbances in these women is highly heritable. Subjects of mothers with PCOS also have increased metabolic dysfunction and prevelance of T2DM and cardiovascular risk factors.

Of note, the extent of insulin resistance, particularly associated with abdominal fat, is a predictor for impaired glucose tolerance, T2DM and CVD[38]. Insulin resistance is known to play a major role in the development of T2DM, as it controls body fat distribution[5].

In an environment of insulin resistance and due to space limitation, the body will direct triglycerides to the abdominal cavity to be deposited as visceral fat[5]. The consequences, if not treated as early as possible, is a vicious circle; the higher hyperinsulinaemic state, the more insulin secreted, the higher the insulin resistance. The net result of this is the exhaustion of pancreatic beta cells, leading to a failure of insulin–mediated glucose uptake, a condition which eventually can lead to impaired glucose tolerance and T2DM (Figure 2). Abdominal obesity or the android pattern of fat distribution is more commonly observed among patients with T2DM than in women with gynoid pattern of adipose tissue distribution. Women without evidence of clinically overt T2DM, who present with upper body obesity are more likely to have hyperinsulinaemia and impaired glucose tolerance than women who have their fat distributed on the hips, thighs and buttocks[5]. Another possible mechanism that may explain the increased rate of T2DM among women with PCOS is through hyperandrogenism. Women with PCOS usually present with low level of SHBG, and this may increase the incidence of T2DM by modulating the biological effect of free

testosterone on peripheral insulin sensitive tissues. Thus, high concentrations of SHBG could be considered as a protective factor against T2DM[39].

In women with PCOS, the possible role of androgenic/oestrogenic hormone imbalance is crucial, as it may contribute to inauspicious distribution of body fat. Genetics, family history of having T2DM, factors related to lifestyle and the possible interaction between two or more of these factors are also important in the initiation and development of T2DM in women with PCOS[36].

### *2. Cardiovascular disease*

An insulin resistant environment is a mechanism that might possibly explain the increase risk of CVD in patients with PCOS[40]. Women with PCOS are associated with an atherogenic lipoprotein profile, characterised by elevated triglyceride-rich lipoproteins, decreased high density lipoprotein (HDL), and elevated low-density lipoprotein (LDL) cholesterol. High-density lipoprotein and triglyceride levels are independent lipid predictors of CVD death in women[41]. Obesity, hyperinsulinaemia and hypertension further increase the risk of CVD[14,42]. Some patients with PCOS and normal BMI may have insulin resistance and metabolic disturbances due to abnormal fat distribution and/or increased visceral fat[5,14,42].

Although total fat mass is a major determinant of insulin resistance, in healthy women, it is independently associated with increased CVD risk[43]. Women with normal insulin levels without PCOS who have a greater fat mass may have a higher CVD risk due to higher levels of proinflammatory cytokines. Aberration in lipid profile is a risk factor for CVD and increases death rate. HDL levels less than 1.30 mmol/L (50 mg/dL) seem to be strongly associated with cardiovascular mortality (RR=1.74) even after adjustment for age and other CVD risk factors. Similarly, triglyceride concentrations of 2.25 to 4.49 mmol/L (200 to 399 mg/dL) seem to be associated with elevated death rate due to CVD (RR=1.65). The risk of death due to CVD increases to 3.44 (RR=3.44) when triglyceride concentrations reached 4.50 mmol/L (400 mg/dL) or greater[41]. Obese women with PCOS witness significant improvement in heart rate recovery after weight loss since several cytokines and inflammatory markers that contribute to the increased risk of cardiovascular diseases are induced by obesity. These markers are usually associated with a significant decrease in adiponectin levels and an increased risk of endothelial dysfunction[38].

In women of normal weight with PCOS, the significant increase in CVD risk may however be due to oxidative stress[44], which is characterized by increased reactive oxygen species (ROS) and decreased antioxidant levels which are independent of insulin resistance. Oxidative stress correlates with abdominal fat, age, hypertension, serum glucose, insulin and triglyceride levels and insulin resistance. All these factors are risk factors for CVD. Excessive and/or persistent rise in ROS plays a crucial role in the initiation, progression and clinical consequences of CVD[45] and leads to reduced antioxidant capacity in the cardiovascular, renal, and nervous systems causing hypertension (Figure 2). Oxidative stress may also link women with PCOS to the development of T2DM and cancer[46]. Abdominal obesity is associated with increased serum C-reactive protein (CRP), a marker of inflammation as well as a marker which reflects elevated CVD risk, and may be increased significantly in patients with PCOS. Other markers of inflammation such as, Neopterin (NEO), fibrinogen and white blood cells may be significantly higher in overweight and normal weight women with PCOS[47]. All this suggests that women with PCOS may develop chronic inflammation independently of weight, although greater waist hip ratio (WHR) may play a role[47]. Chronic inflammation is a key component of oxidative stress and may lead to DNA damage, genome instability, and to the proliferation of cancer cells. Visceral obesity per se is also associated with increased risk of CVD[43]. In lean patients with PCOS, the intrinsic insulin resistance, hyperlipidaemia, hyperandrogenism, genetic predisposition and/or interaction with environmental factors might partially explain the increased CVD risk factors and the disease[48]. These metabolic disturbances may encourage PCOS appearance and promote the development of hypertension, T2DM, atherosclerosis and CVD (Figure 2).

Thus, the increasing prevalence of CVD in patients with PCOS is most likely due to a number of causes including abdominal obesity and other associated risks like hypertriglyceridemia, hypertension, hypercholesterolemia and T2DM. Hypertension and T2DM will eventually lead to

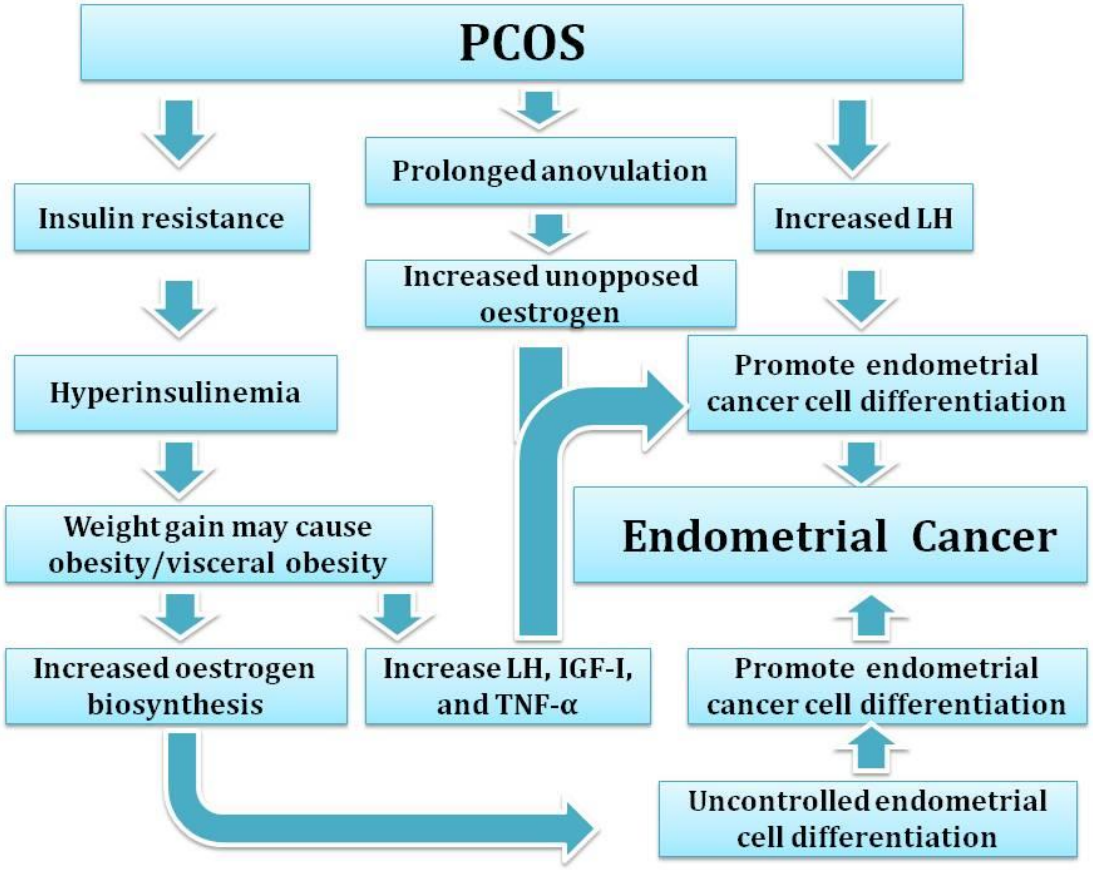


**Figure 4:** Mechanism of endometrial cancer in woman with PCOS[50]

PCOS is associated with prolonged anovulation, increased insulin resistance and increased luteinising hormone levels (LH). Prolonged anovulation is associated with increased unopposed oestrogen that may promote endometrial cancer differentiation. Increase LH also promotes endometrial cancer differentiation. Hyperinsulinaemia may promote endometrial cancer development through hormone disturbances. Abbreviation: LH (luteinising hormone), IGF-1 (Insulin-Like Growth Factor 1), TNF α (tumor necrosis factor alpha).

end stage renal disease (ESDR) which also promotes the development of CVD. In summary, the increased risk of CVD among women with PCOS has to follow one of two scenarios; the first is ruled by the metabolic syndrome with or without environmental and genetics interaction (Figure 2), and the second is ruled by genetics, inflammation, oxidative stress with or without the interaction of environmental factors (Figure 3).

### *3. Cancer's related to PCOS*

The extent to which PCOS directly promotes the development of breast, endometrial and ovarian cancers has been debated for over six decades. The prolonged tissue exposure to unopposed oestrogen has been proposed as a mechanism linking PCOS with these types of cancers[11,13], with endometrial cancer most commonly reported (Figure 4). Since then, several studies have been published that appear to support this association[12-13]. Without treatment, persistent inflammation leads to chronic inflammation and oxidative stress plays a pivotal role in cancer development and metastasis by providing an ideal environment for DNA mutation and cancer growth[49-50].

The existence of abdominal obesity or visceral fat and insulin resistance may exacerbate the situation and increase the risk of endometrial cancer in patients with PCOS[13]. Irregular menstrual periods, anovulation and infertility are common symptoms of PCOS and the resulting high unopposed oestrogen levels encourages the development of endometrial hyperplasia or endometrial cancer if left untreated over a long

period (Figure 4). The alteration in blood chemistry associated with insulin resistance in the women with PCOS may encourage an excessive secretion of androgens, LH and IGF-1, providing a suitable environment for cancer growth[50].

## Conclusion

Polycystic ovarian syndrome (PCOS) is the most common female endocrine disorder, and is characterized by hyperandrogenism, oligo-/amenorrhea and polycystic ovaries. The mechanism of PCOS may involve insulin resistance, abnormal fat distribution, visceral fat, genetic factors and the possible interaction between environmental and genetic factors. A high percentage of women with PCOS suffer from insulin resistance, obesity, especially abdominal obesity and/ or abnormal fat distribution. An increase in the prevalence of T2DM, hypertension and dyslipidaemia also has been reported among women with PCOS. These features are similar to women with the metabolic syndrome. Thus, the high prevalence of T2DM and cardiovascular disease among women with PCOS possibly are not directly related to PCOS but to metabolic disturbances. Increased risk for breast and ovarian cancer in women with PCOS continues to be debatable and ambiguous although the relationship between endometrial cancer and PCOS is supported by concrete evidence. Prolonged exposure of endometrium to unopposed oestrogen is a possible mechanism linking PCOS to endometrial cancer.

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## Conflict of interest

We declare that there is no conflict of interest.

## Authors' contribution

Ali AT: wrote the draft of the article, Al-ani O and Al-ani F: drew the figures and critically revised the article for important intellectual content, Guidozzi F: revised the content of the article and gave it final approval.

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