# Polycystic ovary syndrome (PCOS): Pathophysiology, potential links to the gut microbiota and current treatment strategies for women.

A dissertation submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Dhaka in partial fulfillment of the prerequisites for the degree of Bachelor of Pharmacy

***B. Pharm Research Project***


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# APPROVAL

This is to certify that this project titled **"Polycystic ovary syndrome (PCOS): Pathophysiology, potential links to the gut microbiota and current treatment strategies for women. "**, submitted by ***Nasrin Sultana (Bearing ID: 191-29-1399)*** to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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# DECLARATION

I hereby attest that I am the sole author of this thesis and that no part of it, nor the entire thesis, has been submitted to any other university or institution for a degree. I certify that, this project report is done by me under the supervision of ***Dr. Sharifa Sultana, Associate Professor and Associate Head, Department of Pharmacy***, Daffodil International University. I am announcing that this Project is my unique work. I additionally proclaim that this undertaking works are unique and has never been submitted in its entirety for any degree or diploma at this university.

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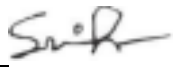

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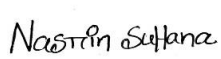

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# DEDICATION

**I devote this work to Almighty Allah first, and afterward to my family, particularly my parents, teachers, and friends….**

**Nasrin Sultana**
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# ABSTRACT

Women of reproductive age are frequently affected by the endocrine condition polycystic ovarian syndrome (PCOS). PCOS is a complicated and multifaceted pathophysiology that includes hormone abnormalities, insulin resistance, hereditary, and environmental variables. Recent research has revealed a potential connection between PCOS and the gut microbiota, suggesting that dysbiosis of gut microbes may be involved in the onset and development of the condition.

Currently available PCOS treatment options include pharmaceutical therapies like metformin and oral contraceptives, as well as lifestyle changes including diet and exercise. The efficacy of these treatments is frequently constrained, and they may also have negative side effects. Therefore, there is a need for more investigation into cutting-edge therapeutic alternatives that focus on the pathophysiology underpinning PCOS.

An overview of the pathophysiology of PCOS will be provided in this review paper, with a special emphasis on any possible connections to the gut flora. Additionally, it analyzes PCOS treatment options currently available and emphasizes their shortcomings. Finally, the report discusses possible future lines of inquiry, such as the creation of PCOS management strategies based on microbiome research. This review's overall objective is to give readers a thorough grasp of PCOS and any possible connections between it and the gut microbiota, with the ultimate goal of enhancing the treatment outcomes for those who are affected.



**Keywords:** polycystic ovarian syndrome, hyperandrogenism, insulin resistance, gut microbiota, metformin.

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# Introduction

## 1.1 Introduction

The most prevalent endocrine disorder in women of reproductive age is polycystic ovarian syndrome (PCOS) [1], which is characterized by prolonged anovulation and hyperandrogenism [2]. Multiple ovarian cysts and hormonal abnormalities that can cause a variety of symptoms, such as irregular periods, acne, excessive hair growth, and weight gain, characterize it [3]. In 1935, Stein and Leventhal provided the earliest detailed description of polycystic ovarian syndrome (PCOS) [4]. In clinical endocrinology, the PCOS diagnosis is still debatable. The National Institutes of Health (NIH) criteria were established in 1990 in attempt to develop a comprehensive and detailed description for the diagnosis of PCOS.[5] The Rotterdam criteria were then developed in 2003 during a workshop in Rotterdam.[6] Out of the following three conditions, this criterion needs the presence of two: oligomenorrhea/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries (12 follicles measuring 2–9 mm in each ovary). The AES (Androgen Excess Society) updated, diagnostic standards in 2006. AES needs the unique condition of oligo anovulation or polycystic ovaries in addition to clinical or biochemical hyperandrogenism [5, 6]. Modern research has demonstrated in recent years that disorders of the- gut microbiota (GM) are directly linked to the manifestation and progression of diseases (metabolic) like; chronic inflammation, insulin resistance, hyperandrogenism and metabolic syndrome (obesity, diabetes), and might also play a role in PCOS [7]. A typical GM delivers sustenance to the host through the exchange of materials and energy. However, GM is also intricate in the formation of blood vessels, metabolism of drugs, the regulation of the neurological scheme, the directive of bone (density), and the storage of fat [8]. Intestinal permeability, short-chain fatty acid (SCFA), energy absorption and lipopolysaccharide metabolic pathways are the main GM pathway processes that contribute to PCOS [7].

# Chapter: 2

# Purpose of the study

## 2.1 Purpose of the study

Women of propagative age are recurrently affected by the hormonal condition identified as polycystic ovarian syndrome (PCOS). Multiple little cysts on the ovaries are present, and blood androgen levels are increased (male hormones are present in higher amounts). Numerous symptoms, such as irregular menstruation cycles, infertility, weight gain, acne, and excessive hair growth, can be brought on by PCOS.

- ✓ An updated summary of the state of knowledge regarding PCOS is what a review of the condition is intended to do. This provides details about PCOS's causes, symptoms, diagnosis, relationship to diseases (gut microbiota) and available treatments.
- ✓ Studying the gut microbiota in PCOS has the potential to advance our understanding of the disorder and may ultimately result in the creation of new diagnostic tools and treatments.
- ✓ Understand the hormonal imbalances that are characteristic of the disorder, including elevated levels of androgens (male hormones).
- ✓ A review of PCOS can help medical professionals better comprehend this disorder and give their patients the best care possible. Healthcare professionals can assist women with PCOS in managing their symptoms and enhancing their quality of life by remaining current on the most recent research and treatment choices.

- ✓ The ultimate goal is to progress the quality of lifecycle for women affected by PCOS.

# Chapter: 3

# Expected outcomes

## 3.1 Expected outcomes

Based on existing knowledge, potential consequences ought to be:

- ✓ Increased knowledge of PCOS's pathogenesis.
- ✓ Investigation of possible connections between gut microbiota and PCOS.
- ✓ Analyses of existing therapies.
- ✓ Patients may see better results if the biology of PCOS is better understood and novel therapeutic options are found. This may include improved symptom management, improved reproductive results, and a lower risk of PCOS-related metabolic and psychological problems.
- ✓ In general, research on PCOS is expected to improve the lives of PCOS-affected women and advance our understanding of the condition.

# Literature Review

# Chapter: 4

# PATHOPHYSIOLOGY

## 4.1 PATHOPHYSIOLOGY OF PCOS

Many theories regarding the emergence of PCOS have been put up over the past ten years. PCOS is the result of multiple genes and proteins interacting with one another, with environmental and epigenetic influences. Although the ovary plays, crucial part in the etiology of PCOS, neuroendocrine besides metabolic dysfunctions are similarly important in the disease's pathophysiology. It is generally recognized that hyperinsulinemia, insulin resistance, and hyperandrogenism are all associated with PCOS. Also, many research have fixated in recent years on the crucial role that persistent low-grade inflammation plays in the emergence of PCOS [9]. It has historically been helpful to think of the polycystic ovarian syndrome as the outcome of a "vicious cycle," which might start at any one of several entry points. Anovulation and ovarian androgen excess are the results of transformed function at any phase of the cycle [10].

Nonetheless, clinical investigations involving adult women have produced the majority of the pertinent data, with a referral bias favoring the study of the further severe phenotypes [11]. preliminary simulations relating animal and studies in vitro are complementary to clinical research besides are aided by additional methods in the study of this complicated condition. New genetic, clinical, and experimental findings underline the role of neuroendocrine systems in; pathogenesis of PCOS [12].

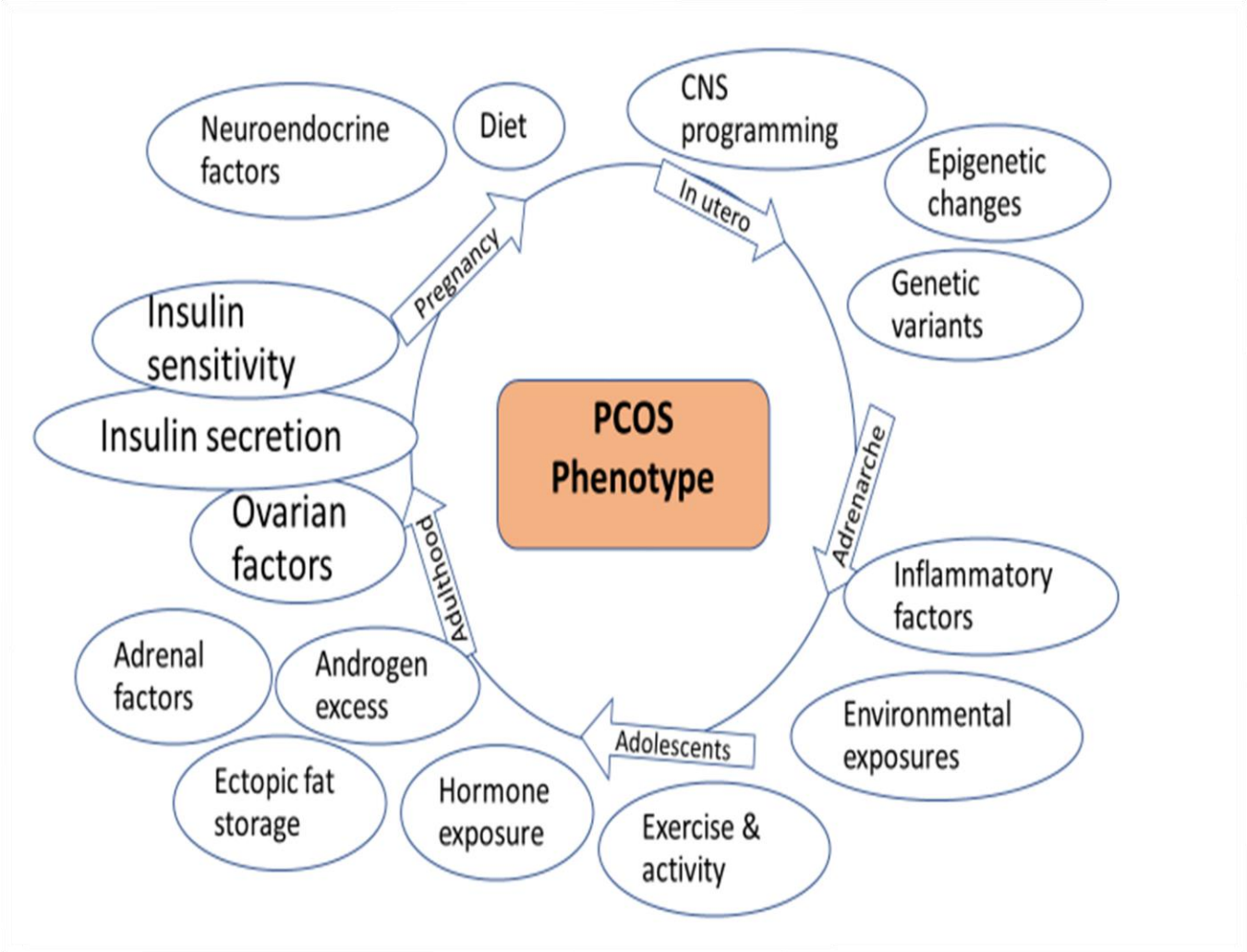


Figure 1. Aspects influencing the phenotype of PCOS. PCOS affects every stage of a woman's life. Circular symbols represent factors that could have an impact on the pathophysiology of PCOS. Not every aspect has an impact on every person. A biological network of interconnected neuroendocrine, hormonal, metabolic, genetic, and environmental factors, including PCOS, are exemplified by.

## 4.2 Factors influencing the Pathophysiology of PCOS

### *4.2.1 Insulin resistance*

Achard & Thiers were the ones who first identified a link between glucose intolerance and hyperandrogenism. It was referred to as "the diabetes of bearded women" (1921). It is nowadays extensively acknowledged that PCOS and elevated insulin resistance are related. Reduced glucose response to a given insulin dose is referred to as insulin resistance [10]. 50–70% of women with PCOS experience insulin resistance, which is a common symptom of the condition. Insulin resistance cannot be fully understood explain how PCOS patients' development of type 2 diabetic mellitus (T2DM) came about. The primary issue in PCOS may be the cell defect [10]. A protein -tyrosine kinase receptor mediates the action of insulin. The augmented -serine phosphorylation of the insulin receptor in afflicted women appears to be a potential explanation for their insulin resistance. IRS1 and IRS2 (Insulin receptor substrates 1 and 2, respectively) appear to be serine phosphorylated, which seems to impede signaling. Moreover, the expression of glucose transporter type 4 (GLUT4), an insulin-sensitive glucose transporter, is lowered as a result of the autophosphorylation of the insulin receptor [13].

A significant link was found between rising levels of androgen and insulin in the connotation among hyperinsulinemia and hyperandrogenism. In PCOS, hyperinsulinemia increases the synthesis of androgen. Being a gonadotropin that increases luteinizing hormone activity by stimulating the ovarian receptors for insulin and insulin-like growth factors, insulin can also operate indirectly by increasing the amplitude of serum LH pulses [14]. The insulin receptor and the insulin-like growth factor 1 (IGF-1) receptor share a similar structural design. As a result, insulin and the IGF-I receptor interact. Insulin-induced IGF-I receptor activation results in enhanced androgen synthesis in theca cells via increasing the theca cell (androgen response) towards LH [9].

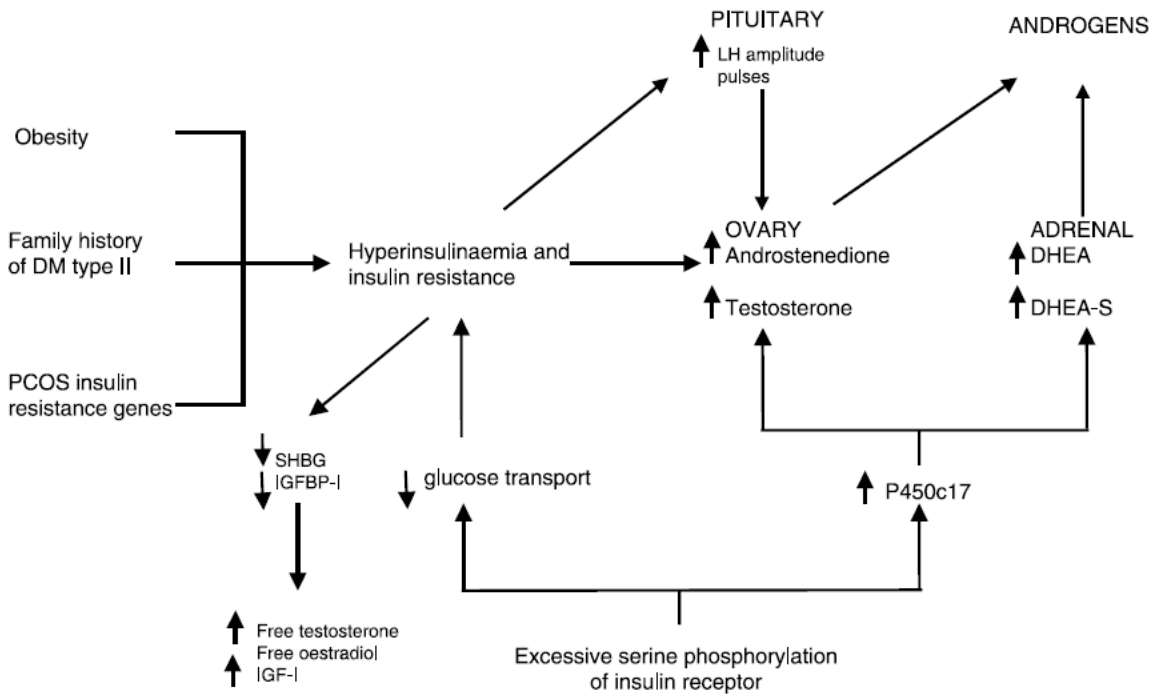


**Figure 2.** Pathways causing an excess of androgen in PCOS [2]. The evidence points to an additional mechanism by which insulin affects PCOS women: an increase in ovarian cytochrome P450c17a activity. Additionally, a greater glucose level inhibits insulin's capacity to produce glucose and over time kills pancreatic beta cells, activating the inflammasome. These findings demonstrate that the insulin signaling pathway's activity acting a crucial part in the expansion and progression of PCOS.

Book & Dunaif (1999) investigated the metabolic and mitogenic activities of insulin and IGF-I in cultured skin fibroblasts from PCOS and control women to further assess the post binding impairment in insulin action in PCOS. They came to the following conclusions: (a) there is a selective defect in insulin action in PCOS fibroblasts that affects metabolic signaling pathways but not mitogenic signaling pathways; (b) there is a comparable defect in IGF-I action, suggesting that insulin and IGF-I stimulate glycogen synthesis by the same post receptor pathways; and (c) Indicating that the metabolic signaling malfunction in PCOS fibroblasts is in a different trail or downstream of; signaling step, the fact that insulin receptor substrate-1-associated phosphatidylinositol 3-kinase activation by insulin and IGF-I is similar to the control value [10].

### *4.2.2 Defect in androgen synthesis*

The primary cause of ovarian hyperandrogenism is believed to be a steroidogenic deficiency in PCOS theca cells. In this condition, elevated LH and the intrinsic dysfunction of theca steroidogenesis can be amplified by insulin levels. Atypical androgen production may result from impaired gonadotropin dynamics. Overproduction of androgen is a result of this PCOS abnormality. Moreover, theca cells produce more androgen when there is an excess of LH. It has been demonstrated that excessive androgenic actions influencing the hypothalamic-pituitary axis can result in poor negative feedback on LH secretion, which in turn results in increased LH levels [15]. Moreover, the LH affects the previously indicated FSH levels, which decreases the activation of aromatase. Due to the decreased androgen to estrogen conversion, the formation of tiny, immature ovarian follicles known as cysts is accelerated. Hence, as was just explained, a cascade that is set off by a reduction in androgen production can lead to the development of PCOS [9]. The reduction of aromatase activity caused by androgens [16] may be a factor in the subsequent stages of folliculogenesis becoming distorted. This anomaly may prevent the subordinate cohort of follicles from being selected as the dominant follicle, which is necessary for mono-ovulation [17].

### *4.2.3. Luteinising hormone and folliclestimulating hormone*

Follicle-stimulating hormone and luteinizing hormone works on Granulosa cells from antral follicles with a diameter of 5 mm might have their LH receptor mRNA overevolved in polycystic ovaries, causing them to become prematurely overresponsive to LH [18] [19]. Follicular maturation has slowed down as a result of LH's excessive and premature effects on PCOS granulosa cells. This impact might also be influenced by the rise in ovarian androgen levels caused by LH [17],[20], [21]. Anovulation in PCOS has also been connected to the absence of the intercycle FSH peak and, more crucially, the granulosa cells' resistance to FSH activity. Elevated AMH levels, which either directly decrease aromatase activity or act to block FSH action, may be responsible for these abnormalities [17].

### *4.2.4. AMH*

Increased levels of intrafollicular AMH found in polycystic ovaries may partially counteract the possessions of FSH on granulosa cell steroidogenesis and folliculogenesis [22], [23], [24], [25]. The presence of AMH receptors (AMHRII) after the preantral stage of the human growing follicle suggests that AMH does not appear to have an impact on the earlier stages of folliculogenesis, though [26]. There may be repercussions for the pathophysiology of PCOS follicular arrest due to the putative role of AMH in inhibiting FSH action. In support of this idea, studies on PCOS women have shown that AMH has inverse negative correlations with FSH, oestradiol serum levels, and follicle count [25], [27].

### *4.2.5. FOLLICULAR ER STRESS*

Gonadotrophins and intraovarian factors regulate the follicular milieu in a coordinated manner. Intraovarian factors are essential in the pathological [28], [29], [30], [31] diseases of the ovary, including PCOS, and perform regulatory functions throughout the complete procedure of follicular development. We showed at initial that ER stress paths are triggered in the granulosa cells of a mouse sample of PCOS caused by constant androgen injection as well as in humans, and this discovery has been. [32], [33-38] validated by other groups. Moreover, we discovered that resident hyperandrogenism in the PCOS follicular milieu activates ER stress in humanoid granulosa cells, 52 and these result has been verified by mice models. The-interstitial fibrosis in the 48 ovary, a symptom of PCOS, is accelerated by ER stress and granulosa cells are stimulated to produce altering growth factor-ß1 (TGF-ß1), a profibrotic growth factor. ER stress is linked to follicular development capture at the antral stage, additional 52 features of PCOS, and causes the testosterone-persuaded apoptosis of granulosa cells through the expression of the proapoptotic factor death receptor 5 (DR5). Additionally, ER stress activates Notch signaling, one of the utmost evolutionarily exceedingly preserved signaling systems, to cause the countenance of numerous genetic factors linked to cumulus oocyte-complex (COC) expansion in granulosa cells. Notch signaling controls a variety of cellular processes through juxtacrine cell-cell communications [39]. The ER stress-Notch pathway increases COC growth, according to measurements of their diameters, however it is yet unclear if this hypermaturity of COCs contributes to the ovulatory failure this distinguishes PCOS [40].

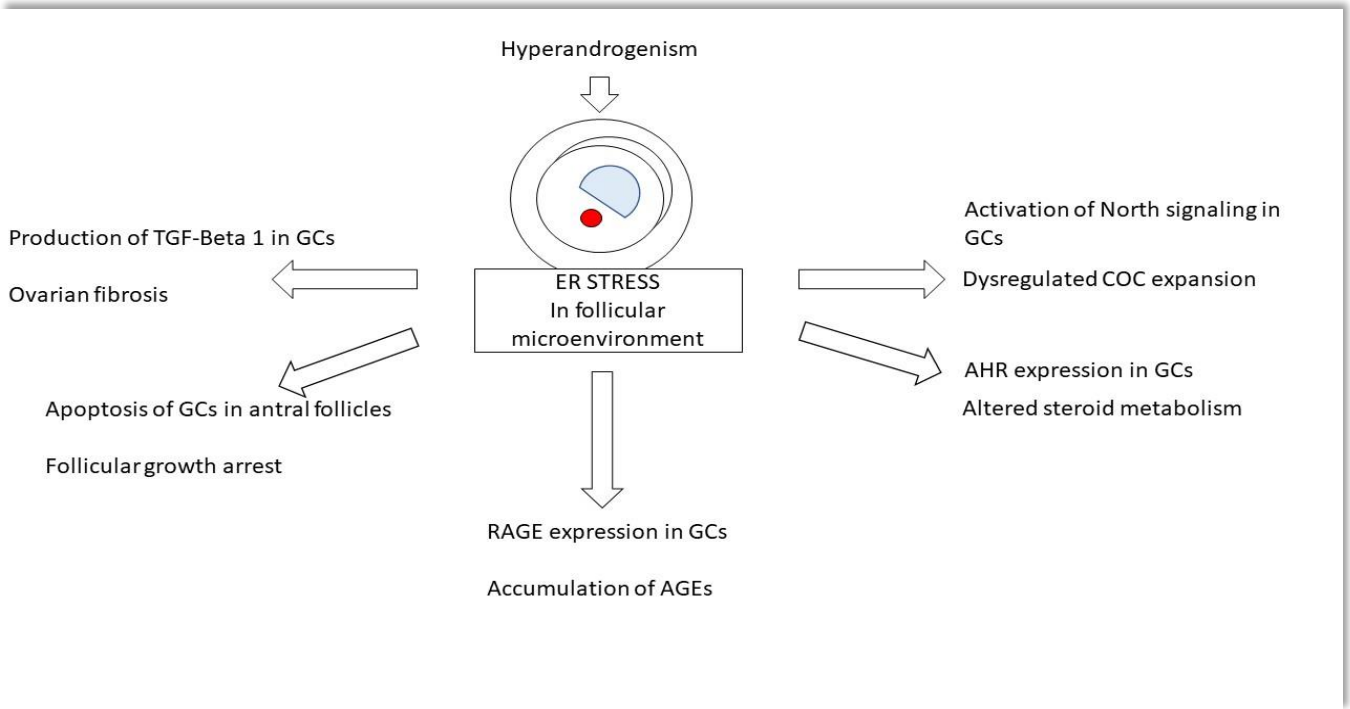


**Figure 3.** Endoplasmic reticulum stress (ER stress), which represents a crucial part of the pathophysiology of polycystic ovarian syndrome (PCOS), emerges in the follicles. ER stress is triggered in PCOS by local hyperandrogenism in the follicular microenvironment. Granulosa cells (GCs) are involved in the pathophysiology of PCOS and are impacted by ER stress in a variety of ways. ER stress promotes transforming growth factor-1 (TGF-1) synthesis, a profibrotic growth factor, in GCs and hastens ovarian interstitial fibrosis. By increasing expression of the proapoptotic factor death receptor 5 (DR5) and causing follicular growth arrest at the antral follicle stage, ER stress mediates the testosterone-induced apoptosis of granulosa cells. Additionally, ER stress mediates how testosterone causes GCs to express the receptor for advanced glycation end products (RAGE), which leads to an accumulation of AGEs and affects a variety of cellular functions. The aryl hydrocarbon receptor (AHR), a typical receptor for endocrine-disrupting substances (EDCs), and its downstream signaling in GCs are also activated by ER stress, which may change the steroid metabolism in these cells. Additionally, through notch signaling, ER stress promotes the expression of numerous genes linked to cumulus oocyte-complex (COC) expansion in GCs.

# Chapter: 5

# PCOS & Gut microbiota Potential links

## 5.1 The microbiota of gut

The term "microbiota" denotes to all microbes (archae, bacteria, protozoa, fungi, etc.) found in the skin, respiratory system, mouth, gastrointestinal system, and vagina [41, 42]. The microbiota weighs roughly 1.5 kg besides is made up of more than 100 trillion microorganisms [42, 43]. The composition of the microbiota is regulated by a variety of factors, including age, the kind of natal, nutrition, genetic predisposition, antibiotic usage and lifestyle and [44]. The microbiota starts to develop shortly after birth.

The five bacterial phyla that make up the mainstream of the human gut microbiota are Firmicutes phylum (which includes the gram-positive species Clostridium, Eubacterium, Lactobacillus, Roseburia, Butyrivibrio, Ruminococcus, Anaerostipes, and Faecalibacterium), Bacteroidetes phylum (which includes the gram-negative species Bacteroides, Porphyromonas, and Prevotella), Proteobacteria phylum (gram-negative species Enterobacteriaceae, etc.), Actinobacteria phylum (gram-negative species Bifidobacterium), and Verrucomicrobia (Akkermansia, etc. gram-negative species) [45].

Firmucutes and Bacteriodetes make up about 90% of the gut microbiota population, whereas Actinobacteria and Proteobacterium make up 10%. Compared to the others, verrucomicrobia are less prevalent [43, 46]. The metabolic protective, structural, and histological tasks performed by the gut microbiota have a variety of effects on host physiology [47]. "Dysbiosis" is described as a disruption of the makeup of the intestinal microbiota [48]. Allergies, cancer, inflammatory bowel disease, lupus, multiple sclerosis, Parkinson's disease, asthma, celiac disease, obesity, diabetes, and cardiovascular diseases, insulin resistance are among the illnesses associated with the process of microbial dysbiosis, which is brought on by a decline in the ratio of helpful/harmful bacteria. [48, 49].

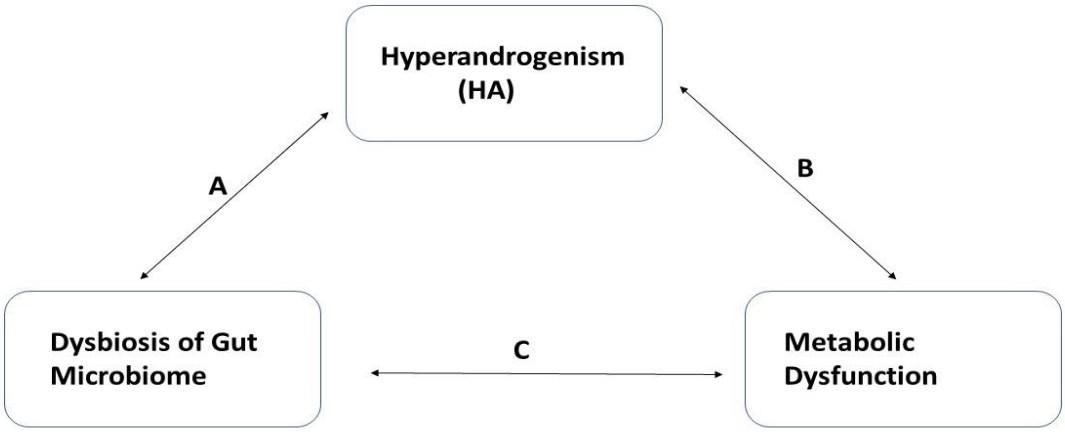


**Figure 4.** Connections between metabolic dysfunction, dysbiosis of the gut microbiota, besides hyperandrogenism (HA). A: The connection between HA and gut microbiota dysbiosis. Recent research in humans and rodents have shown that HA is associated with dysbiosis of the gut microbiome, which includes alterations in both the relative abundance of particular bacteria along with the variety of gut bacteria as a whole. Additionally, one study found that mice treated with antibiotics developed HA after being exposed to PCOS-related faeces or a particular bacterial species (B. vulgatus). This finding raises the possibility that gut microbial dysbiosis otherwise an overpopulation of a particular bacterial species may be adequate to cause PCOS-like symptoms. B: Relationship between metabolic disorders and HA. Independent of body mass index, metabolic dysfunction—including IR, weight gain, and dyslipidemia—predominately affects women through PCOS who have been diagnosed with HA and ovulatory failure. C: The connection between metabolic dysfunction and gut microbiota dysbiosis.

The generation of vitamins, conjugated linoleic acid, short-chain free fatty acids (SCFAs), biotransformation of bile acids, amino acid synthesis, fermentation and hydrolysis of nondigestible meals, detoxification and ammonia synthesis are among the metabolic processes of the gut microbiota [49]. Alterations in the gut microbiota have been linked to cardiovascular disease, autoimmune diseases, neurological disorders, and metabolic diseases (Fig. 4) [50]. A link among dysbiosis of the gut microbiota and the metabolic and reproductive symptoms of

PCOS was suggested by Tremellen and Pearce in 2012 [51]. In a mouse model of PCOS besides in women with the condition, two research published in 2016 and 2017 provided the initial indication that deviations in the gut microbiome were related to PCOS [52, 53]. Since then, numerous other research in people [54–62] and rodents [63–66] have added to the mounting evidence that PCOS and gut microbiota dysbiosis are related.

## 5.2 Mechanisms underlying the association between PCOS and the gut microbiome

In standings of gut microbiota, a decline in a variety and modifications to the composition and b diversity may result in alterations in intestinal mechanism, which might aggravate PCOS [67]. There are some potential explanations for how the gut microbiome contributes to PCOS development. In Figure 4, these potential processes are enumerated. One of these is- dysbiosis of the gut flora, which prompts the host's immune system to respond. Immune system activation disrupts insulin receptor function, leading to hyperinsulinemia, which raises androgen formation in the ovaries and hinders the growth of healthy follicles. As a result, anovulation/menstrual problem, hyperandrogenism (acne, hirsutism), and polycystic ovarian syndrome are the traditional three symptoms of PCOS. The term DOGMA (dysbiosis of gut microbiota) is used to describe this notion. This theory is supported by two basic elements. These elements include the prevalence of obesity and a high-fat, low-fiber diet [68]. Several potential pathways could account for the function of gut microbiome. Regardless of obesity, PCOS is linked to a chronic immune system activation. In women with PCOS, genetic variables are also efficient in maintaining immune system activation; polymorphisms in the genetic factor encoding proinflammatory cytokines including TNF-a and interleukin-6 (IL-6) have been documented to be common [69, 70].

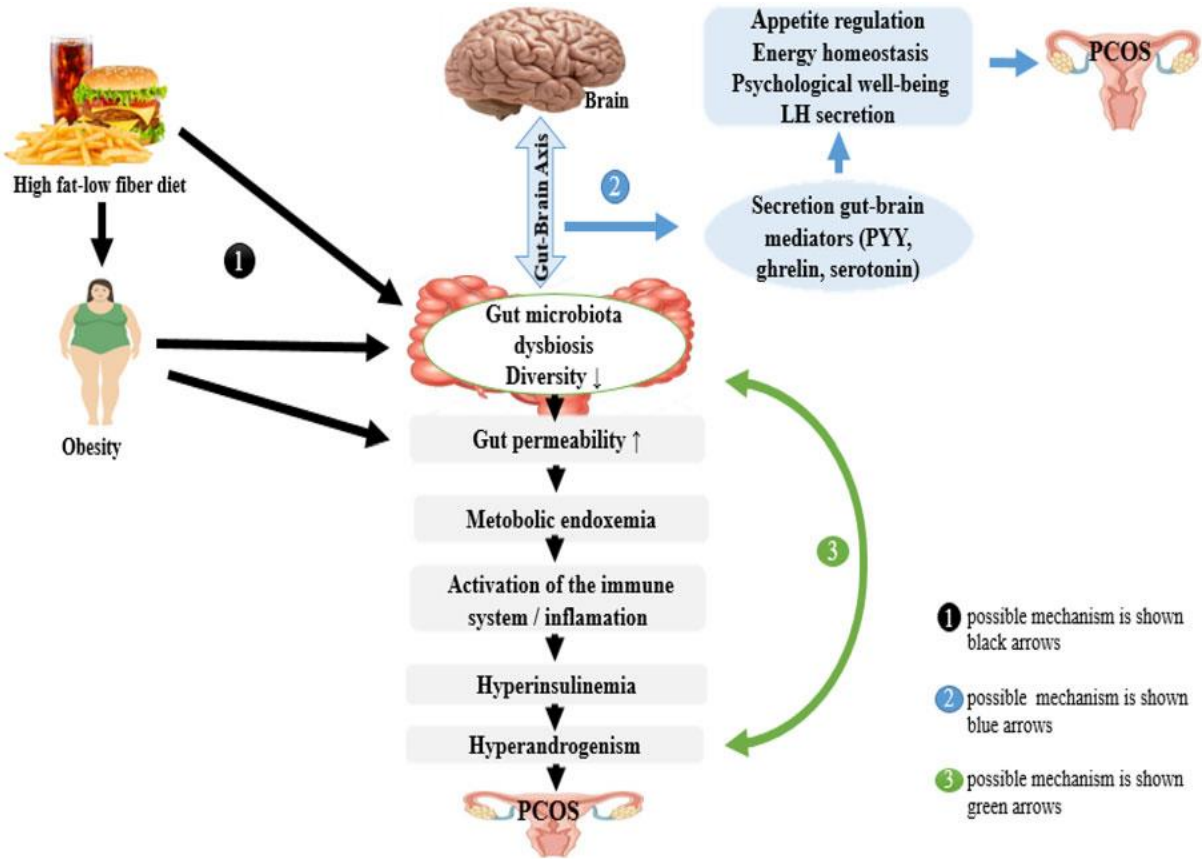


**Figure 5**. Depicts potential explanations for how the gut microbiota contributes to the pathophysiology of PCOS. The host's immune system is activated by the initial potential mechanism, which is the dysbiosis of the gut microbiota brought on by obesity and a diet high in fat and low in fiber. Immune system activation disrupts insulin receptor function, resulting in hyperinsulinemia, which raises androgen formation in the ovaries and hinders the growth of healthy follicles. The second potential explanation is that PCOS is brought on by the gut bacteria increasing the release of gut-brain peptides. Androgens influencing the composition of the gut microbiome as PCOS develops is the third potential mechanism.

Serum zonulin, a measure (biological) for intestinal permeability, was shown to be increased in 78 women with PCOS in contrast to the healthy control group in a research looking at the connection among PCOS and intestinal permeability. Serum zonulin levels, insulin resistance, and the seriousness of menstruation problems all shown favorable correlations [71]. Lymphocytes, leukocytes, and lipid binding protein—which binds endotoxin—were found to be further predominant in PCOS-affected women than in the control group, according to Lindheim et al. [72].

70% of PCOS patients have insulin resistance, which is frequent in both fat and lean patients [73]. In conclusion, three typical symptoms of PCOS emerged early due to hyperinsulinemia [68]. However, there is scant evidence in the literature to support the first mechanism of diet-induced PCOS [74]. Despite the fact that eating a diet heavy in carbohydrates is known to increase the chance of developing PCOS, it has been suggested that diet might not be the root source of the condition [75]. Additionally, they discovered a negative correlation among Escherichia/Shigella, and Streptococcus ghrelin levels and Bacteroides as well as a decline in Clostridial species and an increase in Bacteroides species in PCOS. It's crucial to remember that there is not much data to back up this potential mechanism in PCOS-affected women [76]. Additionally, it has been suggested that sex hormones may circuitously control gut microbiota through the initiation of host steroid receptors [67]. Future research should look into the processes underlying the link between gut microbiome and hyperandrogenism.

## 5.3 Dysbiosis of the Gut Microbiome is Associated with polycystic ovary syndrome (PCOS)

### *5.3.1 Human gut microbiota's Alpha diversity*

Metrics of alpha diversity, which quantify a community's species richness and/or evenness while occasionally taking phylogenetic relationships into consideration, can be used to describe the overall make-up of the gut microbiota. According to recent research, women with PCOS exhibit altered gut microbiome alpha diversity as compared to women without the condition. Numerous studies found that the alpha variety of gut bacteria was lower in premenopausal women through PCOS than in age-matched, hale and hearty women by taking samples of the fecal microbial gratified and sequencing 16S ribosomal RNA (rRNA) genes amplified with universal bacterial primers [53, 56, 60–62, 77]. Contrarily, 3 studies [55, 58, 78] found no appreciable differences in alpha variety between women with PCOS and hale and hearty women. This may have been because of the small sample sizes.

### *5.3.2 Human gut microbiota's beta diversity*

Beta diversity, which measures how alike or dissimilar a gut microbial community's composition is from that of additional community, can also be calculated using distance metrics

that do/ do not take into account phylogenetic relations or profusion. Numerous investigations by means of 16S rRNA gene sequencing found that beta diversity was different in fecal samples taken from women with PCOS associated to women without PCOS [53, 56, 62]. Though, in other investigations, no discernible change in beta diversity between PCOS-affected women and healthy women was seen [55, 60, 77, 78], possibly as a result of limited sample numbers. Variations in beta diversity were similarly seen when adolescent girls with PCOS and obesity were contrasted with BMI matched controls.

### *5.3.3 Rodent PCOS models with diverse alpha and beta*

Using 16S rRNA gene sequencing, alterations in total gut microbial variety were seen in PCOS-alike mouse samples as well as in comparison to placebo controls. According to a recent review [79], letrozole or the nonsteroidal aromatase inhibitor, DHT, have been used to treat hyperandrogenic rat models of PCOS. In a letrozole-induced pubertal PCOS mouse model, letrozole-treated mice had lower alpha diversity of the gut microbiota than placebo controls, and beta diversity similarly differed among the 2 groups [52]. In contrast, adult mice and rats with PCOS caused by letrozole did not exhibit any alteration in alpha diversity [80, 81]. Although grownup mice treated with letrozole exhibited an alteration in beta diversity, differences in certain bacterial taxa among the pubertal besides the adult PCOS mouse models were noted [80], and adult rats treated with letrozole did not exhibit any changes in beta diversity [81]. When compared to rats given a placebo, alterations in beta diversity were seen in a cohort of 6-week-old rats cured with letrozole, although there was no difference in alpha diversity among the 2 groups [82]. These findings imply that the phase that PCOS is created in mouse models might be crucial for accurately recreating the metabolic dysregulation also gut microbial alterations that are typical of PCOS in humans.

# Chapter: 6

# Treatment strategies of PCOS

## 6.1 Approaches to treating polycystic ovarian syndrome in women

### *6.1.1 Lifestyle modification*

Insulin resistance affects 60 to 80 percent of people with PCOS, and it affects 95 percent of people who are obese [83], increasing their risk of cardiovascular disease and type 2 diabetes [84]. Regardless of the need for birth, lifestyle modification (LSM) is regarded as the first-line treatment. According to Panidis et al. [85], overweight people along with PCOS should manage their diets, eat 1200–1500 kcal per day (1 kcal equals 44.184 kJ), and make sure they exercise moderately for at least 30 minutes per day, five days a week at the very least. Patients can progress insulin resistance and permitted testosterone levels as well as behavior by limiting calorie consumption, exercising, addressing behavior, receiving pharmacological treatment, having surgery to treat overweightness to lower BMI to a typical range, and quitting smoking and drinking. Patients can progress insulin resistance and free testosterone levels, along with menstrual disorders, excessive hair growing, acne, and other indicators, by addressing behavior, limiting calorie intake, exercising, receiving drug treatment, having surgical treatment for obesity to reduce BMI to a normal range, and giving up smoking and alcohol. [86] conducted a randomized study of the impact of restricting calories and/or exercise on metabolic parameters and ovarian function in overweight women. The body mass index (BMI) was lowered by 6% by food management, 3% by exercise, and 5% by the combined interventions after four months, according to the authors. In addition, 30 patients (69%) had their menstrual periods restored. Serum testosterone levels dropped, while sex hormone binding globulin (SHBG) levels rose. These results imply that weight loss in overweight/obese women with PCOS can be accomplished just as effectively by food and exercise, either separately or together. [87]

### *6.1.2 Regulation of menstrual disturbances*

The greatest option for restoring the rhythm of bleeding, lowering HA, and lowering the risk of endometrial hyperplasia appears to be OCP. These outcomes rely on OCP's capacity to reduce levels of free androgens, raise SHBG levels, and suppress pituitary LH. The antiproliferative actions of the progestin component of the OCP formulation are primarily responsible for the protection in contradiction of proliferative endometrial diseases (such as endometrial hyperplasia and cancer), for which oligomenorrheic and insulin-resistant women are particularly at risk [88].

OCP treatment improves hyperandrogenism and menstrual control in PCOS-afflicted women, according to a comprehensive systematic review and meta-analyses published in 2019. Overall, larger dose estrogen preparations shouldn't be advised, and lower dose preparations should be favored. However, no particular OCP type is sufficiently demonstrated to be superior in efficacy and safety to another. It is necessary to take into account and have personalized discussions about the OCPs' comparative and complete contraindications and adverse effects [89]. Consideration must be given to risk factors specific to PCOS, for example excessive BMI, hyperlipidemia, and hypertension [90].

### *6.1.3 Reduction of hyperandrogenism's symptoms*

As a result of increased androgen production, hirsutism, acne, androgenetic alopecia, as well as acanthosis nigricans, are frequently the main symptoms that prompt women with PCOS to seek medical attention [91]. A pharmaceutical and non-pharmacological strategy can be taken into consideration in these situations. Anti-androgen medications, such as cyproterone acetate or spironolactone, are frequently recommended in combination with ethinylestradiol (in OCP formulation), or metformin. Additionally, according to Thuzar et al.'s assessment, spironolactone may help with obesity since it appears to improve how human brown adipose tissue responds to meals and cooling, changing energy use from storage to heat dissipation [92]. With just a little contribution from reduced androgen production and increased androgen to estrogen conversion, spironolactone inhibits the androgen receptor to exert its anti-androgen actions. For PCOS-related hyperandrogenism, low-dose spironolactone provides an additional benefit [93]. A recent study suggests that treatment with SPIOMET, a low-dose combination of spironolactone (to antagonize androgen and mineralocorticoid impacts, and to triggers BAT thus increasing the energy expenditure), pioglitazone (to enhance circulating HMW adiponectin concentrations), and metformin, is an alternative strategy that holds the potential to attenuate the PCOS phenotype [94]. Other medications such flutamide, long-acting GnRH analogs, glucocorticoids, ketoconazole, and finasteride are not frequently utilized in this situation.

Another well-liked medication for treating acne is isotretinoin. It works by lowering sebum production, preventing bacterial and cell growth, encouraging cell type differentiation and apoptosis, regulating the growth of microcomedones, and restoring normal desquamation of

the epithelium. Isotretinoin also has anti-inflammatory qualities [95, 96]. Additionally, there are local methods designed to lessen hirsutism, such as beauty treatments (hair removal, electrolysis, laser follicle destruction, and/or cream application). Patients with PCOS have reportedly had less hair growth after using certain lotions containing 13.9% ornithine and 13.9% eflornithine (decarboxylase inhibitors) twice a day for six months [97]. Recent research found that metformin, specifically working on skin signs (hirsutism, acne, and acanthosis nigricans), could reduce clinical symptoms of hyperandrogenism [98].

### *6.1.4 Oral contraceptive therapy*

For the long-term management of PCOS, oral contraceptive (OC) tablets are the first line of management [99]. Estrogen and progesterone make up the majority of these pills' ingredients. By decreasing FSH besides progesterone, estrogen slows the development besides maturity of ovarian follicles. Progesterone also suppresses ovulation by reducing LH, thickens cervical mucus, and prevents sperm from reaching and fertilizing the egg [100]. In addition, OCs have been shown to lower free testosterone levels, diminish the peripheral role of androgens, besides promote androgen deficiency by raising the density of sex hormone binding globulin (SHBG). The endometrium can be protected by OC therapy, which can also assist to reduce hyperandrogenism and improve contraception and hyperandrogenism [99]. cyproterone acetate/ethinylestradiol (Diane-35), Desogestrel/ethinylestradiol (Marvelon), and drospirenone/ethinylestradiol (Yasmin) are some of the current clinical OCs that are often used. According to some research, ethinylestradiol affects liver metabolism more strongly than natural estradiol, which includes the production of SHBG, angiotensin, and several blood clotting components that depend on estrogen [101]. According to the most recent study by Harris et al. [102], patients with PCOS and unequal menstrual cycles have a lower risk of developing an ovarian serous tumor. However, individuals who have not ever received OC treatment or who are overweight will have an increased risk of developing an ovarian serous border tumor. Third-generation aromatase inhibitor letrozole prevents androgens from being converted to estrogens in the brain, peripheral tissues, and ovarian follicles. This positive feedback loop with the estrogen of the HPO axis leads to the endogenous release of GnRH, encourages the secretion of FSH, and results in follicular growth. Beginning on days 3–7 of the menstrual cycle, LE is given in doses ranging from 2.5 to 5 mg/day for five days [103]. According to recent studies, letrozole aromatase inhibitors will eventually take the position of the selective estrogen receptor controller clomiphene as a first line ovulation treatment option

[104] and that LE has a special benefit in boosting ovulation in obese PCOS patients. In order to treat ovulatory infertility, it was suggested in a 2015 article with an impression factor of 20 that drugs could be used to interrupt the ovarian Hippo gesturing pathway in patients with POI, PCOS, and poor ovarian response to FSH stimulation. This pathway excites the activity of the AKT protein by activating the dormant follicle and promoting the growth of sinus anterior follicles. [105]

### *6.1.5 Vitamin D deficiency theory*

In a study by Skowronska et al. [106], it was discovered that serum 25 (OH) vitamin D stages are related to sex hormone binding globulin (SHBG), a marker for PCOS metabolism or endocrine disorders. Vitamin D supplements improve insulin sensitivity and insulin production in people with vitamin D insufficiency. Supplemental vitamin D, meantime, is anticipated to be a medication for PCOS treatment due to its ability to lower total testosterone and androgen levels [106].

### *6.1.6 GLP-1 receptor agonist therapy*

Exenatide and liraglutide are beneficial in reducing weight when used alone or in combination with metformin, according to the trials that have been conducted on GLP-1 RA therapy for the treatment of extra body weight in women with PCOS [107]. A few research suggested that menstruation frequency may rise and testosterone levels may be slightly lowered. Limited data, however, demonstrate no clear impact on blood pressure and lipid metabolism, while the medicine's most prevalent side effect, nausea, has no bearing on drug promotion or treatment [107].

### *6.1.7 Bariatric surgery*

According to Charalampakis et al.'s research [26], bariatric surgery can efficiently increase unprompted ovulation rates and pregnancy rates in obese patients with PCOS and decrease the risk of preeclampsia and gestational diabetes. However, a slight percentage of bariatric procedures may extend the gestational age and raise the risk of stillbirth or neonatal death.

Presently, surgical options include sleeve gastrectomy, adjustable gastric banding, and Roux en Y gastric bypass (GBP). Long-term, surgery has a positive impact on lipid metabolism, and around clear effects on side effects including endometrial hyperplasia [108].

### *6.1.8 Treatment theory through Inositol*

According to Nestler et al., women with PCOS have ovaries that are more active as a result of their phenotypic, which increases the conversion of Myo-inositol (MI) to D-chiro-inositol (DCI) and decreases MI in follicles. However, the study discovered that the quantity of follicular fluid in a fertilized egg or the number of normal, mature follicles was much larger in MI compared to the quantity of undeveloped or infertile follicles. Therefore, inositol therapy can lessen insulin resistance in PCOS-affected women and enhance the health of ovarian follicles and menstrual cycles. Future PCOS sufferers are anticipated to benefit from this treatment [109].

# Chapter: 7

# Conclusion

## 7.1 Conclusion

To summarize, polycystic ovarian syndrome (PCOS) is a complex illness that affects many people worldwide. PCOS pathophysiology is multifaceted, with genetic, environmental, and lifestyle variables interfering with normal ovarian function and resulting in hormone abnormalities. Recent study has shown a possible link between PCOS and the gut flora, which may play a role in the disorder's development and progression. While much remains to be discovered about the gut-ovary axis in PCOS, it does provide intriguing pathways for future study and treatment interventions. Current PCOS therapy options try to address the disorder's many symptoms, including as menstrual abnormalities, hyperandrogenism, and insulin resistance. As first-line therapy, lifestyle changes such as diet and exercise are encouraged, although drugs such as oral contraceptives, anti-androgens, and insulin sensitizers may also be provided. These treatments, however, are not always effective and may cause side effects, emphasizing the importance of ongoing research into novel therapeutic techniques. In conclusion, PCOS is a widespread and complicated illness that affects many people. Future research and therapy approaches have interesting new directions because of the potential connections between PCOS and the gut flora. There is still much to learn about the underlying pathophysiology of the illness and how it can be properly treated to enhance the health and well-being of women with PCOS, even if current medicines can be effective in managing symptoms.

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