

Review on Polycystic Ovarian Syndrome (PCOS) in Case of Pregnancy

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Abstract

Women with polycystic ovary syndrome (PCOS) have a higher risk of infertility, miscarriage, obesity, cardiovascular disease, diabetes mellitus, obstructive sleep apnea, depression, nonalcoholic fatty liver disease, endometrial hyperplasia, and cancer. Women with PCOS are more likely to undergo cesarean or c-section deliveries, which are associated with a high risk of early pregnancy loss. The most effective therapies for PCOS include regular exercise, a good diet, and weight management. In fact, the harmful consequences of obesity on reproductive potential can be reversed with effective therapy, whether or not there is insulin resistance. Based on the outcomes of trials conducted in recent years, this promise appears to be coming true.

Keywords: PCOS (Polycystic Ovarian Syndrome); polycystic ovary, infertility, reproductive age, gestational diabetes, early pregnancy loss, metformin.

INTRODUCTION

In 2023, PCOS is the most common female endocrine condition and the main contributor to infertility, with a global prevalence of 6-26% and a range of 3.7-22.5% in India. The majority of disorders that endanger women's health in the twenty-first century include PCOS/PCOD (Polycystic Ovarian Syndrome), which affects women between the ages of 18 and 44 while they are fertile.¹ When a woman has polycystic ovary syndrome (PCOS/PCOD), her hormones are out of balance. It may disrupt their menstrual cycles and make pregnancy more difficult. If left untreated, it can lead to serious health problems such as diabetes and heart disease. The majority of PCOS patients develop many small cysts on their ovaries. Due to this they refer to it as polycystic ovary syndrome. Though the cysts are not hazardous, they cause an imbalance in hormones. Early detection and treatment can aid in symptom control and shorten the term issues.²

A mature follicle, which is also a cystic structure, develops throughout a typical menstrual cycle that includes ovulation. A developed follicle that is prepared to ovulate measures between 18 and 28 mm in diameter. The main distinction between polycystic and normal ovaries is that, despite having a large number of tiny antral follicles with eggs inside of them, polycystic ovaries do not adequately develop and mature these follicles, which prevents ovulation. Women who have polycystic ovaries do not experience normal menstrual cycles because they do not ovulate on a regular basis.^{3,4} The male

hormones testosterone and androstenedione are frequently in excess in women with polycystic ovaries. High blood levels of testosterone cause increased face and body hair growth.^{2,5,6}

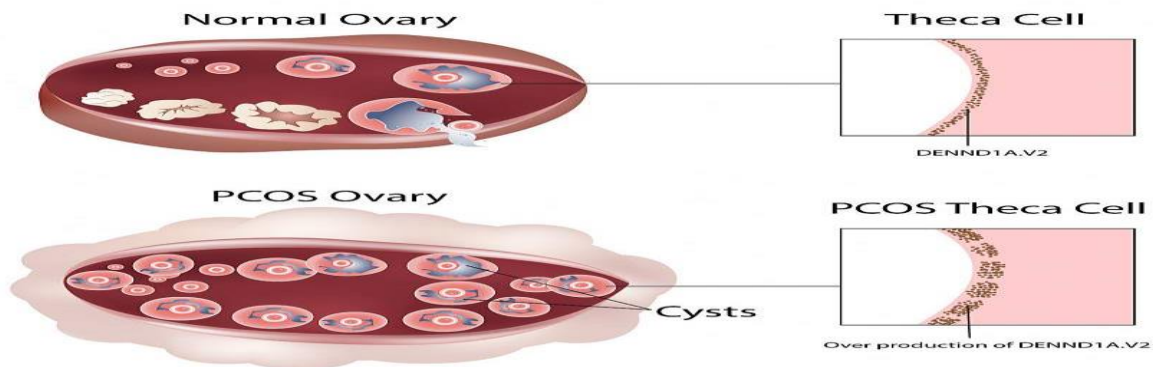


Fig:-Normal ovary - The egg normally develops inside a sphere known as a follicle. The follicle bursts and the egg is discharged when the egg is fully developed. PCOS ovary-Follicles that have PCOS fail to mature and develop cyst formations.

PROLIFERATION OF PCOS

The precise prevalence of PCOS is unknown because the syndrome is not well-defined and largely depends on the selection of diagnostic standards. According to the WHO, 116 million women (3.4% of women) worldwide were affected. According to a community-based prevalence survey that used the Rotterdam criteria, around 18% of women had PCOS, and 70% of them had never received a diagnosis. 8–25% of normal women have polycystic ovaries as detected by ultrasonography. Ovaries with polycystic growths were discovered in 14% of oral contraception users.⁷

Menstrual abnormalities in women with PCOS range from amenorrhea to menorrhagia, with a prevalence of 14.6 to 22.8% in the Indian context. Indians are known to have a high prevalence of insulin resistance, which is crucial to the pathophysiology of PCOS. Consequently, it is anticipated that a large percentage of Indians would have PCOS.⁸

The incidence is gradually rising in India. Due to the way that individuals live their lives, it has been reported that PCOS is becoming "epidemic" in Bangalore (Indian Express, 2013). Women and adolescents with PCOS have shown increased LH pulse amplitude and frequency, pointing to an abnormal pattern of hypothalamic gonadotropin-releasing hormone (GnRH) secretion as the likely cause.⁹

Approximately 5–10% of women of reproductive age experience symptoms related to PCOS. It is considered to be one of the main factors contributing to problems during pregnancy and female infertility. Amenorrhea, oligomenorrhea, dysfunctional uterine hemorrhage, acne, hirsutism, obesity, etc. are major symptoms. Because PCOS patients have a higher risk of infertility, miscarriage, obesity, cardiovascular disease, diabetes mellitus, obstructive sleep apnea, depression, nonalcoholic fatty liver disease, endometrial hyperplasia, endometrial cancer, etc., PCOS is a serious health concern. Anovulation causes infertility in 75% of cases. Diabetes can occur in up to 43.6% of people with the metabolic syndrome, as can depression in 40% of cases, hypertension issues, gestational diabetes, perinatal mortality, and multiple pregnancies following infertility therapy.¹⁰

In Andhra Pradesh, South India, 460 girls between the ages of 15 and 18 participated in a prospective study that determined the prevalence of PCOS in young people to be 9.13%. In the community from three different nations, the prevalence has been estimated to be between 4.0 and 11.9%, according to an

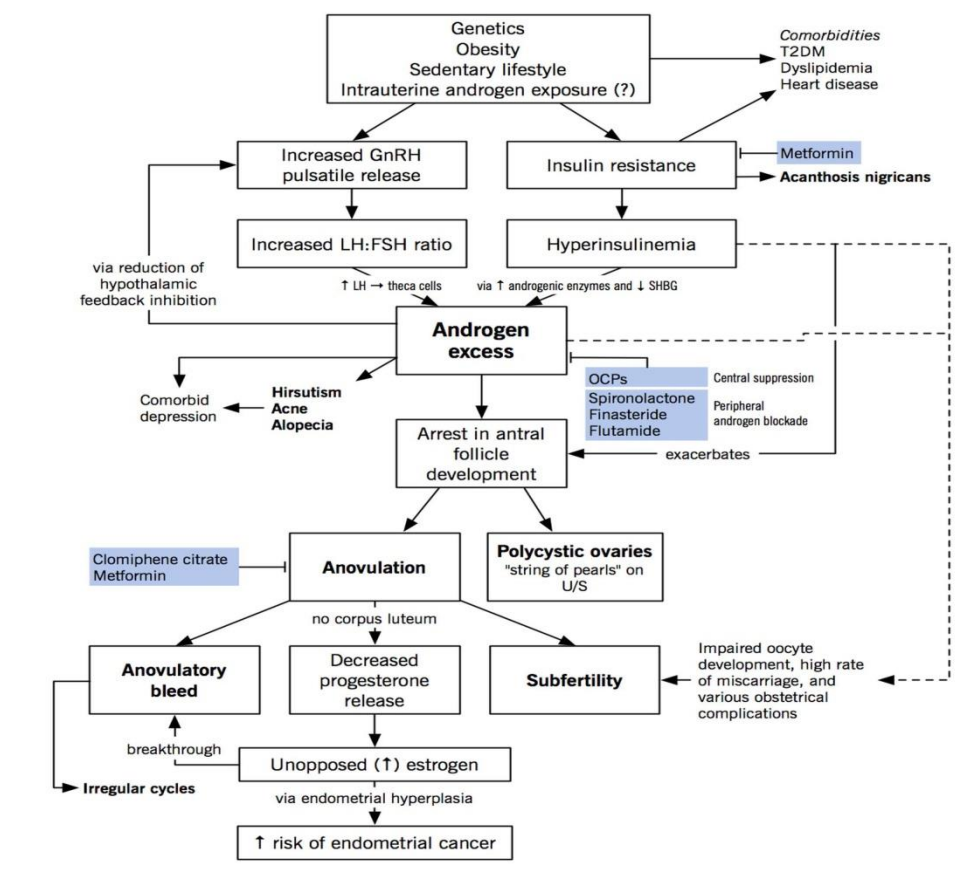
ovarian ultrasound investigation. According to a community-based prevalence survey that used the Rotterdam criteria, roughly 18% of women had PCOS, and 70% of them had never received a diagnosis.¹¹

AGE-WISE PROLIFERATION

According to age distribution research, PCOS was widespread among women of reproductive age. Beyond the age of 45, there were no PCOS patients to be detected. The age range of 15 to 24 years had the highest prevalence (i.e., 48%).¹²

Pathophysiology of PCOS

Alex Rotstein, Ragini Srinivasan, and Eric Wong



SIGNS AND SYMPTOMS OF PCOS

1. Menstrual disorders: Oligomenorrhea or amenorrhea are the most common symptoms of PCOS.
2. Infertility: Chronic anovulation is typically the direct cause of this.
3. Hyperandrogenism is another term for high levels of hormones that promote masculinity. Acne and hirsutism are the typical symptoms, although it can also cause hypermenorrhea, androgenic alopecia, or other symptoms.
4. The symptoms of the metabolic syndrome include a propensity for central obesity and other signs of insulin resistance. Women with PCOS had elevated serum levels of homo cysteine, insulin, and insulin resistance.¹⁰

CAUSES OF PCOS

1. **SUGARY FOODS:-** Many PCOS patients have elevated insulin levels. This may make it challenging to lose weight. They can reduce their chances of developing diabetes and lose weight by consuming fewer sweets and simple carbohydrates.
2. White flour is a simple carbohydrate that the majority of PCOS sufferers should avoid. White flour is frequently used in baked items such as breads, bagels, cereals, muffins, and cupcakes.
3. **SODIUM-RICH FOODS:** PCOS patients should keep their daily sodium intake to a maximum of 2,300 mg, or to be on the safe side, 1,500 mg. Foods high in sodium should be avoided, such as smoked meats, canned vegetables, chips, sauces, salted nuts, and canned soups.
4. Saturated fats, meats, fat-free dairy, fat-free dressing, white meat, and skinless chicken should all be avoided by PCOS patients. To reduce the amount of oil used, cook food by steaming, broiling, baking, grilling, or microwaving it.^{7,13}

PCOS - Related Pregnancy Complications Include

1. Early pregnancy loss or miscarriage: Women with PCOS are three times more likely than women without PCOS to miscarry in the first trimester.
2. Only pregnant women can get K diabetes, a specific kind of diabetes. It can be treated, and if it is under control, neither the mother nor the fetus experience serious consequences.
3. Preeclampsia is a condition that occurs after the 12th week of pregnancy and causes an abrupt rise in blood pressure. It can harm the mother's kidneys, liver, and brain. Preeclampsia can develop into eclampsia if neglected. Organ damage, seizures, and even death can result from eclampsia.
4. Infants are referred to as "preterm" if they are born before 37 weeks of pregnancy.
5. Pregnant women with PCOS are more likely to undergo cesarean or c-section deliveries. Recovery from a c-section delivery can take longer than from a vaginal birth, and there are dangers involved for both the mother and the child.^{2,5,14}

DIAGNOSIS OF PCOS

PCOS is a complex condition that is typically diagnosed by the presence of two of the three following criteria: oligo- or anovulation. Hyperthyroidism, hypothyroidism, hyperprolactinemia, hypogonadotropic hypogonadism, and suboptimal ovarian dissatisfaction must also be avoided. If hirsutism is present along with peace, exogenous androgen use as well as late-onset naturally occurring adrenal hyperplasia, androgen-emitting ovarian tumors, androgen-discharging adrenal tumors, Cushing disease, and other conditions must be prohibited.²⁹ Pathognomonic ovarian endings and the clinical combination of hirsutism, amenorrhea, and chunkiness were necessary for assurance.³⁰ Thirty years later, in the late 1960s and early 1970s, researchers recognized abnormalities in the hypothalamic-pituitary pivot. This was the next symptomatic defining point.

Hyperandrogenism: One important component of PCOS is hyperandrogenism. Although the adrenal gland may play a role, hyperandrogenism in women with a primary diagnosis of PCOS primarily has an ovarian origin. Serum androgen levels have been reported to be elevated in the majority of PCOS-affected women among populations around the world, however some women may have normal levels. It

is sufficient to have elevated serum androgen levels or an organic manifestation of hyperandrogenism (skin breakout or hirsutism) for an analysis of PCOS.³²

Heftiness: Between 40% and 50% of PCOS women are overweight. With enlarged midsection to hip proportions, this mass is often of the android kind. When present, obesity increases the risk for diabetes and cardiovascular disease by aggravating insulin blockage. For women with PCOS, preventive social insurance should place a significant emphasis on the treatment of obesity. But with these people, weight loss is challenging to achieve. Due to the debilitation of adiposity lipolysis, which is consequently linked to insulin blockage, this may only be anticipated to a certain extent.³³

The Ovarian Diagnosis: Effective analysis of the polycystic ovary is performed. It is encircled by an enlarged stromal mass (25% of the ovarian capacity), and is frequently larger than 9 mL with more than 8 mL incidentally located cystic structures (10 mm). Even still, there is a sonographic range even if we and others have requested these stringent standards. Some women with PCOS may not have polycystic ovaries despite having the bulk of the other excellent clinical characteristics.³⁴ A thorough history and physical examination should be the first steps in the symptomatic workup. Clinicians should focus on the patient's menstrual history, any changes in the patient's weight and how these may affect PCOS symptoms, and any coincidental findings (such as terminal hair, skin breakouts, alopecia, Nigerian acanthosis, and skin labeling). Additionally, patients should get knowledge on factors related to PCOS's basic co-morbidities.³⁵ According to the Rotterdam criteria, the presence of at least two of the additional three findings—hyperandrogenism, ovulatory brokenness, and polycystic ovaries—must be close by. Finding polycystic ovaries requires only one ovary that fits one of these categories, if not both.³⁴

FEATURES OF THE DIAGNOSIS OF PCOS⁴⁵

Feature	Recommended Diagnosis	Considerations
Biochemical Hyperandrogenism	<ul style="list-style-type: none"> Increased levels of total or free testosterone, or computed free testosterone indices (FAI, BioT). DHEAS and ANSD may be taken into account. 	The examination of analytes should utilize high-quality assays.
Clinical Hyperandrogenism	<ul style="list-style-type: none"> Modified Ferriman-Gallwey score between four and eight 	In the context of p, threshold level should be taken into account.
Oligo-anovulation	<ul style="list-style-type: none"> Oligo-amenorrhea (8 menses a year or periods more than 35 days apart) 	If PCOS is highly suspected but oligo-amenorrhea is not present, serum progesterone or luteinizing hormone testing may be an option.
Polycystic ovarian morphology	<ul style="list-style-type: none"> 20 or less follicles in each ovary Ovarian volume of 10 cm³. 	Using transvaginal ultrasound with a transducer frequency of less than 8 MHz

Norms based on the 2003 Rotterdam criteria as updated. BioT stands for "bioavailable testosterone," DHEAS for "dehydroepiandrosterone sulfate," and ANSD for "androstenedione."⁴⁵

Prevention Of PCOS In Young Females

The most effective therapies for PCOD include regular exercise, a good diet, and weight management.

1. Try to schedule frequent periods of strenuous and/or moderate exercise. Most folks can walk, which is a fantastic kind of exercise.
2. Consume heart-healthy food. This includes a lot of whole grains, nuts, legumes, and fruits and vegetables. It restricts meals including meats, cheeses, and fried items that are high in saturated fat.
3. Most PCOD sufferers can gain by losing weight. Even a 10-pound (4.5-kg) weight loss may help balance your hormones and control your menstrual cycle.
4. Give up smoking.
5. A doctor may also recommend Metformin, which helps to regulate menstrual periods, or fertility medications if a woman is having problems conceiving in order to alleviate symptoms.
6. Treatments for symptoms like facial hair or acne may not work right away. For acne, patients have access to both over-the-counter and prescription medications.
7. Managing PCOD can be challenging. If a patient is feeling down or depressed, talking to a therapist or other women who have PCOD or other comparable clinical disorders may be helpful.^{11,14,15}

Recommended methods of therapy for PCOS to lessen early pregnancy loss

METFORMIN

A biguanide oral anti-diabetic medication called metformin is able to lower insulin levels and, as a result, PAI-1 levels without altering normal glucose levels. Additionally, it appears to have the power to improve uterine vascularity and blood flow, lower plasma endothelin-1 levels, raise luteal-phase serum glycodelin concentrations, decrease androgen and LH concentrations, and even cause weight reduction in some people. These characteristics would point to its potential clinical utility in preventing early pregnancy loss in PCOS, and based on the outcomes of trials conducted in recent years, this promise appears to be coming true.

In the biggest documented study, metformin was used to treat 328 pregnancies prior to and during pregnancy, and had a 20% probability of early pregnancy loss in contrast to 319 previous pregnancies without metformin treatment in which the baby was born prematurely 65% loss rate. In a second retrospective series, metformin was given to 65 women during pregnancy, and 8.8% of women miscarried compared to 42% in a 31 participants made up the control group. Even if these studies were retrospective and only included a small number of patients, they at the very least call for further research in properly conducted, randomized prospective trials. The use of metformin against laparoscopic ovarian diathermy of the ovaries for overweight, clomiphene-resistant PCOS women was the first of two such trials, carried out by Palomba et al. The second experiment evaluated metformin versus clomiphene for non-obese, anovulatory PCOS. The noteworthy aspect of both trials was the finding that metformin produced a higher live birth rate than its "opponents" because, in both series, despite identical pregnancy rates, metformin's early pregnancy loss rates were much lower.

The overwhelming body of research indicates that metformin is safe when used during pregnancy because there hasn't been a rise in teratogenicity, congenital abnormalities, or harmful effects on baby

development. Metformin has been placed in FDA pregnancy category B due to its apparent lack of teratogenicity. According to preliminary research, this approach of taking metformin continuously during pregnancy may dramatically lower the high rate of miscarriage that is typically linked to PCOS and even lower the occurrence of gestational diabetes, pre-eclampsia, and fetal macrosomia. However, it must be noted that if metformin is stopped after a pregnancy has been established, it would appear that the same impact may be obtained in terms of early pregnancy loss.¹⁶⁻²⁶

MODIFICATION IN LIFE STYLE

More than half of PCOS patients are overweight or obese³⁶, so weight loss is the main recommendation for PCOS patients since it can increase metabolism, enhance insulin sensitivity, and facilitate weight loss safely.³⁷ PCOS patients are fat, have high blood cholesterol levels, and have hormonal irregularities. It is crucial to realize that exercise by itself will never be sufficient to aid in weight loss. A good diet is more crucial than everything else. Diet is rarely a top concern for Indian women. Protein and fiber should make up one gram per kilogram of body weight of a healthy diet. It should be emphasized that a 30% calorie deficit, or 500–750 kcal per day (1200–1500 kcal per day), must be achieved. People who are overweight can lose weight, and women with PCOS who are infertile have irregular ovulation and are more receptive to ovulation induction medications, which increases the likelihood of pregnancy and live birth. Research indicates that losing up to 5% of one's starting weight can aid in reestablishing regular menstruation and enhance the response to ovulation and reproductive drugs.³⁸

GENETICS

In terms of genetics, the strong correlation between PCOS susceptibility variants in the meta-analysis of genome-wide association (GWAS) data using the key PCOS-associated variables, ovulatory dysfunction (OD), hyperandrogenism (HA), and polycystic ovarian morphology (PCOM), supported the notion that different variations can lead to PCOS through various mechanisms.³⁸

OVULATION INDUCER

Because 70% of women with PCOS experience dysovulation or no ovulation, ovulation induction is the cornerstone of treatment for infertile PCOS patients who desire to get pregnant.³⁸

Clomiphene citrate is a serotonin receptor modulator (SERM)

The preferred medication for ovulation induction in teenagers with polycystic ovarian syndrome is clomid citrate (CC).³⁹ CC functions as an anti-estrogen by blocking estrogen receptors in the hypothalamus, increasing the pulse width of gonadotropin-releasing hormone (GnRH) in the anterior pituitary and boosting the synthesis of follicle-stimulating hormone (FSH). Follicle formation is aided by the hormone luteinizing hormone (LH). Between the second and fifth day of the period, CC is typically administered for five days, starting at 50 mg per day and gradually increasing to 150 mg per day. For women with PCOS who are resistant to CC, CC can be given in addition to metformin (conditional evidence-based recommendations, moderate-quality data). About 30% of successful pregnancies are caused by clomid, while 20% of these pregnancies result in miscarriage or stillbirth. Ovarian enlargement, hyperstimulation syndrome, fatigue, gas bloating and multiple pregnancies are side effects.⁴⁰

Aromatase inhibitors (AI)-letrozole

Androgens are converted to estrogen via aromatase. Letrozole is the most used non-steroidal selective AI for ovulation induction in the third generation. Ovarian estradiol secretion is inhibited by letrozole. When the pituitary secretes more FSH, the follicles become more sensitive to it, increasing the ovulation rate. Negative feedback from the hypothalamus and a brief increase in androgens in the ovary are to blame for this.³⁹

GONADOTROPINS

For women with anovulatory PCOS, gonadotropin therapy. Consider this as a second-line alternative, such as AI and SERM, for patients who have not responded to first-line oral ovulation stimulation medications.⁴⁰

INSULIN SENSITIZING AGENTS

PCOS patients have abnormal insulin secretion and function. Insulin resistance and hyperinsulinemia have long been linked to elevated androgen levels in PCOS patients. Ovarian health is impacted by high insulin levels, which regulate ovarian function. As a result of excessive insulin production in muscle cells, follicular growth is delayed, leading to the polycystic ovarian shape that is a hallmark of PCOS. Acanthosis nigricans has been used for a long time to denote insulin resistance. Patients with PCOS who have insulin resistance are more susceptible to long-term health problems such type 2 diabetes and cardiovascular disease, both of which can be fatal.⁴⁰ Therefore, it is crucial for PCOS therapy to address insulin resistance with drugs and lifestyle changes.⁴¹

Acanthosis nigricans is a typical indicator of insulin resistance. Long-term insulin resistance may result in harmful systemic consequences. As a result, PCOS therapy must include medication and lifestyle adjustments to address insulin resistance.⁴²

ANTIANDROGENS

Antigens that involve spiro lactone, flutamide, and finasteride treat PCOS patients with hirsutism and acne. These antigens could help those with high lipid levels, which are typical in PCOS patients. The effects of flutamide 250 mg, finasteride 5 mg, and spironolactone 100 mg were studied for six months in 40 hirsute women.⁴²

MEDICATIONS TO WEIGHT LOSS

In women with PCOS, being overweight or openly obese, which amplifies insulin resistance, has a significant impact on miscarriage rates. Therefore, it would be expected that losing weight before getting pregnant by a lifestyle change would lower the likelihood of early pregnancy loss. In fact, the harmful consequences of obesity on reproductive potential can be reversed with effective therapy, whether or not there is insulin resistance. In a research looking at the impact of a change in lifestyle program on 67 anovulatory, obese (BMI>30) women who had been trying to get pregnant for at least two years without success with traditional treatment, the mean weight loss after six months was 10.2 kg. Following the weight decrease, 67 of the women regained ovulation, and 52 of them got pregnant—18 of them naturally. The most significant difference was that only 18% of these pregnancies ended in miscarriage, compared to a miscarriage incidence of 75% in conceptions obtained before to weight loss.^{27,28}

ORLISTAT

A lipase inhibitor called orlistat reduces the absorption of dietary fat by preventing the breakdown of triglycerides in the pancreas and stomach. Orlistat is a weight-loss drug that has been demonstrated to be beneficial, while some have questioned its efficacy. In a study comparing the effects of orlistat vs. metformin treatment on biochemical and hormonal variables in women with PCOS, orlistat treatment resulted in statistically significant reductions in body weight and blood levels. Levels of androgen are higher than those of metformin.⁴³

SIBUTRAMINE

Sibutramine, an appetite suppressant, is used to treat obesity together with dietary and lifestyle modifications. It prevents monoamines from reuptaking. It blocks the absorption of neurotransmitters like serotonin, norepinephrine, and dopamine.⁴⁴

DISCUSSION

PCOS is a problem that affects a growing number of women of reproductive age and is complicated clinically with lifetime difficulties. The vague diagnostic criteria and the extraordinarily complicated nature of this syndrome's features present the greatest challenges. It will be easier to control PCOS overall, lessen comorbidities, and boost quality of life if individualized therapy options are used in a timely manner. The prognosis of infertility in females who may encounter it during their reproductive years can be improved with early detection and treatment. The early detection and screening of PCOS subtypes may benefit from key gene polymorphisms. To find both efficient preventive measures and therapeutic options, additional research on the genetics and pathophysiology of PCOS will be required. Further investigation is necessary to determine whether steroid variations and the mechanisms underlying them in PCOS patients influence the makeup of gut microorganisms. Prebiotic, probiotic, and synbiotic supplementation appears to enhance a number of biochemical outcomes and have positive benefits on women with PCOS, while the underlying mechanisms are yet understood. The importance of these drugs in PCOS therapy or perhaps prevention requires further study. To understand the processes behind the link between gut microbiota dysbiosis and PCOS, randomized clinical trials are required. The targeted, individualized alteration of gut microbiota will progress the research, and complete, functional research in the future will enable the use of gut microbiota as a biomarker for PCOS. Since treatments have been focused on symptoms rather than the underlying cause of the illness, there is currently no cure. To improve treatment and prevent the catastrophic long-term effects of the disease on patients' health, extensive efforts should be made to completely investigate the syndrome. The management of the metabolic features of PCOS may benefit directly from a number of developing medications for T2DM; however, clinical trials are required to assess the clinical efficacy and safety of these medicines in PCOS-affected individuals. To demonstrate the efficacy of new medicines, such miRNA therapy, IL-22 therapy, and other therapies, in effectively treating PCOS, more research is necessary.

CONCLUSION

Hormonal imbalance is a key feature of the complicated disorder known as polycystic ovarian syndrome, which frequently causes irregular periods, ovarian cysts, and other metabolic problems. While the precise etiology is yet unknown, genetic and environmental factors are involved. Many different symptoms that can impact cardiovascular, metabolic, and reproductive health can be experienced. Analyzing symptoms, medical history, and test results to rule out other diagnoses are all part of the diagnosis process.

Along with drugs that target symptoms, management entails modifying one's lifestyle, such as nutrition and exercise. If you're attempting to get pregnant, fertility treatments can be necessary. Diabetes, heart disease, and endometrial cancer risk are among the long-term effects. Anxiety and despair are two additional psychological side effects of PCOS. In conclusion, PCOS is a complex disorder with a range of consequences that necessitates a varied strategy to care and ongoing medical research.

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