Association of polycystic ovarian syndrome with multiple disorders

Polycystic syndrome association with a variety of disorders.

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Abstract:
The polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age. The aim of this study was to investigate main mechanism of different disorder with PCOS. Importantly, PCOS women are at increased risk for glucose intolerance, type 2 diabetes and cardiovascular disorders. Complications of pregnancy associated with maternal PCOS include increased prevalence of early pregnancy loss (EPL), gestational diabetes (GDM), pregnancy-induced hypertensive disorders (PET/PIH), and the birth of small-for-gestational-age (SGA) babies. Recently reports indicate an unexpectedly high prevalence of obstructive sleep apnea (OSA) in PCOS. Alterations in sex steroids (i.e., high androgen and low estrogen levels) and increased visceral adiposity in PCOS could potentially contribute to the increased prevalence of OSA in this disorder. This holistic review with multiple hypotheses might facilitate to devise better PCOS management approaches.

Keywords: PCOS; psychological stress; eating disorders; PCOS, insulin resistance, diabetes, dyslipidemia, fatty liver disease.

Introduction

There are number of ailments which are gender-specific, in females, Gynecological issues involves impairment in the reproductive or estrogen monitoring system of the body. Although some of these Gynecological problems are curable, whereas some can be chronic, or fatal and Some of these disorders interfere with fertility. With the upsurge in the exposure to chemicals and sedimentary lifestyle, the hormonal disturbances are on sharp rise causing endocrine dysfunction to a greater extent. Some of the commonly arising hormonal and reproductive anomalies include fibroids, amenorrhea, infertility, endometriosis, polycystic ovary syndrome, ectopic pregnancy, miscarriage, ovarian cancer etc. [1–6]. PCOS is also a heterogeneous disorder that affects many body functions, resulting in several health complications, including infertility, menstrual dysfunction, hirsutism, acne, obesity, metabolic syndrome as well as autoimmune disease.

PCOS is a common endocrine disorder with a collection of symptoms, affecting women of reproductive age. It is a heterogenous disorder affecting different body functions resulting in severe complications such as menstrual dysfunction, acne, hirsutism, infertility, oligomenorrhea, obesity and also impairs functioning of other systems as well. This is due to the imbalance in female sex hormones, leads to the formation of cysts in the ovarian antral follicles.

A cyst is a water-filled sac containing ovum, that should be released from the ovary for the fertilization. The conversion of the ovum into a cyst, called 'functional cyst', which prevents ovulation, is resulting in the disruption of the menstrual cycle causing oligomenorrhea, amenorrhea and dysmenorrhea. When multiple cysts are formed in the antral follicle of ovary it is termed as Polycystic ovary syndrome (PCOS). The cysts can be of 10mm size, which can increase the ovary size up to 10mm wide. Anovulation caused due to the PCOS prevents fertilization and thus cause infertility [5,7] and if implantation occurs, abortion, eclampsia and birth risk may occur. It can cause pregnancy associated other complications such as pregnancy-induced hypertension, gestational diabetes, [8]. Normally, ovarian theca cells support the growth of ovarian follicles assisting the formation of mature oocyte [9]. But in PCOS, these cells become hyper responsive to the stimulatory effects of insulin, proliferating and causing ovarian hyperthecosis. Insulin resistance is exacerbated which amplifies the synthesis of androgen aggravating PCOS [10]. Also, the hyper sensitivity of theca cells to gonadal steroid gonadotropin stimulation promotes androgens in PCOS. Disrupted pulsating secretion of gonadotropin-releasing hormone (GnRH) from hypothalamus is a major factor responsible for PCOS [11], which impairs the secretion of hormone Follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. These two hormones are essential for the both the phases of menstruation. But in PCOS, these hormones are in small amount, therefore the egg is either not formed, or cannot be released from the follicle. So, the menstrual cycle is disturbed and amenorrhea occurs, which can be classified as two types i.e., primary and secondary amenorrhea. Primary amenorrhea is the inability to reach menarche due to the chromosomal issue whereas, secondary amenorrhea is the absence of menstrual cycle up to 3 or more consecutive months, also termed as hypothalamic amenorrhea [12].

As human body is a complex and all the systems are inter-related, the disturbances in any can affect the other as well. Disrupted level of hormones (anti- Müllerian hormone (AMH), insulin, cortisol, prolactin, androgens), neurotransmitters, lipids, proteins, glucose and peptide are associated with PCOS manifestation. Several researches also suggest the comorbidities, such as coronary heart disease including dyslipidemia, hypertension and visceral obesity [13,14], impaired glucose tolerance (IGT), and type 2 diabetes mellitus (DM) [15], metabolic syndrome [16], psychiatric disorders [17,18,19,20] associated with this syndrome. The main aim of the study is to emphasis on the pathophysiological mechanisms that may underlie in the disorders associated with PCOS.

Disorders Associated With PCOS:

Metabolic syndrome: The prevalence rate of the metabolic syndrome with PCOS is 43-47%, which is two times as high with general population of comparable age, even after anormal BMI [21]. The manifestations of metabolic syndrome most commonly occur in PCOS are central obesity, elevated blood pressure, low high-density lipoprotein cholesterol (HDL), impaired glucose tolerance [21].

Dyslipidemia: Lipid abnormality is highly prevalent i.e., 70% in women with PCOS. Dyslipidemia with PCOS, is characterized by increased serum level of low-density lipoprotein cholesterol (LDL-c) and very-low density lipoprotein cholesterol (VLDL-c), and increased free fatty acid concentration and serum triglycerides (Tg) with decreased serum level of high-density lipoprotein cholesterol (HDL-c) levels, due to decreased apolipoprotein A-I (apo A-I) [22-24]. In PCOS, smaller and dense LDL particles predominate to form more atherogenic lipids converging TYPE2 Diabetes mellitus [25]. Women with PCOS have high concentration of oxidized LDL-c irrespective of BMI, which can further raise a risk for CVD [26]. The atherogenic profile is exacerbated in patients with obesity and insulin resistance (IR) [22-25]. In particular, IR decreases the elimination of VLDL and chylomicrons and enhance the hepatic secretion of VLDL whereas increases the elimination of apolipoprotein A, the major component of HDL-c [27].

Hypertension: Obesity is one of the common manifestations in PCOS and is itself a major risk factor for hypertension. Additionally, a study monitoring day time ambulatory blood pressure among young (approx. 26yr) over-weight women (mean BMI approximately 26 kg/m2) found that women with PCOS had high blood pressure as compared to regularly -menstruating women. Although, the pathogenesis has not been fully and clearly understood [28], but there are several mechanisms possibly responsible for the development of hypertension in PCOS. Thus, the etiology of hypertension associated with PCOS is also multifactorial, including factors such as, obesity, insulin resistance, hyperandrogenemia and increased sympathetic nervous system activity.

Androgen Excess: Excess androgens have also been associated with increased cIMT in women with PCOS. Increased cIMT has been widely used as a preclinical biomarker for atherosclerotic disease, a contributing factor for hypertension [29]. However, Insulin resistance can be another major factor the development of hypertension in PCOS.

Insulin Resistance: Hypertension may be the secondary factor to enhance sodium retention, contributing for hyperinsulinemia [30]. Hyperinsulinemia has been associated with subsequent increased in the intracellular sodium and calcium level [31] and increased insulin-like growth factor-1 (IGF-1) which may be associated with vascular smooth muscle hypertrophy.

Obesity: obesity is the primary etiology implicating high blood pressure in women with PCOS [32]. It estimates 60% of the women with PCOS are obese or overweight. [33-35]. A population study established that women with PCOS were four times more prone to be obese as compared to non-PCOS women. Therefore, Obesity can be a key contributor for to elevate blood pressure in women with PCOS.

Sympathetic Nervous System: In addition, some studies demonstrated the effect of sympathetic nervous system in the etiology of hypertension in PCOS. Greater sympathetic nerve activity was found to be increased in women with PCOS, which is highly correlated with testosterone and cholesterol level. In addition, excess androgen

[36] increased insulin resistance [37] and increased obesity [38] have been implicated in stimulating the autonomic nervous system each serving as a potential mediator for hypertension in PCOS.

Coagulation disorders: Increased fibrinogen and plasminogen activator inhibitor 1 (PAI-1) level have been found in women with PCOS as compared to non-PCOS, irrespective of BMI. This impairment of fibrinolysis and coagulation are associated with low SHBG level and hyperinsulinemia [41]. Increased Homocysteine concentrations have been found in PCOS, Irrespective of BMI [39]. The effect of oral contraceptives (OC) also augments the risk of venous thromboembolism in women with PCOS [40].

Insulin resistance and Type 2 diabetes mellitus: Insulin resistance (IR) is the key factor in the metabolic manifestations in PCOS women, independent of obesity. 30% of lean and 70% of obese women acknowledging insulin resistance with PCOS [42]. Women with PCOS have a higher risk of glucose intolerance and IR compared to the women with same age and weight without PCOS [42,43]. 68-82% of the females of reproductive age with PCOS suffers with type2 diabetes mellitus (DM2) [44]. More than50% of women develop symptoms of irregular menstruation and hyperandrogenism. Low sex hormone-binding globulin (SHBG) and high testosterone level are associated with IR [43,45]. With respect to PCOS and IR phenotype, it has been found that anovulatory and hyperandrogenic is the most insulin resistant, independent of BMI and central adiposity [45]. follicle number per ovary (FNPO) is also related to both biochemical hyperandrogenemia and IR [45]. The main defect is in insulin signaling occurred due to decreased tyrosine phosphorylation and increased serine phosphorylation of insulin receptor and insulin receptor substrate-1affecting metabolic pathway in adipocytes, skeletal muscles and ovaries. Decreased insulin receptor-β abundance in omental adipose tissue, decreased glucose transporter 4 (GLUT4) in subcutaneous adipocytes (leading to decreased glucose uptake), constitutive activation of serine kinases in the mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK-ERK) pathway, mitochondrial dysfunction and genetic disruption of insulin signaling in the central nervous system are the additional contributing factors in the development of IR in women with PCOS[46].

Endometrial cancer:

There is molecular evidence that suggest the role of insulin resistance in endometrial cancer (EC). Risk factors of insulin resistance include excessive androgens, adipokines and inflammatory mediators which are also contribute in the etiology of EC. Elevated level of insulin directly and indirectly augment the development of EC. The direct mechanism involves the activation of signaling pathway involving Ras/MAPK and PI3K/Akt, IGF-1, estrogen and signaling pathway crosstalk among insulin whereas indirect mechanism involves the elevated level of androgen, high estrogen level and low blood SHBG levels due to excess insulin.

Depression and anxiety:

The detailed mechanism is currently not clear, although many factors may play a potent role for predisposition for these disorders. Obesity is one of the common morbidities seen in up to 80% of the women with PCOS, which play an important role in the increased risk of metabolic complications such as type 2 DM and dyslipidemia [47]. Increased insulin resistance is another cause for anxiety

and depression, which is known to present in both lean and obese women with PCOS when compared with the non PCOS women [48]. Elevated androgens level such as testosterone and clinical hyperandrogenism are associated with higher depression scores [49, 50]. The prevalence of depression and anxiety has been reported to 7-26% and 14-23% [51-55] respectively, making infertility a key player for occurrence of psychiatric disorders in women with PCOS. Abnormalities of the Hypothalamic–Pituitary–Adrenal Axis Stress increased cortisol, increased corticotropin-releasing hormone (CRH) and associated alteration in the hypothalamic–pituitary–adrenal (HPA) axis, are the factors implicating a probable mechanism for depression and anxiety in women with PCOS [56]. PCOS is the disorder with chronic low- grade inflammation associated with some markers such as IL-6, IL-8IL-18 and TNF-αetc., but not all markers have been described [57]. Low vitamin D has been associated with inflammation which estimates from 37-72% in women with PCOS [58]. In both depression and anxiety, serotonin imbalances have also been observed [59].

Psychological Distress and Eating Disorders:

In most of the studies, it has been observed that Women of reproductive age with PCOS are affected by mild to moderate psychiatric disorders, such as eating and mood disorders [65,66– 68]. Around 20% of them developed a depressive disorder within two years [60]. Firstly, associated symptoms are subfertility and menstrual irregularity can contribute to psychological stress, which can eventually result in psychiatric disorder [61]. Similarly change in physical appearance like Acne vulgaris, weigh gain, scalp hair thinning may diminish the self-esteem and may alter the body image. The exact mechanism of this pathology is not known. Stressors may also affect health and well-being by impairing neuroendocrine functioning. Stressful events may lead to the production of epinephrine, norepinephrine and cortisol associated with the sympathetic response. While chronically elevated level of stress hormones may exacerbate the PCOS. Elevated testosterone level may promote food craving via a poor impulse control [62], which attributes for the link between PCOS and eating disorders. The psychological stress may also seem to interfere with the serum Anti-Müllerian Hormone level and decreases its level in sub fertile women [63]. Studies reported the reduced serotonin level in the women with PCOS, inhibiting the pulsatile release of GnRH/LH [64], that regulate both appetite, mood and circadian rhythm.

Cardiovascular Risk:

High serum level of sensitive C-reactive protein (hs CRP), a vascular inflammatory marker, may predict the development of type 2 DM [70] and CVD [69].Elevated insulin level seems to affect Homocysteine (Hcy) and also affects its metabolism by affecting glomerular filtration or influencing enzymes activity involved in Hcy metabolism [i.e., Hepatic Cystathionin β-Synthase (CBS) and Methyl tetrahydrofolate Reductase (MTHFR)] [71, 72]. Elevated Hcy level is the major factor for the development of cardiovascular disease [73]. It also induces endothelial cell injury, increased inflammatory cytokine expression/activity, muscle cells proliferation and atherogenesis, and thereby deteriorate the established atherosclerotic plaque [74]. It has been established by the available data that cerebrovascular diseases as well as coronary heart diseases are common in postmenopausal PCOS patients.

Thyroid Dysfunction:

The most common connection is the increased BMI and insulin resistance in both the condition. Obesity, associated with altered milieu with increasing insulin resistance and pro-inflammatory markers. Through this undefined mechanism, it leads to decrease deiodinase-2 activity at pituitary level resulting in elevated TSH level and relative T3 deficiency [75].Another pathway is based upon leptin, whose level gets increased in obesity and has been proposed to act directly on hypothalamus resulting in increased TRH secretion [76]. Raised TSH levels, with either of the above pathway act on adipocyte and increase their proliferation. In Culture studies, TSH has been shown to increase the production of inflammatory mediators or increases the adipocyte proliferation via acting on TSH receptors present on adipocytes. Thyroid peroxidase (TPO) antibodies have shown to be present more in PCOS patients when compared to non PCOS i.e., 27% and 8% respectively [77]

Menstrual irregularity:

In fourth decade of life more than 70% of women with PCOS spontaneously reach the menstrual irregularity. Amenorrhea and oligomenorrhea are the conditions of the chronic state of anovulation present in these patients [78]. The anovulation is associated with the alterations in the endocrine and paracrine due to an increased pulse frequency for the luteinizing hormone (LH). The increased pulse frequency of the hypothalamic GnRH promotes the transcription of the beta subunit of LH compared to the beta subunit of follicle-stimulating hormone (FSH). [79] It is not clear whether this increased pulse frequency is due to an abnormality of the intrinsic GnRH pulse generator or caused by low levels of progesterone due to the chronic state of anovulation as the progesterone slows the GnRH pulse generator [80]. Increased concentration of intrafollicular androgens acts in a paracrine manner. The cause of such menstrual like bleeding is not always due to an occurrence of ovulation but also it may be caused by a sharp fall in plasma levels of estrogen [81].

Infertility:

The main cause of infertility in women with PCOS is due to chronic an ovulation. The subfertility may be related to the increase in plasma levels of the LH in the follicular phase of the cycle that causes a resumption of the second meiotic division of the oocyte and the premature release of the oocyte [82]. The mechanism linking PCOS and miscarriage is not yet well known; however, various factors involved in the process of steroidogenesis, estrogen [oocyte maturation and reduced endometrial receptivity contribute to this vicious cycle between PCOS and miscarriage [83].

Non-alcoholic steatohepatitis or Nonalcoholic fatty liver disease (NAFLD):

Increased prevalence of NAFLD has been reported in patients with polycystic ovary syndrome (PCOS), one of the most common endocrinopathies in premenopausal women, which 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 [84,85].

Polycystic ovary syndrome and spontaneous miscarriage:

PCOS women are at risk of early pregnancy loss (EPL), defined as clinically as first trimester miscarriage. EPL occurs more in PCOS women with 30 to 50% than normal women with 10 to 15%. [86,87] There are several confounding factors related to EPL in PCOS with several mechanisms underlying the increased risk of EPL in women with PCOS have been proposed and they are not exclusive.

Luteinizing Hormone and Early Pregnancy Loss:
There are many studies which link the elevated LH levels with EPL in women with PCOS. The likelihood of miscarriage was increased and conception rate decreased as compared to those with normal LH in PCOS women.[88] Decreased miscarriage rate in PCOS patients who experience long-term pituitary suppression with a GnRH agonist.[89] However, two succeeding studies in women with PCOS of normal BMI have not shown the improvement in live birth rate with LH suppression using GnRH agonists.[90] The differing results from earlier studies may be confounded by the effects of obesity on pregnancy outcome.

Androgens and Early Pregnancy Loss:
Hyperandrogenemia and/or clinical hyperandrogenism is currently considered as an essential precondition for diagnosis of PCOS.[91] Elevated free/total testosterone ratios and isolated elevated free and total testosterone levels were found to be predictive of EPL in PCOS women.

Impaired Fibrinolysis and Early Pregnancy Loss:
High plasminogen activator inhibitor-1(PAI-1) activity has been found to be associated with recurrent pregnancy loss in women with unexplained recurrent miscarriages and has also been found to be significantly higher in women with PCOS independent of BMI. PAI-1 activity to be an independent risk factor for miscarriage, possibly due to impaired fibrinolysis, which results in placental insufficiency through increased thrombosis of the placental bed 92].

Insulin Resistance and Early Pregnancy Loss:
PCOS women are believed to be strongly associated with insulin resistance and compensatory hyperinsulinemia, which has shown to be independently contributed by obesity prevalent among PCOS women.[93] This hyper insulinemic insulin resistance is implicated in pathophysiology of EPL. This includes its effect on oocyte maturation, glucose uptake and metabolism, implantation, altered expression of HOXA10 gene, and reduction of serum glycodelin and IGF-binding protein-1 (IGFBP-1) concentrations.
Impaired glucose uptake caused by downregulation of the IGF-I receptor has been documented to result in blastocyst apoptosis.[94] Additionally, GLUT 4 expression was revealed to be significantly lower in endometrial cells of hyper insulinemic obese PCOS patients compared with those from norm insulinemic PCOS patients or controls.

Endometrial Dysfunction and Early Pregnancy Loss:
Endometrial receptivity is the main factor which seems to be affected in PCOS or other gynecological disorder. Initial attachment of the embryo occurs via certain cell adhesion molecules like β3 integrin located on endometrium of the luminal surface [95] and these molecules are decreased in PCOS women.[96] Endometrial secretory proteins like glycodelin and IGFBP-l are crucial for implantation and maintenance of pregnancy. The Glycodelin help in early placental development through its modulatory effect on immune and trophoblast cells whereas IGFBP-1 plays an important role in human female reproductive physiology regulating menstrual cycles, puberty, ovulation, decidualization, and fetal growth. Both serum glycodelin and IGFBP-l levels were shown to be significantly lower in women with EPL in first trimester. [97]

Obesity and Early Pregnancy Loss:
There is a strong inverse relationship between BMI and serum IGFBP-1 in the general population.[98] A recent studies show the role of IGFBP-1 in PCOS pathogenesis controlling for the influence of BMI.[99] It suggested that a decreased serum level of IGFBP-1 does not have a role in the pathogenesis of PCOS but is likely to result from the high prevalence of obesity in the PCOS women.

Gestational diabetes:
Recently it has been observed that GDM complicates 40 to 50% of PCOS pregnancies. GDM occurs in pregnancy when pancreatic β cells cannot overcome the superimposed insulin resistance of pregnancy on intrinsic insulin resistance of PCOS women. GDM can be treatable and if controlled, does not cause significant problems for the mother or fetus. PCOS women to be at increased risk of gestational diabetes independent of body mass index. An increased risk of GDM and preeclampsia is shown in non-overweight/obese women. BMI >25 kg/m2 to be the greatest predictor for GDM [100,101].

Pregnancy-induced high blood pressure-Preeclampsia:
HDP occurs in 8% of PCOS pregnancies. Preeclampsia is a sudden increase in blood pressure after the 20th week of pregnancy. It can affect the mother's kidneys, liver, and brain. If left untreated, preeclampsia can turn into eclampsia. Eclampsia can cause organ damage, seizures, and even death. Currently, the primary treatment for the condition is to deliver the baby, even preterm if necessary. The precise mechanism of link between PCOS to preeclampsia remains unknown, although it seems an aberrant placental growth may play a role. Pregnant women with preeclampsia may require a C-section delivery, which can carry additional risks for both mother and baby. [102]

Pre-term birth:
Infants are considered to be preterm, if they are delivered before 37 weeks of pregnancy. Preterm infants are at risk for many health problems, both right after birth and later in life, and some of these problems can be serious. Preterm births complicate 6 to 15% of pregnancies of PCOS women. [103] It may be associated with confounding factor of multiple pregnancies induced as a result of use of various ovulation induction regimens in PCOS women. Preeclampsia itself is a risk factor for preterm deliveries. [103]

Cesarean or C-section delivery:
Pregnant women with PCOS are more likely to have C-sections because of the pregnancy complications associated with PCOS, such as pregnancy-induced high blood pressure. Because C- section delivery is a surgical procedure, recovery can take longer than recovery from vaginal birth and can carry risks for both the mother and infant.[104]

Polycystic Ovary Syndrome and Obstructive Sleep Apnea:
In PCOS, there is high prevalence to occur obstructive sleep apnea (OSA). Alterations in sex steroids (i.e., high androgen and low estrogen levels) and increased visceral adiposity in PCOS could potentially contribute to the increased prevalence of OSA in this disorder. Causal mechanisms in the link between PCOS and OSA remain to be elucidated. Clinicians who manage PCOS patients should be aware of the high prevalence of OSA in these patients and systematically evaluate these women for sleep

disturbances.[105]

Polycystic Kidney Disease (PKD):

Autosomal dominant and autosomal recessive polycystic kidney disease (ADPKD and ARPKD) are two of the most common PKD diseases, which result in end-stage kidney failure in adults and children, respectively. ADPKD is caused by mutations in PKD1 (encoding polycystin-1) and PKD2 (encoding polycystin-2), while ARPKD arises due to mutations in PKHD1 (encoding fibrocystin). PKD is characterized by the presence of fluid-filled cysts in the kidneys, finally resulting in renal failure. Along with cystic manifestation, PKD patients and animal models also exhibit non-cystic phenotype, including hypertension, left ventricular hypertrophy, abnormal arterial remodeling, intracranial aneurysm, among others. Not surprisingly, autopsy results of PKD patients show that more than 80% patients die of cardiovascular reasons than end-stage renal failure.[106]

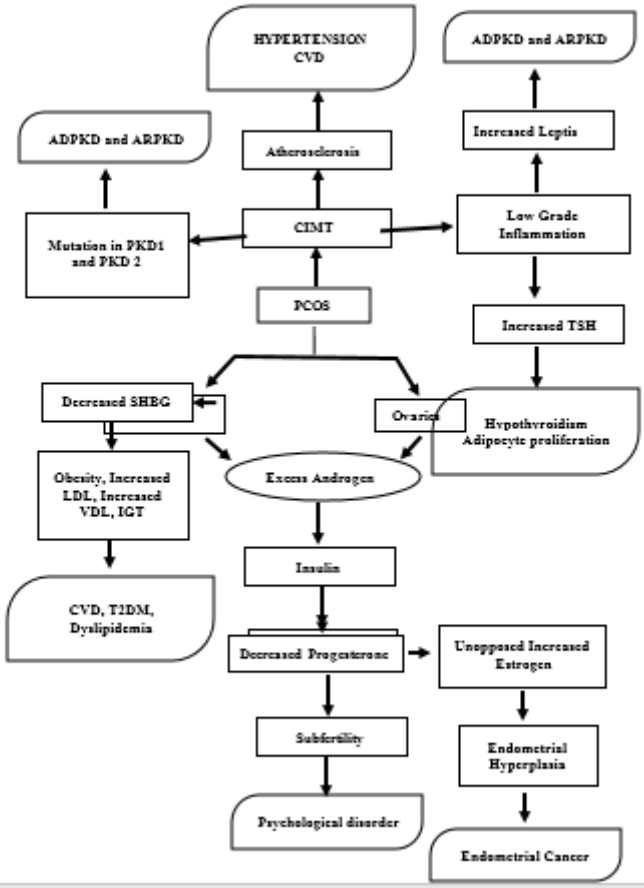

Figure 1: Pathophysiology of PCOS associated Disorder

Conclusion:

The findings are hormonal dysfunctions in PCOS manifested together or independently. PCOS women are at higher risk of cardiovascular diseases, linked to metabolic dysfunction due to its

pe-culiar hormonal pattern, characterized by hyperandrogenism, insulin resistance, dyslipidemia, and inflammatory state. Apart from well-known cardiovascular risk factors i.e., hypertension, diabetes, inflammation and hypercholesterolemia, the recent foregoing studies underline interesting common features among these patients. Women with PCOS are also at increased risk of adverse pregnancy and birth outcomes and may need increased surveillance during pregnancy and parturition.

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