https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27(4s) (December 2024); 6246-6254
Research Article

Polycystic Ovarian Disease: Current Insights and therapeutic Strategies

Shreya Shakya[1*], Dr. Nishkruti Mehta[2], Dr. Pragnesh Patani[3], Poonam Gupta[4], Harit Dudharejiya[5]

[1*]Department of Pharmacology, Khyati College of Pharmacy, India.
[2] Professor, Department of Pharmacology, Khyati College of Pharmacy, Palodia, Ahmedabad
[3] Principal and Professor, Department of Pharmacology, Khyati College of Pharmacy, Palodia, Ahmedabad
[4] Department of Pharmacology, Khyati College of Pharmacy, India.
[5] Department of Pharmacology, Khyati College of Pharmacy, India.

***Corresponding Author:** Shreya Shakya Manekbhai
*Khyati College of Pharmacy, Palodia, Ahmedabad, Email id: shakyashreya8733@raiuniversity.edu

Abstract
Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder, typically characterized by anovulation, infertility, obesity, insulin resistance, and polycystic ovaries. Lifestyle or diet, environmental pollutants, genetics, gut dysbiosis, neuroendocrine alterations, and obesity are among the risk factors that predispose females to PCOS. These factors might contribute to upsurging metabolic syndrome by causing hyperinsulinemia, oxidative stress, hyperandrogenism, impaired folliculogenesis, and irregular menstrual cycles. Dysbiosis of gut microbiota may play a pathogenic role in the development of PCOS. The restoration of gut microbiota by probiotics, prebiotics, or a fecal microbiota transplant (FMT) might serve as an innovative, efficient, and noninvasive way to prevent and mitigate PCOS. This review deliberates on the variety of risk factors potentially involved in the etiology, prevalence, and modulation of PCOS, in addition to plausible therapeutic interventions, including miRNA therapy and the eubiosis of gut microbiota, that may help treat and manage PCOS.

Keywords: PCOS, gut microbiome, probiotics, FMT, gut dysbiosis, hyperinsulinemia, hyperandrogenism, metabolic disorders, miRNA therapy

***Author for correspondence: Email:** *shakyashreya8733@raiuniversity.edu*

Received: 02/11/2024 *Acceptance: 03/12/2024*

DOI: https://doi.org/10.53555/AJBR.v27i4S.4760

1.Introduction

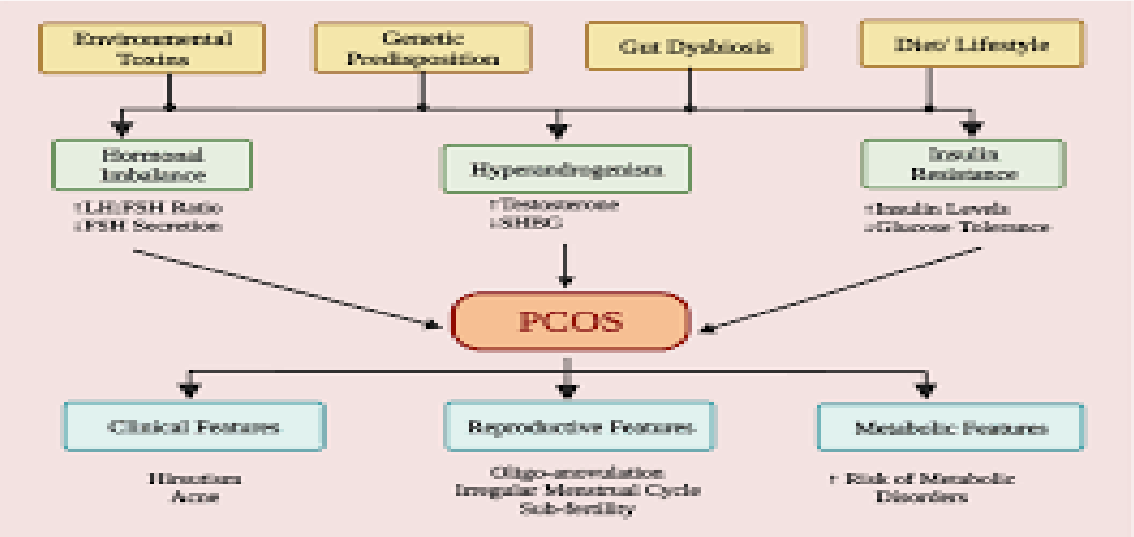
One of the most prevalent endocrine system conditions affecting women of reproductive age is polycystic ovary syndrome (PCOS), also known as hyperandrogenic anovulation (HA) or Stein–Leventhal syndrome. This chronic and heterogeneous disorder manifests itself as menstrual dysfunction, infertility, hirsutism, acne, and obesity. [1]It describes a condition where at least one ovary has an ovarian volume greater than 10 mL and at least one ovary has an estimated ten small cysts, with diameters ranging from 2 to 9 mm, develop .[2] It is usually only diagnosed when complications develop that significantly reduce a patient's quality of life (e.g., hair loss, alopecia, acne, and infertility-related problems) [4].

According to a systematic screening of women using the National Institutes of Health (NIH) diagnostic standards, 4–10% of reproductive-age women are predicted to have PCOS worldwide [1]. The World Health Organization (WHO) estimates that in 2012 PCOS affected 116 million women (3.4%) globally [5]. This high frequency, as well as its link with ovulation and menstruation abnormalities, infertility, hair loss, and metabolic issues, underscores PCOS's significant financial burden [2,6]. Although PCOS can occur at any age, beginning with menarche, the majority of instances are identified between the ages of 20 and 30 [7]. PCOS affects 1.55 million women of reproductive age worldwide, resulting in 0.43 million disability-adjusted life years (DALYs). The age-standardized incidence rate of PCOS in women of reproductive age was 82.44 per 100,000 in 2017, 1.45% higher than in 2007 [8]. Recent research reveals that PCOS is a lifelong syndrome that first manifests during pregnancy, although it was traditionally thought to be a disorder that only affected adult women [9]. While the exact cause of this multifactorial disorder is unknown, a combination of inherited and environmental factors is thought to play a primary role. The pathophysiology of PCOS is 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 type II diabetes. According to international recommendations, the three main factors used to diagnose PCOS are hyperandrogenism, ovarian morphology, and anovulation [10]. A range of environmental factors, including geography, diet and nutrition, socioeconomic status, and environmental pollutants, are possibly contributing to the development, occurrence, and management of PCOS [11]. In recent years, the link between PCOS and the microbiome has been established, and it is believed to have contributed to the establishment of the syndrome. Dysbiosis of the gut microbial community, caused by environmental risk factors, might be a potential pathogenic factor in the development and progression of PCOS. Different pathogenic aspects of PCOS are caused by different microbiota, and essential routes linking their involvement in the onset of various clinical manifestations of PCOS bring up new therapy options for the condition [12]. Prebiotics, probiotics, synbiotics, and fecal microbiota transplants (FMTs) help manage the variety of phenotypes associated with PCOS by boosting eubiosis and reducing the impact of altered microbial profiles. Microbiota-mediated therapies might improve the metabolic, inflammatory, and hormonal characteristics of PCOS women.

This review summarizes the risk factors that may contribute to the development, prevalence, and modulation of PCOS, as well as its possible treatment approaches, including IL-22 and miRNA therapy. Additionally, we discuss the importance of gut dysbiosis in the pathogenesis of PCOS and evaluate several microbiota-focused intervention options that could help manage the disorder.

1.1Disease Pathophysiology:

Across the globe, PCOS affects between 8% and 20% of women of reproductive age annually, according to the diagnostic criteria [14].The pathophysiology of this condition is influenced by alterations in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors, and sympathetic nerve function [15]. According to Barre et al., the high consumption of carbohydrates, hyperinsulinemia, hyperandrogenemia, and persistent low-grade inflammation are the four key contributors to pathophysiological alterations in PCOS



A. Hyperandrogenism

The biochemical hallmark of PCOS is hyperandrogenemia, which manifests clinically as hirsutism, acne, and alopecia. High levels of androgens are observed in 75–90% of PCOS patients with oligomenorrhea, and their concentrations frequently increase with the severity of the phenotype. Excessive androgen synthesis by the ovaries as well as the adrenals contributes to hyperandrogenism [17]. Increased levels of free (unbound) testosterone, a major hormone

contributing to the pathogenesis of PCOS, are indicative of hyperandrogenism. Abnormal ovarian or adrenal function leads to the overproduction of androgens. In PCOS, impaired folliculogenesis is the initial effect of excess androgens disrupting normal androgen synthesis. At the early gonadotropin stage, excess androgens encourage the growth of primordial follicles and a rise in the antral follicles [18]. The release of gonadotropin hormones from the pituitary is triggered by GnRH production from the hypothalamus. To increase androgen synthesis in ovarian theca cells, luteinizing hormone (LH) activates the LH receptor. At the same time, follicle-stimulating hormone (FSH) activates the FSH receptor in ovarian granulosa cells to convert androgens into estrogens, which stimulate follicle growth. The dysregulation of the neuroendocrine system is thought to cause an imbalance in the hypothalamic–pituitary–ovarian (HPO) axis, which then leads to an excess of gonadotropin. The rise in GnRH promotes the production of LH over FSH, resulting in a substantial hormonal surge in the LH:FSH ratio in PCOS [19]. Theca cells in the ovaries undergo hyperplasia as a result of increased LH stimulation, which also causes a build-up of follicular fluid that forms cystic structures along the ovary's periphery, giving it the appearance of a string of pearls. This is because many follicles in the theca cells of the ovaries become arrested, mostly in the preantral and antral stages. Due to a rise in follicles and the expression of essential enzymes involved in androgen synthesis, an excessive amount of androgens are produced [20].

An altered cortisol metabolism is another proposed mechanism that contributes to excess androgens 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]. Various genetic factors are associated with abnormal steroidogenesis. CYP genes involved in steroidogenesis play an important role in androgen production and are considered key players in hyperandrogenism in PCOS [20].

B. Hyperinsulinemia

Insulin is the main hormone in charge of both lipogenesis and glucose homeostasis. Insulin serves as a mitogenic hormone in addition to having an impact on the metabolism of carbohydrates, fats, and proteins. Insulin receptors, which are present in many tissues of the HPO axis, mediate the activities of insulin. Insulin potentiates the corresponding trophic hormones in steroidogenic tissues, such as the ovary and the adrenal cortex, to encourage steroidogenesis [20]. As insulin directly mimics the action of LH and indirectly raises GnRH, hyperinsulinemia is the primary cause of excessive androgen production. Sex hormone binding globulin (SHBG), a key circulatory protein that regulates testosterone levels, is decreased by insulin. Therefore, lower SHBG levels would lead to higher levels of free androgens, which cause clinical symptoms of PCOS, such as hirsutism, alopecia, and acne [20]. Numerous studies have shown that lowering insulin resistance will ultimately result in reduced androgens and an improvement in the disease condition

C. Hyperandrogenism

The biochemical hallmark of PCOS is hyperandrogenemia, which manifests clinically as hirsutism, acne, and alopecia. High levels of androgens are observed in 75–90% of PCOS patients with oligomenorrhea, and their concentrations frequently increase with the severity of the phenotype. Excessive androgen synthesis by the ovaries as well as the adrenals contributes to hyperandrogenism [20]. Increased levels of free (unbound) testosterone, a major hormone contributing to the pathogenesis of PCOS, are indicative of hyperandrogenism. Abnormal ovarian or adrenal function leads to the overproduction of androgens. In PCOS, impaired folliculogenesis is the initial effect of excess androgens disrupting normal androgen synthesis. At the early gonadotropin stage, excess androgens encourage the growth of primordial follicles and a rise in the antral follicles [20]. The release of gonadotropin hormones from the pituitary is triggered by GnRH production from the hypothalamus. To increase androgen synthesis in ovarian theca cells, luteinizing hormone (LH) activates the LH receptor. At the same time, follicle-stimulating hormone (FSH) activates the FSH receptor in ovarian granulosa cells to convert androgens into estrogens, which stimulate follicle growth. The dysregulation of the neuroendocrine system is thought to cause an imbalance in the hypothalamic–pituitary–ovarian (HPO) axis, which then leads to an excess of gonadotropin. The rise in GnRH promotes the production of LH over FSH, resulting in a substantial hormonal surge in the LH:FSH ratio in PCOS [20]. Theca cells in the ovaries undergo hyperplasia as a result of increased LH stimulation, which also causes a build-up of follicular fluid that forms cystic structures along the ovary's periphery, giving it the appearance of a string of pearls. This is because many follicles in the theca cells of the ovaries become arrested, mostly in the preantral and antral stages. Due to a rise in follicles and the expression of essential enzymes involved in androgen synthesis, an excessive amount of androgens are produced [20].

An altered cortisol metabolism is another proposed mechanism that contributes to excess androgens 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]. Various genetic factors are associated with abnormal steroidogenesis. CYP genes involved in steroidogenesis play an important role in androgen production and are

considered key players in hyperandrogenism in PCOS [21].

d. Hyperinsulinemia

Insulin is the main hormone in charge of both lipogenesis and glucose homeostasis. Insulin serves as a mitogenic hormone in addition to having an impact on the metabolism of carbohydrates, fats, and proteins. Insulin receptors, which are present in many tissues of the HPO axis, mediate the activities of insulin. Insulin potentiates the corresponding trophic hormones in steroidogenic tissues, such as the ovary and the adrenal cortex, to encourage steroidogenesis [14]. As insulin directly mimics the action of LH and indirectly raises GnRH, hyperinsulinemia is the primary cause of excessive androgen production. Sex hormone binding globulin (SHBG), a key circulatory protein that regulates testosterone levels, is decreased by insulin. Therefore, lower SHBG levels would lead to higher levels of free androgens, which cause clinical symptoms of PCOS, such as hirsutism, alopecia, and acne [21]. Numerous studies have shown that lowering insulin resistance will ultimately result in reduced androgens and an improvement in the disease condition

2.Treatment and Management

Treatments of PCOS must be tailored to the specific needs of each patient; goals of therapy may include ameliorating hyperandrogenic symptoms, inducing ovulation, regulating menstruation, and preventing cardiometabolic complications. For women with PCOS, irregular menstruation, hirsutism, and infertility are the most distressing symptoms. Due to the complex etiology of PCOS, its treatment is rarely monotherapeutic, rather being personalized based on prevailing signs and symptoms. Several complementary therapies have been suggested for the management and treatment of PCOS. Diet and lifestyle changes are regarded as the cornerstone of PCOS management. Different pharmacological and non-pharmacological interventions can be used to relieve the most prominent symptoms of PCOS, such as menstrual irregularities, androgen-related symptoms, and infertility-causing anovulation. For the regulation of metabolic comorbidities in PCOS, there are numerous therapeutic approaches with potential benefits; however, it is also crucial to acknowledge that no single treatment can fully address the range of metabolic abnormalities in PCOS-diagnosed women. Combining lifestyle changes with medications for various ailments results in greater metabolic benefits and improvements in metabolic comorbidity parameters than monotherapies do. Additionally, treatment should also take into consideration increased levels of anti-Müllerian hormone (AMH), plasma metabolomics, and gut microbiota composition, which are severe characteristics of PCOS, in addition to focusing on primary traits.

5.1. Oral Contraceptives and Anti-Androgens:

Oral contraceptives (OCs) are the first-line management protocol for menstrual abnormalities and hirsutism/acne in women with PCOS [22]. OCs function by encouraging negative feedback on LH secretion, which leads to less androgen production in the ovaries and reduces hyperandrogenism. They raise liver-produced SHBG while lowering blood levels of free androgens. OCs also work by inhibiting the peripheral conversion of testosterone into dihydrotestosterone (DHT), binding DHT to androgen receptors, and decreasing the release of adrenal androgens [22]. The risk–benefit ratios of OC preparations can vary depending on their doses and medication combinations. The majority of OC preparations include estrogen (ethinylestradiol) and anti-androgens, such as cyproterone acetate (CPA), drospirenone, norgestimate, levonorgestrel, and desogestrel [22]. Anti-androgens, including spironolactone, CPA, flutamide, and finasteride, systematically lower levels of androgens [22], therefore being used in the medical management of hyperandrogenism. Antiandrogens are frequently used to treat PCOS because they help with hirsutism and other androgen-related issues. The anti-androgens have slightly distinct mechanisms of action, but they all impede testosterone's function. Anti-androgen receptor drugs have been effective in treating PCOS characteristics. The main result of using OCs is a decrease in hyperandrogenism due to its effects on the hypothalamus and pituitary, in addition to ovarian steroidogenesis [23]. Due to these effects it is an effective pharmacological intervention for the treatment of menstrual irregularity, acne, hirsutism, and androgenic alopecia linked to PCOS [22,23]. Third-generation combination OCs, which contain antiandrogenic compounds, have been shown to improve the metabolic phenotypes of PCOS, lipid, and adipokine profiles in patients. The most prevalent competitive antagonist of ARs, flutamide, has been shown to benefit PCOS-affected women by reducing hirsutism and acne [20,21,22]. Patients with PCOS receiving flutamide medication also reported improved ovulation and menstrual cycle regularity [23]. Additionally, therapy with flutamide in both obese and lean PCOS women showed that flutamide improved the lipid profiles of women with PCOS, with a substantial decrease in total cholesterol, LDL, and TGs, regardless of weight changes [24]. 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 dramatically reduce hirsutism and acne [23]. Additionally, spironolactone medication was found, in one trial, to improve metabolic characteristics in PCOS-affected individuals [24]. Finasteride, a 5-alpha reductase inhibitor that inhibits the conversion of T into DHT, is another treatment used to effectively manage hirsutism and alleviate hyperandrogenic symptoms in PCOS patients [23,24]. When considered collectively, findings from the use of anti-androgenic medications in PCOS patients, either alone or in combination, have shown that the targeted reduction in hyperandrogenism and consequently androgenic activity has a positive effect, with improvements seen in a variety of PCOS traits. Comprehensive screening should be performed on women with PCOS to identify risk factors for severe side effects from OCs, such as a history of smoking, the presence of hypertension and obesity, and a history of clotting issues, to name a few very important factors.

5.2. Insulin Sensitizers

Defective insulin secretion and function are part of the pathophysiology of PCOS [24]. The elevated levels of androgens in PCOS are known to be influenced by hyperinsulinemia and insulin resistance. Ovarian function is regulated by insulin, and excessive insulin levels can have negative effects on ovarian function. In reaction to excessive insulin, theca cells release large levels of androgens, which in turn cause follicular maturation to be arrested, which increases the risk of polycystic ovarian morphology, a sign of PCOS [24]. In addition to playing a crucial part in the pathophysiology of PCOS, insulin resistance negatively affects PCOS patients by predisposing them to long-term health issues, such as T2DM and CVD. To effectively manage PCOS, a therapeutic approach that addresses insulin resistance, including pharmaceutical and lifestyle changes, is essential. By reducing insulin secretion and stabilizing glucose tolerance, insulin sensitizers increase insulin sensitivity in target tissues [. It has been demonstrated that insulin sensitizers, such as metformin and thiazolidinediones (TZDs), can trigger ovulation by reducing insulin resistance. Metformin (a biguanide) use is linked to improved ovulation, decreased levels of circulating androgens, and enhanced menstrual cyclicity [25]. It acts by reducing hepatic glucose synthesis, increasing glucose absorption, and improving peripheral tissues' sensitivity to insulin. In research comparing metformin and lifestyle interventions in PCOS-afflicted women both groups experienced a significant decrease in BMI; however, only the metformin group experienced a decrease in testosterone levels [25]. 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 . Metformin has been shown in numerous trials to have a significant effect on dyslipidemia .It either directly affects the hepatic metabolism of free fatty acids or indirectly acts by lowering hyperinsulinemia to improve dyslipidemia. Additionally, TZDs (pioglitazone and rosiglitazone) lower insulin levels by increasing insulin sensitivity, which reduces levels of androgens in the blood. Women with PCOS have reported that pioglitazone had an impact on reducing insulin resistance, hyperandrogenism, and ovulatory dysfunction. It significantly decreased fasting serum insulin and free androgen levels while increasing SHBG levels in an RCT that compared the effectiveness of the drug vs. a placebo in PCOS patients[26]. In a meta-analysis comparing the effectiveness of metformin and pioglitazone in treating PCOS, the pioglitazone group showed a substantial improvement in ovulation and the menstrual cycle. According to the findings of a meta-analysis of 22 trials for women with PCOS, metformin combined with TZD appear to be more effective than metformin alone in improving insulin resistance and lipid metabolism while lowering total testosterone levels.

5.3. Ovulation Inducers

Ovulatory dysfunction is one of the diagnostic criteria for PCOS patients, and ovulation induction is an effective treatment for PCOS patients with fertility requirements. Anovulation in PCOS is associated with low FSH levels and the arrest of antral follicle growth during its final stages of maturation. The overproduction of LH, androgens, and insulin may all work together or separately to influence this process directly or indirectly, enhancing steroidogenesis but preventing follicular growth. The first-line medication for ovulation induction is still clomiphene citrate (CC), a partially selective estrogen receptor modulator. As an estrogen receptor antagonist, CC inhibits negative feedback in the estrogen signaling pathway, leading to increased FSH availability. Increased FSH causes follicular growth, which is followed by an LH surge and ovulation. Low-dose gonadotropin therapy can also be used for the induction of ovulation and mono-follicular development [45]. It is thought that women with PCOS have a relative decrease in aromatase, which reduces the production of follicles responsible for effective ovulation. Aromatase inhibitors (AIs) are considered to induce ovulation because of their selective action of blocking the conversion of androgens into estrogens in ovarian follicles, peripheral tissues, and the brain, creating a positive feedback loop with the estrogen of the HPO axis, which causes the endogenous release of GnRH, promotes FSH secretion, and causes follicular growth. Selective Ais, such as letrozole and anastrozole, have been suggested as primary and secondary treatments for ovulation induction[27]. Letrozole has the advantage of avoiding peripheral antiestrogenic effects on the endometrium while stimulating mono-follicular growth

5.4. Calcium and Vitamin D Supplements:

Vitamin D plays a physiologic role in reproduction, including in ovarian follicular development and luteinization, via altering AMH signaling, FSH sensitivity, and progesterone production in human granulosa cells. Through a variety of functions, it also impacts glucose homeostasis. The presence of a specific vitamin D receptor (VDR) in pancreatic β-cells and skeletal muscle, the expression of the enzyme 1α-hydroxylase, which can catalyze the conversion of 25-hydroxyvitamin D [25(OH)D] into 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the human insulin gene promoter are some of the potential effects of vitamin D on glucose homeostasis Low 25(OH)D levels may aggravate PCOS symptoms, such as insulin resistance, ovulatory and menstrual irregularities, infertility, hyperandrogenism, and obesity, as well as increase the risk of cardiovascular disease. In vitamin-D-deficient individuals with PCOS, vitamin D administration can lower abnormally increased serum AMH levels while increasing serum anti-inflammatory soluble receptors for advanced glycation end products. In particular, vitamin D and calcium supplementation, in addition to metformin therapy, may improve menstrual regularity, ovulation, hyperandrogenism, and follicular development in PCOS patients [29]. Women with PCOS have high AMH levels, which lead to aberrant ovarian folliculogenesis. Vitamin D therapy restores serum AMH levels, which may lead to improved folliculogenesis. Results from a meta-analysis showed that combining metformin with a

calcium/vitamin D supplement improved menstrual regularity and follicular maturation, significantly reduced serum insulin levels, fasting blood sugar (FBS), and homeostasis model assessment insulin resistance (HOMA-IR), and significantly increased the quantitative insulin sensitivity check index (QUICKI). Additionally, it decreased hirsutism and testosterone levels, serum TG and VLDL-C levels, and cholesterol as well as LDL levels in PCOS patients.[37],[38]

6. Emerging Therapeutics:

6.1. Statins

Women with PCOS frequently have dyslipidemia, which is a significant predictor of cardiovascular risk due to increased LDL-C, triglyceride (TG), and low HDL-C levels [101]. Therefore, the effective treatment of PCOS involves improving the lipid profile and subsequently reducing cardiovascular disease morbidity. Statins (atorvastatin, pravastatin, rosuvastatin, fluvastatin, and simvastatin) help treat PCOS because they lower sex steroid production, improve dyslipidemia, improve inflammation, and lower ovarian androgen production by preventing thecal cells from producing androgen . The rate-regulating enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is necessary for the process of cholesterol production, is inhibited by statins. By blocking this enzyme, cholesterol formation will also be prevented because HMG-CoA will not be converted into mevalonate .When the atorvastatin and placebo groups were both given metformin for another 12 weeks, the atorvastatin pretreated group significantly outperformed the placebo pretreated group in terms of HOMA-IR, the free androgen index (FAI), total testosterone, and SHBG, indicating that atorvastatin enhances the effect of metformin . In this investigation, atorvastatin dramatically decreased acylation stimulating protein (ASP), IL-6, and monocyte chemoattractant protein-1 (MCP-1), which are markers of inflammation and adipose tissue dysfunction, followed by a significant improvement in HOMA-IR and testosterone levels . In randomized placebo-controlled research, atorvastatin significantly decreased hyperandrogenism, inflammatory markers, and insulin resistance in PCOS-affected women compared to a placebo [32]. A measure of oxidative stress, serum malondialdehyde (MDA), was dramatically lowered in obese women with PCOS receiving atorvastatin treatment [108]. In addition, the group of PCOS-afflicted women had considerably lower levels of androstenedione and dehydroepiandrosterone sulfate (DHEAS) after taking atorvastatin Additionally, compared to a placebo, a 12-week course of atorvastatin significantly increased the levels of serum vitamin D (25OH-D) in PCOS women The results of a meta-analysis of nine RCTs supported the use of statins as a viable treatment for PCOS by showing that they could lower androgen levels and improve the cutaneous symptoms of hyperandrogenism in PCOS patients Another meta-analysis revealed that the statin group experienced a significant drop in total testosterone, free testosterone, androstenedione, DHEAS, LH, the LH-to-FSH ratio, and prolactin. In addition to demonstrating a significant drop in fasting glucose, the insulin sensitivity index, and high-sensitivity C-reactive protein, the study also showed a significant decline in total cholesterol, LDL-C, and TGs in the statin group [30],[37]

6.2. Glucagon-Like Peptide-1 (GLP-1) Agonist:

Incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are well-known stimulators of glucose-dependent insulin release, particularly after a meal, a phenomenon known as the incretin effect [32]. In cases of insulin resistance, incretin action is frequently impaired. According to a recent study, lower levels of the incretin hormone have been found in PCOS patients. This being the case, targeting this mechanism might be a useful therapeutic strategy for PCOS treatment. Given that insulin resistance is the primary cause of metabolic and endocrine dysfunction in PCOS, GLP-1 agonist therapy has obvious therapeutic benefits in this population. Although the primary effect of GLP-1 agonists is not to stimulate insulin secretion, their weight loss effect may indirectly improve insulin sensitivity. According to a study, these agents improve insulin sensitivity by acting on eight different molecular pathways, including those of inflammation, oxidative stress, lipid metabolism, GLUT-4 expression/translation, β-cell function, the endoplasmic reticulum (ER), and insulin signaling [32]. Commercially available GLP-1 agonists include liraglutide, semaglutide, dulaglutide, and exenatide. A recent systematic review and meta-analysis that compared the efficacy of GLP-1 agonists and metformin in women with PCOS have shown a significant improvement in insulin sensitivity, reduced BMI, and abdominal girth compared with metformin ./In addition, GLP-1 receptor agonist therapy has shown positive results in terms of weight reduction and a decrease in testosterone levels in obese women with PCOS .Another study that examined the effect of liraglutide on depression and quality of life (QOL) in obese PCOS patients found a significant improvement in QOL with dramatic weight loss. Dual GLP-1/GIP receptor agonists (twincretins) have shown better potency in inducing glycemic control and weight loss, reducing hepatic fat content, and improving adiposity, lipid profiles, and metabolic parameters than GLP-1 agonists alone in different disease models. From the current data, it would seem that these are promising new therapies with potential utility for PCOS treatment. Therefore, these could potentially be novel therapeutic options in women with PCOS to improve metabolic risk if proven beneficial in clinical studies.[34],[35]

6.3. Inositols:

Inositol is a carbocyclic sugar found in high concentrations in human and plant cells. It exists in nine different isomeric forms, the most common of which are myoinositol (MI) and d-chiro-inositol (DCI). The inositols found in fruits and beans are incorporated into cell membranes as phosphatidyl-MI, a precursor of inositol triphosphate (InsP3). InsP3 acts as an intracellular second messenger and regulates a variety of hormones, including thyroid-stimulating hormone (TSH), FSH, and insulin. MI-based secondary messenger activation regulates glucose intake by

increasing the activity of glucose transport proteins, whereas DCI secondary messenger activation stimulates glycogen synthesis. Defects in this pathway can cause insulin resistance by impairing insulin signaling. The enzyme epimerase converts MI into DCI while maintaining a physiological ratio that varies from tissue to tissue. A 40:1 ratio is thought to be physiological for most tissues [32]. Insulin triggers the NAD–NADH-dependent enzyme epimerase to function in accordance with tissue needs. When there is insulin resistance in the systemic milieu, this stimulus is lost. The main inositol isomers are distributed differently in the three insulin target organs—adipose tissue, liver, and skeletal muscle—and each requires a substantially higher proportion of DCI to maintain homeostasis. In the presence of epimerase deficiency, less MI can be converted into DCI, resulting in a state of relative DCI deficiency and the promotion of insulin resistance [32]. This, in turn, causes the metabolic complications of hyperinsulinemia, a feature of PCOS.

In PCOS-afflicted women who are otherwise infertile, MI intake has been demonstrated to improve ovulation and responsiveness to fertility treatments. A recent systematic analysis that evaluated the effects of MI in PCOS-affected women concluded that MI supplements improved PCOS-related hormonal and reproductive issues. Additionally, it improved oocyte maturation as well as follicular development and raised the likelihood of clinical pregnancies in PCOS patients. With MI therapy, ovulation induction time and recombinant FSH dosage requirements were both dramatically reduced [32]. As a result, it positively modifies the reproductive axis. Treatment with MI markedly decreased LH, prolactin, androstenedione, insulin, and LH/FSH ratio concentrations, in addition to enhancing insulin sensitivity. Since MI supplements are often well-tolerated at the current dose recommendations of 2–4 g/day with few safety concerns, their clinical use in the management of PCOS is worth taking into account. It has been demonstrated that DCI plays a role in insulin metabolism. Both at baseline and after the administration of glucose loads, women with PCOS are reported to have decreased serum levels of DCI. In PCOS patients, DCI therapy has been shown to improve endocrine, metabolic, and reproductive parameters by lowering blood pressure, lipid, and insulin levels as well as improving the maturity and quality of oocytes significantly, while reducing oxidative stress in follicular fluid .All PCOS symptoms, signs, and test abnormalities may be improved with Myo- + D-chiro-inositol (MDI) therapy. Together, the two inositols should be able to increase the necessary inositol concentrations in the ovary and systemic circulation, resolving the ovarian inositol paradox. The metabolic characteristics of PCOS will be treated by MI, which will correct systemic insulin resistance. A healthy intraovarian environment will be produced simultaneously by sufficient DCI levels, which will treat hyperandrogenism, enhance menstrual regularity, and promote ovulation as well as fertility. Exogenous DCI administration may be a method of circumventing defective epimerase activity and achieving the downstream metabolic effects of insulin in DCI-deficient tissue. Due to the unidirectional nature of epimerase activity, administering DCI by itself will not be able to imitate the effects of MI. As a result, it makes sense to provide a combination of both to ensure optimal insulin sensitivity. At the same time, the beneficial effect of MI on ovarian physiology could be attributed to its low conversion into DCI. Lower doses of MI may be enough if coadministered with DCI, according to this hypothesis. Considering the physiologic and pharmacological evidence presented above, we propose the pragmatic use of inositol therapy in the prevention and management of PCOS. Through the use of MDI therapy, MI and DCI deficiency can be treated concurrently, which may help to reduce the menstrual/ovulatory, metabolic, and cutaneous hyperandrogenic symptoms of PCOS. The above being the case, MDI, both as a monotherapy and in combination, is a sensible treatment option for PCOS management. Ongoing research will contribute to increased confidence in the scientific application of these molecules.[33],[36]

6.4. MicroRNA (miRNA) Therapy:

Evidence is growing about the therapeutic potential of miRNAs in the management of numerous diseases, including PCOS [32] The post-transcriptional regulation of gene expression is carried out by miRNAs, which are small non-coding RNAs with a length of about 22 nucleotides. They attach selectively to the 3’ untranslated region (UTR) of the target genes, inhibiting their translation and/or causing instability [33]

Reference:

1. .El Hayek S., Bitar L., Hamdar L.H., Mirza F.G., Daoud G. Poly Cystic Ovarian Syndrome: An Updated Overview. Front. Physiol. 2016;7:124. doi: 10.3389/fphys.2016.00124. [DOI] [PMC free article] [PubMed] [Google Scholar]
2. 2.Motlagh Asghari K., Nejadghaderi S.A., Alizadeh M., Sanaie S., Sullman M.J.M., Kolahi A.-A., Avery J., Safiri S. Burden of polycystic ovary syndrome in the Middle East and North Africa region, 1990–2019. Sci. Rep. 2022;12:7039. doi: 10.1038/s41598-022-11006-0. [DOI] [PMC free article] [PubMed] [Google Scholar]
3. 3.Balen A.H., Tan S.L., MacDougall J., Jacobs H.S. Miscarriage rates following in-vitro fertilization are increased in women with polycystic ovaries and reduced by pituitary desensitization with buserelin. Hum. Reprod. 1993;8:959–964. doi: 10.1093/oxfordjournals.humrep.a138174. [DOI] [PubMed] [Google Scholar]
4. 4.Azziz R., Woods K.S., Reyna R., Key T.J., Knochenhauer E.S., Yildiz B.O. The prevalence and features of the polycystic ovary syndrome in an unselected population. J. Clin. Endocrinol. Metab. 2004;89:2745–2749. doi: 10.1210/jc.2003-032046. [DOI] [PubMed] [Google Scholar]
5. 5.Vidya Bharathi R., Swetha S., Neerajaa J., Varsha Madhavica J., Janani D.M., Rekha S.N., Ramya S., Usha B. An epidemiological survey: Effect of predisposing factors for PCOS in Indian urban and rural population. Middle East Fertil. Soc. J.

2017;22:313–316. doi: 10.1016/j.mefs.2017.05.007. [DOI] [Google Scholar]

6. 6.Azziz R., Marin C., Hoq L., Badamgarav E., Song P. Health care-related economic burden of the polycystic ovary syndrome during the reproductive life span. J. Clin. Endocrinol. Metab. 2005;90:4650–4658. doi: 10.1210/jc.2005-0628. [DOI] [PubMed] [Google Scholar]
7. 7.Bremer A.A. Polycystic ovary syndrome in the pediatric population. Metab. Syndr. Relat. Disorders. 2010;8:375–394. doi: 10.1089/met.2010.0039. [DOI] [PMC free article] [PubMed] [Google Scholar]
8. 8.Liu J., Wu Q., Hao Y., Jiao M., Wang X., Jiang S., Han L. Measuring the global disease burden of polycystic ovary syndrome in 194 countries: Global Burden of Disease Study 2017. Hum. Reprod. 2021;36:1108–1119. doi: 10.1093/humrep/deaa371. [DOI] [PMC free article] [PubMed] [Google Scholar]
9. 9.Hashemipour M., Amini M., Iranpour R., Sadri G.H., Javaheri N., Haghighi S., Hovsepian S., Javadi A.A., Nematbakhsh M., Sattari G. Prevalence of congenital hypothyroidism in Isfahan, Iran: Results of a survey on 20,000 neonates. Horm. Res. 2004;62:79–83. doi: 10.1159/000079392. [DOI] [PubMed] [Google Scholar]
10. 10.Lujan M.E., Chizen D.R., Pierson R.A. Diagnostic criteria for polycystic ovary syndrome: Pitfalls and controversies. J. Obstet. Gynaecol. Can. 2008;30:671–679. doi: 10.1016/S1701-2163(16)32915-2. [DOI] [PMC free article] [PubMed] [Google Scholar]
11. 11.Merkin S.S., Phy J.L., Sites C.K., Yang D. Environmental determinants of polycystic ovary syndrome. Fertil. Steril. 2016;106:16–24. doi: 10.1016/j.fertnstert.2016.05.011. [DOI] [PubMed] [Google Scholar]
12. 12.Batra M., Bhatnager R., Kumar A., Suneja P. Interplay between PCOS and microbiome: The road less travelled. Am. J. Reprod. Immunol. 2022;88:e13580. doi: 10.1111/aji.13580. [DOI] [PubMed] [Google Scholar]
13. 13.Mumusoglu S., Yildiz B.O. Polycystic ovary syndrome phenotypes and prevalence: Differential impact of diagnostic criteria and clinical versus unselected population. Curr. Opin. Endocr. Metab. Res. 2020;12:66–71. doi: 10.1016/j.coemr.2020.03.004. [DOI] [Google Scholar]
14. 14.Witchel S.F., Oberfield S.E., Peña A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment With Emphasis on Adolescent Girls. J. Endocr. Soc. 2019;3:1545–1573. doi: 10.1210/js.2019-00078. [DOI] [PMC free article] [PubMed] [Google Scholar]
15. 15.Ibáñez L., Oberfield S.E., Witchel S., Auchus R.J., Chang R.J., Codner E., Dabadghao P., Darendeliler F., Elbarbary N.S., Gambineri A., et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm. Res. Paediatr. 2017;88:371–395. doi: 10.1159/000479371. [DOI] [PubMed] [Google Scholar]
16. 16.Barrea L., Marzullo P., Muscogiuri G., Di Somma C., Scacchi M., Orio F., Aimaretti G., Colao A., Savastano S. Source and amount of carbohydrate in the diet and inflammation in women with polycystic ovary syndrome. Nutr. Res. Rev. 2018;31:291–301. doi: 10.1017/S0954422418000136. [DOI] [PubMed] [Google Scholar]
17. 17.Kanbour S.A., Dobs A.S. Hyperandrogenism in Women with Polycystic Ovarian Syndrome: Pathophysiology and Controversies. Androg. Clin. Res. Ther. 2022;3:22–30. doi: 10.1089/andro.2021.0020. [DOI] [Google Scholar]
18. 18.Bulsara J., Patel P., Soni A., Acharya S. A review: Brief insight into Polycystic Ovarian syndrome. Endocr. Metab. Sci. 2021;3:100085. doi: 10.1016/j.endmts.2021.100085. [DOI] [Google Scholar]
19. 19.Walters K.A., Gilchrist R.B., Ledger W.L., Teede H.J., Handelsman D.J., Campbell R.E. Metabolism. New perspectives on the pathogenesis of PCOS: Neuroendocrine origins. Trends Endocrinol. Metab. 2018;29:841–852. doi: 10.1016/j.tem.2018.08.005. [DOI] [PubMed] [Google Scholar]
20. 20.Ashraf S., Nabi M., Rasool S.u.A., Rashid F., Amin S. Hyperandrogenism in polycystic ovarian syndrome and role of CYP gene variants: A review. Egypt. J. Med. Hum. Genet. 2019;20:25. doi: 10.1186/s43042-019-0031-4. [DOI] [Google Scholar]
21. 21.Tsilchorozidou T., Honour J.W., Conway G.S. Altered cortisol metabolism in polycystic ovary syndrome: Insulin enhances 5alpha-reduction but not the elevated adrenal steroid production rates. J. Clin. Endocrinol. Metab. 2003;88:5907–5913. doi: 10.1210/jc.2003-030240. [DOI] [PubMed] [Google Scholar]
22. 22.Ding H., Zhang J., Zhang F., Zhang S., Chen X., Liang W., Xie Q. Resistance to the Insulin and Elevated Level of Androgen: A Major Cause of Polycystic Ovary Syndrome. Front. Endocrinol. 2021;12:741764. doi: 10.3389/fendo.2021.741764. [DOI] [PMC free article] [PubMed] [Google Scholar]
23. 23.Marshall J.C., Dunaif A. Should all women with PCOS be treated for insulin resistance? Fertil Steril. 2012;97:18–22. doi: 10.1016/j.fertnstert.2011.11.036. [DOI] [PMC free article] [PubMed] [Google Scholar]
24. 24.De Leo V., la Marca A., Petraglia F. Insulin-Lowering Agents in the Management of Polycystic Ovary Syndrome. Endocr. Rev. 2003;24:633–667. doi: 10.1210/er.2002-0015. [DOI] [PubMed] [Google Scholar]
25. 25.Kandaraki E., Chatzigeorgiou A., Livadas S., Palioura E., Economou F., Koutsilieris M., Palimeri S., Panidis D., Diamanti-Kandarakis E.

Endocrine disruptors and polycystic ovary syndrome (PCOS): Elevated serum levels of bisphenol A in women with PCOS. J. Clin. Endocrinol. Metab. 2011;96:E480–E484. doi: 10.1210/jc.2010-1658. [DOI] [PubMed] [Google Scholar]

26. 26.Takeuchi T., Tsutsumi O., Ikezuki Y., Takai Y., Taketani Y. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocr. J. 2004;51:165–169. doi: 10.1507/endocrj.51.165. [DOI] [PubMed] [Google Scholar]
27. 27.Konieczna A., Rachoń D., Owczarek K., Kubica P., Kowalewska A., Kudłak B., Wasik A., Namieśnik J. Serum bisphenol A concentrations correlate with serum testosterone levels in women with polycystic ovary syndrome. Reprod. Toxicol. 2018;82:32–37. doi: 10.1016/j.reprotox.2018.09.006. [DOI] [PubMed] [Google Scholar]
28. 28.Vagi S.J., Azziz-Baumgartner E., Sjödin A., Calafat A.M., Dumesic D., Gonzalez L., Kato K., Silva M.J., Ye X., Azziz R. Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol a in polycystic ovary syndrome: A case–control study. BMC Endocr. Disord. 2014;14:86. doi: 10.1186/1472-6823-14-86. [DOI] [PMC free article] [PubMed] [Google Scholar]
29. 29.Priya K., Setty M., Babu U.V., Pai K.S.R. Implications of environmental toxicants on ovarian follicles: How it can adversely affect the female fertility? Environ. Sci. Pollut. Res. 2021;28:67925–67939. doi: 10.1007/s11356-021-16489-4. [DOI] [PMC free article] [PubMed] [Google Scholar]
30. 30.Ananthasubramanian P., Ananth S., Kumaraguru S., Barathi S., Santosh W., Vasantharekha R. Associated Effects of Endocrine Disrupting Chemicals (EDCs) on Neuroendocrine Axes and Neurotransmitter Profile in Polycystic Ovarian Syndrome Condition. Proc. Zool. Soc. 2021;74:378–386. doi: 10.1007/s12595-021-00411-4. [DOI] [Google Scholar]
31. 31.Palioura E., Diamanti-Kandarakis E. Polycystic ovary syndrome (PCOS) and endocrine disrupting chemicals (EDCs) Rev. Endocr. Metab. Disord. 2015;16:365–371. doi: 10.1007/s11154-016-9326-7. [DOI] [PubMed] [Google Scholar]
32. 32.Rutkowska A.Z., Diamanti-Kandarakis E.J. Polycystic ovary syndrome and environmental toxins. Fertil. Steril. 2016;106:948–958. doi: 10.1016/j.fertnstert.2016.08.031. [DOI] [PubMed] [Google Scholar]
33. 33.Zhang B., Zhou W., Shi Y., Zhang J., Cui L., Chen Z.-J. Lifestyle and environmental contributions to ovulatory dysfunction in women of polycystic ovary syndrome. BMC Endocr. Disord. 2020;20:19. doi: 10.1186/s12902-020-0497-6. [DOI] [PMC free article] [PubMed] [Google Scholar]
34. Dr. Pankti Dalwadi, Dr. Nishkruti Mehta, Dr. Pragnesh Patani, A Review on Animal Models for Screening of Anti-Diabetic Drugs, Aegaeum Journal, Volume 8 (4), 2020
35. Dr. Pankti Dalwadi, Dr. Nishkruti Mehta, Dr. Pragnesh Patani, The Life Threatening Breast Cancer: A Review at Glance, Aegaeum Journal, Volume 8 (4), 2020
36. Jahanvi Goswami, Dr. Nishkruti Mehta, Dr. Pragnesh Patani, THE METAMORPHOSIS OF FAT LOSS: BARIARTIC SURGERY, NEUROQUANTOLOGY, 2022 | VOLUME 20 | ISSUE 15 | PAGE 3849-3862
37. Krutarth Akhani, Dr. Nishkruti Mehta, Dr. Pragnesh Patani, A COMPREHENSIVE REVIEW OF ACNE PREVENTION AND CONTROL WITH INDIAN HERBS, Journal of Population Therapeutics & Clinical Pharmacology, Volume 30, Issue 9, 2023.
38. Darshit Kumar, Dr. Nishkruti Mehta, Dr. Pragnesh Patani, Unlocking The Potential Of Hemoglobin Enhancement Agents: A Comprehensive Review, Journal of Advanced Zoology, Volume 44 Issue 05Year 2023 Page 01:12.
39. Luckyrajsinh Vaghela, Dr. Nishkruti Mehta, Dr. Pragnesh Patani, Marvels Of Natural Phytomedicines In Treatment Of Skin Issues: Natural Healthcare Perspective, Journal of Advanced Zoology, Volume 44 Issue 05Year 2023 Page 01:16.