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Original Research Article

Poly Cystic Ovarian Syndrome is a Disease of Ovary that Can Causes Cyst

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Abstract

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder, typically characterized by anovulation, infertility, obesity, insulin resistance and polycystic ovaries. Different reason can causes PCOS. Environmental pollutants, genetics, gut dysbiosis, neuroendrocrine alterations and oxidative stress are some reasons, This PCOS result in irregular menstrual cycle and obesity.

Keywords: PCOS, Gut Microbiome, Probiotics, Gut Dysbiosis, Obesity.

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Introduction

One of the most prevalent endocrine systems was polycystic ovary syndrome (PCOS)affect women during their reproductive ages. It was also known as hyper androgenic an ovulation (HA) or Stein-Leventhal syndrome [1]. Menstrual disorders result in menstrual dysfunction, infertility, hirsutism, acne or obesity [2]. PCOS occur when there was at least 10 cyst in one ovary and ovary have volume greater than 10 ml. The diameters of each cyst varies from 2-9 mm [3]. It was only diagnosed when body shape get changed due to side effects. The side effects were hair loss, alopecia, acne and infertility-related problems [4]. Among reproductive age women 4-10% of women acquired PCOS, according to standard screening done by NIH (National Institute of Health Standard) [1]. About 116 million of women (3.4%) affected by PCOS world wide in 2012 [5]. This high frequency, as well as its link with ovulation and menstruation abnormalities, infertility, hair loss and metabolic issues, underscores PCOS significant financial burden [2,6]. PCOS can occur in any age specially at the age of 25-30 [7].

Worlwide PCOS affects 1.55 million women (0.43 million) get affected. The reproductive age was 82.44 per 100000 in 2017, 1.45% higher than in 2007 [8]. PCOS was a lifelong syndrome manifests during pregnancy , traditionally it was going to affect adult women [9].

Different environmental factors and for genetic disorders PCOS occurs among adult women contain a lifelong syndrome. The pathophysiology of PCOS was chiefly concerned with hormonal imbalance, chronic low-grade inflammation, insulin resistance and hyperandrogenism, which impair folliculogenesis and increase the risk of related comorbidities, such as endometrial cancer and typeII diabetes. Hyperandrogenism, ovarian morphology and anovulation were three main factors used for the treatment of PCOS [11]. In the last decade the relation between PCOS and the microbiome have been established and have contribution to the syndrome. Environmental risk factorsmight be all pathogenic potential factors used in the development and progression of PCOS. Different pathogenic aspects of PCOS were caused by different microbiata. Linkage invoved in between various clinical manifestations. It brings up new therapy condition [12]. Prebiotics, probiotics, synbiotics and fecal microbiata transplants system were some system. It helps to manage the variety of phenotypes associated with PCOS. It boosteubiosis and reduce the impact of altered microbial profiles. Microbiota-mediated therapies might improve the metabolic, inflammatory and hormonal characteristics of pcos system.

Phenotypes of PCOS

Table 1: Four major clinical phenotypes of PCOS

Feature	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Biochemical/clinical hyperandrogenism	+	+	+	-
Chronic Anovulation	+	+	-	+
Polycystic ovaries	+	-	+	+

Four phenotypes have been considered for three main features of PCOS [Table 1]. For all three features (biochemical, chronic and polycystic ovaries) phenotypes were mostly positive. Phenotype D, C, B were only negative.

Disease Pathophysiology: If we diagnose women 8% and 20% women of reproductive ages were affected by PCOS[14]. The pathophysiology of this condition was influenced by alterations in steroidgenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors and sympathetic nerve function [15].

Carbohydrates, hyperinsulinemia, hyperandrogenemia and persistent low-grade inflammation were the four key factors [16]. (Figure 1). The risk factors were environmental toxins, genetic predisposition, gut dysbiosis and diet for PCOS. LH: lutenizing hormone; FSH: Follicle stimulating hormone; SHBG: Sex horone binding globulin.

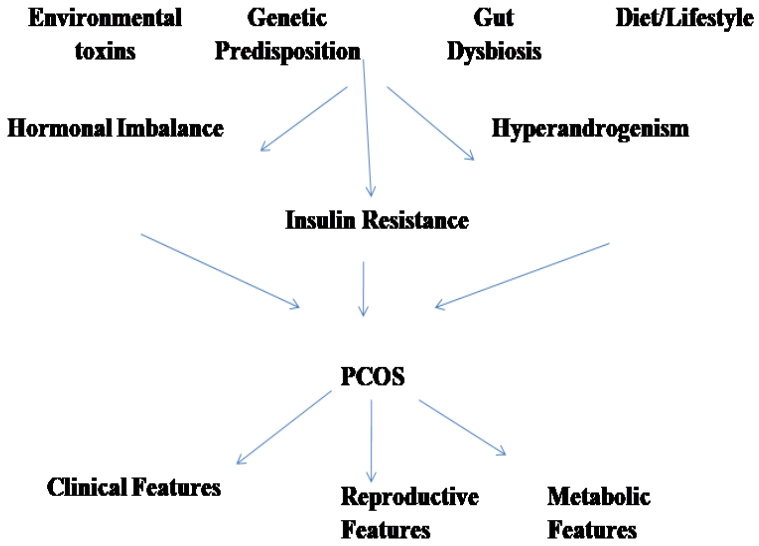

Figure 1: Schematic representation of pathophysiology features of PCOS

Hyperandrogenism: The biochemical hallmark of PCOS was hyperandrogenemia, which manifests clinically as hirsutism, acne and alopecia. Patients with PCOS have oligomenorrhea (high level of androgen) about 75-90%. The ovaries synthesis excessive androgen as well as it contributes to hyperandrogenism [17]. Testosterone was a major hormone contribute to the pathogenesis of PCOS. Testosterone increases the risk of hyperandrogenism. Abnormal ovarian or adrenal production lead to the over production of androgen.

PCOS impaired with folliculogenesis have initial effect of excess androgens disrupt normal androgen synthesis. At the early gonadotrophin stage excess androgens trigger the growth of primodal follicles and a rise in the antral follicles [18]. GnRH produced from the hypothalamus triggered the production of gonadotrophin hormones. To increase androgen synthesis in ovarian theca cells, luteinizing hormone (LH) activates the LH receptor. Follicle stimulating hormone (FSH) stimulate the follicle growth. FSH receptors in ovarian granules convert androgens into estrogen. The dysregulation of the neuroendocrine system in the hypothalamic-pituitary-ovarian (HPO) axis, leads to an excess secretion of gonadotrophin hormones. This secretion lead to the production of LH over FSH, result in change in LH:FSH ratio in pcos [19].

Hyperplasia occur among the theca cells in the ovaries result in the increased stimulation in LH. It causes building up of follicular fluid along the ovary's periphery. This situation arises due to many follicles in the theca cells of the ovaries, present on the preantral and antral stages. Follicles concentration arises result in the increase in the androgen synthesis, an excessive amount of androgens were produced [20].

In cortisol metabolism, there was another proposed mechanism which result in excessive androgens

production in PCOS patients. The enhanced inactivation of cortisol by 5alpha-reductase (5alpha-R), or the impaired reactivation of cortisol from cortisone by 11 beta-hydroxysteroid dehydrogenase type 1 (11beta-HSD1), may cause increased peripheral cortisol metabolism, which results in less negative feedback suppression of adrenocorticotropic hormone (ACTH) secretion while maintaining normal plasma cortisol concentrations at the expense of excess androgens [21]. Abnormal steroidgenesis also associated with various genetic factors. In steroidgenesis CYP genes involved in the production of androgen plays an important role in hyperandrogenism in PCOS [20].

Hyperinsulenemia: Insulin was the main hormone use for both lipogenesis and glucose homeostasis. Insulin involved in the metabolism of carbohydrates, proteins and fats. Insulin also act as a mitogenic hormone. On HPO axis many insulin receptors present , activates insulin. Insulin help in the steroidgenic tissues adrenal and cortex to steroidgenesis [14]. As insulin direct mimics the action of LH and indirectly raises GnRH, hyperinsulinemia was the primary cause of excessive androgen production. Sex hormone binding globulin (SHBG) was a circulatory protein regulates testosterone levels which decreases insulin level. Lower the level of SHBG higher the levels of androgen. It causes PCOS, also increases hirsutism, acne and alopecia [18]. Numeous studies have shown that lowering insulin resistance will ultimately result in reduced amdrogens and an improvement in the disease condition [22-24].

Causes and Risk Factors: It was very difficult to understand the causative factors responsible for interlinked pathophysiology. The origin, prevalence, and modulation of the PCOS phenotype may be affected by environmental pollutants, diet and lifestyle choices, genetic factors, obesity and gut dysbiosis. These factors lead to the activation of a lot of factors like excessive androgen secretion from the ovaries, insulin resistance, partial folliculogenesis arrest, chronic low-grade release of inflammatory mediators from the white blood cells, upsurging metabolic syndrome.

Etiological Role of Environmental Pollutants: Human health and reproduction were significantly affect by heavy-metals, insecticides and endocrine –disrupting chemicals. Environmental pollutants have a mounting evidence against the development of PCOS. Takeuchi and Kandaraki et al. discovered that serum BPA levels in hyperandrogenic women with PCOS were greater than in non-hyperandrogenic women with PCOS and healthy controls [25,26]. Serum testosterone levels varies among PCOS women versus healthy women. Blood BPA levels increases were associated with testosterone level [27]. Vagi et al. reported that higher serum levels of perfluorooctanoate and perfluorooctanesulfonate in women with PCOS related with environmental factors [28].A negative association between phthalate body burden and PCOS was also noted by the group. To be more precise, mono benzyl phthalate (mBzP) urine concentrations were lower in PCOS-afflicted women [28], indicating an impaired xenobiotic metabolism. In the nuclear hormone system BPA and phthalates (EDCs) affects thyroid, estrogen, progesterone and androgen receptors. EDCs can also influence nonnuclear hormone receptors, orphan receptors and neurotransmitter receptors. They can directly change steroidogenesis or hormonal metabolism [29]. EDCs were a group of ubiquitous contaminants that have been well-researched as potential environmental contributors to the path physiology of PCOS. Higher levels of oxidative stress and inflammation were higher order disorder linked to insulin resistance, infertility and obesity. EDC s also have similar profile as in animal like in human being [30]. Endocrine disruptors were implicated in the induction of metabolic and reproductive abnormalities that resemble PCOS symptoms in vitro and animal investigations [31]. It is conceivable that developmental exposure to particular EDCs could alter metabolic, reproductive, and neuroendocrine regulation permanently in ways that favor PCOS development in people who were genetically predisposed to it, or that it could hasten and/or exacerbate the syndrome's natural course throughout life cycle exposure [31]. DNA of the female reproductive system may alter by EDCs. It may alter the PCOS traits [32]. Overall, EDCs can interfere with the regulation of hypothalamic-gonadal hormones, as well as local paracrine and autocrine systems, which can eventually result in PCOS pathogenesis.

A positive correlation between PCOS incidence, smoking and exposure to cigarette smoke [33-35]. Ovulatory dysfunction occur which was a dose-dependent manner. Women with normal anovulation in PCOS and healthy controls[33].An inflammatory condition arises due to an increase in mononuclear cells, mitochondrial dysfunction, reduction in GSH (glutathione) as well as oxygen uptake. Also reduction in the antioxidant levels associated with PCOS and smoking [34]. These inflammatory stimuli can alter the enzymes and causes steroidgenesis in theca cells. Polycyclic aromatic hydrocarbons (PAHs) produced from cigarette smoke, burnt coal, gas, wood, garbage and meat cooked at high temperature constitute a major part of the air pollutants that were positively correlated with the risk of developing PCOS [35].

Different type of air pollutants such as nitrogen oxides, sulphur dioxide, PAHs, and particular

contaminants exposed women and alter normal steroidogenesis. It may help in the development in PCOS. Result from an exposure study revealed that pollutant gases SO2, NO, NO2 were also affected animal models [36]. DDT was associated with the development of ovarian abnormalities consistent with PCOS in three subsequent generations via epigenetic processes [37,38].

Role of Diet and Lifestyle: Lifestyle changes were the primary line of treatment for women with PCOS, but they were not an alternative to pharmacological treatments. Regular physical exercise, maintaining a healthy body weight, adhering to healthy dietary habits, and obtaining from tobacco use were all important in the prevention and treatment of metabolic diseases, and were recommended in clinical guidelines for a variety of ailments.

Sedentary lifestyles and high calorie diets might be possible causes of exacerbating PCOS. High sugar diets may contribute in PCOS by altering normal gut flora, inducing chronic inflammation, increasing insulin resistance and increasing androgen production. A lot of syndrome observed in the women including obesity and weight gain. In comparison to high-glycemic-index (HGI) meals, low-GI (LGI) diets reduced fasting insulin, total and LDL-C , TGs, waist circumference, and total testosterone without altering fasting glucose, HDL-C, weight, or the free androgen index in PCOS patients.

Body fat get reduced due to LGI diet, exercise, omega supplemented boosted HDL, SHBG synthesis [39.40]. Gonzales et al. reported that saturated fat ingestion promotes LPS-mediated inflammation and insulin resistance by enhancing the circulation of TNF-α and peripheral leukocytic suppressor of cytokine-3 (SOCS-3) expression in PCOS [41]. Removal of saturated fats from patients diet was essential. Linolenic-acid rich flaxseed oil work in PCOS via the sex steroid hormones microbiata generated an equivalent effect [42]. Epidemiological evidence were more confirmed via genetic investigations, obesity and PCOS were closely related [43]. LH change and obesity increases androgen production , which can causes hyperandrogenism [44]. Fermentable fiber offers metabolic benefits for the gut flora, resulting in the release of SCFAs [45]. Low-GI diets lowered ghrelin while increasing glucagon [46,47]. High fructose consumption (HFC) exacerbated endocrine but not metabolic alterations in PCOS, implying that HFC may worsen endocrine related phenotypes in PCOS [48]. An LGI diet was an effective, acceptable, safe intervention for IR relief , that professional diet provided to all PCOS patients [49,50]. Women who have gained obesity with PCOS and liver dysfunction improve the menstrual cycle. It lower the blood glucose and body weight, improves liver function and treats fatty liver [51]. 12 weeks in women with PCOS Paoli et al discovered more interesting results [52]. Some hormones level increases while LH/FSH ratio, LH total, free testosterone, DHEAS of blood level decreases [52]. Women who was under treatment of PCOS lose weight permanently regulated mensuration and improved reproductive outcomes[53]. In health sector women with PCOS suffered from pains may get cured by physical exercise. Improvements in health outcomes were more reliant on exercise intensity than dose, according to a recent meta-analysis. The analysis findings show that exercise was beneficial and suggest that vigorous exercise may have the cardiorespiratory fitness [55]. Women with PCOS should engage in vigorous aerobic exercise and resistance training to improve their insulin sensitivity and androgen levels [54].

Role of Genes and Genetics: PCOS was a polygenic and multifaceted disorder, and it has been shown that certain genes, gene-gene interactions, or interactions between genes and the environment might affect a person's propensity to develop PCOS [56]. Several genetic studies have revealed that potential genes and single-nucleotide polymorphism were connected to a variety of PCOS symptoms. PCOS linked directly or indirectly to the ovaries [57]. The pathophysiology of PCOS was most frequently mediated by genes encoding signaling elements related to steroidogenesis, steroid hormone action , gonadotrophin action and control, insulin action and secretion, energy metabolism and chronic inflammation (Figure2)[57,58]. Gene variation occur and gene expression occur and correlated with protein function. Genetic markers may identify the disease syndrome, early intervention as well as phenotypes and more tailored treatments.

Gut Microbiota Dysbiosis: Critical Correlation: The gut nicrobiome becomes an organ by its own as it contain 200 time nore genome than normal genome. The gut microbiome was made up of million of microbiomes [59]. Gut inflammation and gut permeability was the root of gut dysbiosis. It can effect host health. Among the gut microbiata and the host , under physiological conditions a delicate balance exists. This balance generally influences physiology, metabolism, nutrition and immune function. In addition it can prevent various diseases. Between healthy adults there are substantial variances in microbiome composition, and variations also can susceptibility to certain diseases.

A connections between PCOS and gut microbiota have been examined in different studies [60-62].A difference between the composition of the gut microbiome among healthy controls and PCOS patients were revealed by some investigations.

Diversity and structure of the gut microbiata in PCOS affected women related to different reason. They may be impacted by insulin resistance, sex hormone levels and obesity [53]. PCOS have a close relation with gut microbiota and their metabolites. Microbial diversity decreases and characterized by some pathogenic bacteria like E.coli and Shigella. Metabolites decrease in beneficial bacteria Lactobacillus and Bifidobacteria and increase in pathogenic bacteria [60,61]. Various host tissues such as ovary, liver, skeletal muscle and adipose tissue altered by gut microbiata metabolites in PCOS [62]. Numerous human and rodent model have shown a changes between gut microbiata and PCOS. A biodiversity and alterations in particular bacterial taxa varies 16 SrRNA and metagenomic gene sequencing. Three basic aspects –anovulation, menstrual irregularity, hyperandrogenism and some small ovarian cysts can be explained by dysbiosis of gut microbiata (DOGMA) theory of PCOS [63]. DOGMA explained that gut microbiatadysbiosis may lead to increase of passage of lipopolysaccharides (LPS) from gram- negative bacteria to the blood stream. It increase in serum insulin levels, production of androgen in the ovaries increases. It also related with normal follicle formation [63].

Treatment and Management: Treatments of PCOS must be tailored to the specific needs of each patient, goals of therapy may include ameliorating hyperandrogenic symptoms, including ovulation, regulating menstruation, and preventing cardiometabolic complications. Women with PCOS have irregular menstruation, hirsutism and infertility were the most distressed symptoms. For complex PCOS, treatment was rarely monotherapeutic rather being personalized prevailed on signs and symptoms. A lot of therapies available for management and treatment of PCOS. Menstrual irregularities, androgen related symptoms, infertility causing anovulation were most prominent causes of infertility. Metabolic comorbidities in PCOS may regulate numerous therapeutic approaches that have potential benefits. It can be fully acknowledge that range of metabolic abnormalities in PCOS diagnosed woman was observed. Combined lifestyle can changes medications for various alignment with greater metabolic benefits and parameters better than monotherapies represent. Additionally, treatment should also take into consideration increased levels of anti-Mullerian hormone (AMH), plasma metabolomics, and gut microbiota composition, which were severe characteristics of PCOS, in addition to focusing on primary traits.

Oral Contraceptives and Anti-Androgens: For women with PCOS have menstrual abnormalities with first-line management protocol. Oral contraceptives were used for menstrual abnormalities [64]. OCs function encourages negative feedback on LH secretion. This leads to less androgen production in the ovaries that reduces hyperandrogenism. They raise liver produced SHBG while lowering blood levels of free androgens. OCs can also inhibit conversion of testosterone into dihydrotestosterone. This DHT bind to androgen receptors and decreases the release of adrenal androgens [65]. The benefit of OC preparation depends on the doses and medication combinations. The majority of OC preparations include estrogen and anti-androgen such as cyproterone acetate, drospirenone, norgestimate, levonogestrol and desogestrol [66]. Anti-androgen, CPA, flutammide, finasteride were some lower levels of androgens [66]. They can use in hyperandrogenism. Anti-androgen receptors drug have been effective in treatment of PCOS. If we use OCs it result in the decrease of hyperandrogenism as hypothalamus and pituitary glands result in ovarian steroidogenesis [67]. Due to these effects it is an pharmacological intervention in the treatment of menstrual irregularity, acne, hirsutism, androgenic alopecia linked to PCOS [68,69]. Third generation combination of OCs, that contain antiandrogenic compounds improve the metabolic phenotypes of PCOSs, LIPID and alpokine profiles in patients [70-72]. Patients with PCOS receiving flutamide medication also reported improved ovulation and menstrual cycle regularity [73,74]. Flutamides increase the lipid profiles in women whereas decreases total cholesterol, LDL, TGs etc [75]. Steroidal AR blockers, such as CPA and spironolactone, compete with T and DHT for binding to ARs. In PCOS patients both of these AR blockers have been found to be dramatically reduce hirsutism and acne [76]. A-5α reductase inhibitor that inhibits the conversion of T and DHT, was another treatment used to effectively manage hyperandrogenic symptoms in PCOS patients [77-79].

Insulin Sensitizers: Defective insulin secretion and function were part of the pathophysiology of PCOS[80]. The elevated levels of androgens in PCOS were known to be influenced by hyperinsulinemia and insulin resistance. Ovarian function was regulated by insulin, and excessive insulin levels can have negative effects on ovarian function. In presence of excessive insulin theca cells release large levels of androgens, which can cause follicular maturation, increase symptoms of PCOS [80].A crucial part of pathophysiology of PCOS, insulin resistance negatively affects patients, such as T2DM and CVD. To effectively manage PCOS, insulin resistance , pharmaceutical and lifestyle changes. Insulin sensitizers increase insulin sensitivity in target tissues [81]. Insulin sensitizers trigger insulin resistance. Metamorfin use to improve ovulation, decreased the level of

androgen and enhance menstrual cyclicity[66]. Hepatic glucose synthesis decreases, increase glucose absorption, and peripheral tissues sensitivity to insulin. In research comparing metformin and lifestyle interventions in PCOS-afflicted women both groups experienced a significant decrease in BML; however only the metformin group experienced a decrease in testosterone levels [82]. Another RCT evaluating the impact of metformin on body weight in obese and severely obese PCOS women found that the drug significantly reduced BMI without the need for lifestyle changes [83]. Metaformin have significantly effect on dyslipidemia [84,85]. Additionally, TZDs lower insulin levels by increasing insulin sensitivity, reduces levels of androgens in the blood [86,87]. It significantly decreased fasting serum insulin and free androgen levels while increasing SHBG levels in an RCT that compared the effectiveness of metformin and treating PCOS, improved ovulation and the menstrual cycle[89]. Metformin can also decreases the level of testosterone level[90].

Conclusion

For PCOS patients ovulatory dysfunction was one of the diagnostic criteria. Ovulation induction was an effective treatment for PCOS patients who have requirement of fertility. The timely implementation of personalized therapy approaches will enhance pcos management. PCOS will increase bleeding during mensuration or will decrease it.

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