

Polycystic Ovarian Syndrome: A Comprehensive Review of Mechanisms and Management Strategies

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Abstract- Polycystic ovarian syndrome is a prevalent endocrine condition that affects females, especially in their reproductive years. It is characterized by a wide range of symptoms, including irregular menstrual periods, hyperandrogenism, and metabolic abnormalities. This review article offers a thorough summary of the state of knowledge about PCOS, including its complex pathophysiology, range of clinical manifestations, and changing diagnostic standards. In this article, we will come to know about the complex interactions between genetic, environmental, and hormonal factors that lead to the development of PCOS. We will also get the insights about the connection between metabolic comorbidities like insulin resistance and cardiovascular risks and PCOS. A review of therapeutic approaches is also provided with a focus on the customized care that is necessary for PCOS patients to get the best possible results. These methods include lifestyle changes, medication interventions and assisted reproductive technologies. The goal of this review work is to give academics, physicians, and other healthcare professionals a more precise understanding of PCOS so they can improve patient treatment and diagnostic accuracy.

Keywords: Pregnancy, infertility, hyperandrogenism, ovulatory dysfunction, hirsutism.

I. INTRODUCTION

5-20% of women in this world, who are fertile, suffer from polycystic ovarian syndrome, also known as PCOS. The main characteristics of this disorder are hyperandrogenism and ovulatory dysfunction. Excessive androgen production by the ovaries is a major aspect of PCOS. Most people who are affected by PCOS have metabolic dysfunction, which is marked by hyperinsulinemia and insulin resistance. PCOS enhances the risk of endometrial cancer, venous thromboembolism, cerebrovascular and cardiovascular events, type 2 diabetes mellitus, gestational diabetes, and other pregnancy-related problems. PCOS requires customized treatment for each patient according to her needs and complaints, focusing on her lifestyle, metabolic imbalances, psychological needs, hormonal imbalance etc.^[1]

PCOS has become very common nowadays. Nearly, one female in each household is suffering with PCOS. Thus, this topic needs urgent attention. It is the high time that women, healthcare professionals try to research on this concern and take the required action. Studies conducted in Greece, Spain, and the USA has estimated that the prevalence of PCOS is between 4% and 8%.^[2] Hormonal imbalances are the leading cause of ovarian follicular arrest, infertility, and metabolic abnormalities. According to histology, a cyst is a fluid-filled, epithelial-lined sac that is typically larger than 2 cm. The ovaries are often enlarged in PCOS and contain many follicles, which are usually smaller than 8 mm in size and lack epithelium lining in them. Despite so much advancement, only ultrasonography is a method that is commonly used to diagnose and evaluate the ovaries during PCOS condition, which is still unreliable.^[3]

Stein and Leventhal (1935) recognized oligomenorrhea, infertility, hirsutism, and bilateral enlarged polycystic ovaries as a distinct entity and named the syndrome after themselves. In the 1960s, the diagnosis of Stein-Leventhal syndrome was replaced by the term "polycystic ovary syndrome," or PCOS. As the cyst are larger in number, multifollicular term was found to be more accurate but it was replaced by the term "polycystic" to make it more precise. Follicle excess is the primary feature of polycystic ovarian morphology (PCOM) since the development of ultrasonography.^[4]

II. HISTORICAL CONTEXT

Hippocrates wrote about two women who had beards in 400 B.C. One of them suffered menopause after that and passed away. Other one gave birth and then suffered from hirsutism. During the middle Ages, hirsutism and menstruation dysfunction were considered normal. It was Stein and Leventhal who initially identified the polycystic/sclerocystic ovaries, hirsutism, and amenorrhea clustering. When Janet MacArthur, Joseph W. Goldzieher, and others started researching on PCOS in the late 1950s and early 1960s, the syndrome was first extensively characterized in women. A few characteristics of PCOS, including insulin resistance and larger ovaries were highlighted in the research.^[5, 6] The condition of PCOS was originally studied by Italian scientist Vallisneri in 1721.

Numerous studies were conducted and numerous scientists attempted to explain the pathophysiology of PCOS. [7] Genetics is also considered as a contributing factor for PCOS. PCOS affected women who also have hyperandrogenism are known to show insulin resistance and also, women with PCOS have higher risk of cardiovascular diseases and metabolic abnormalities. [8]

III. EPIDEMIOLOGY AND RISK FACTORS

PCOS is one of the most prevalent endocrine/metabolic disorders that affect women. The main characteristics of PCOS are excess androgen, ovulatory failure and polycystic ovaries. Hyperandrogenism is also known as androgen excess, which can be identified by clinical examination and laboratory testing by measuring androgen levels. Ovulatory dysfunction can also be identified by oligo-amenorrhea and oligo-anovulation. Pathological examination and ultrasonography is also used to evaluate the polycystic ovaries. [9, 10] PCOS is also identified by excessive facial and body hair, acne and hirsutism. Irregular menstruation is also a mark for PCOS shift. [11, 12]

PCOS has also been linked to obesity, insulin resistance, diabetes and oligo-ovulatory infertility. Family history is also one of the risk factors for the occurrence of this disease. The primary symptom of PCOS includes abnormal weight gain which can be reversed by maintaining a healthy lifestyle which reduces belly fat, testosterone levels, and hirsutism and increases the insulin. Type 2 diabetes and poor glucose tolerance are more common in people with PCOS. The risk of dyslipidemia is also found to be high during PCOS. Reduced high density lipoprotein-cholesterol (HDL-C), elevated triglycerides, and elevated low density lipoprotein-cholesterol (LDL-C) are examples of lipid abnormalities.

IV. ETIOLOGY AND PATHOGENESIS

Various pathogenic mechanisms of PCOS include abnormal gonadotropin-releasing hormone, increased luteinizing hormone, decreased follicle stimulating hormone, decreased ovarian follicle response, increased anti-Mullerian hormone, follicular arrest and increased secretion of testosterone and estradiol. Adipocyte malfunction is responsible for the obesity and abnormal weight gain during PCOS. [13, 14] The etiology of PCOS is also influenced by epigenetic programming. In many species, prenatal androgen treatment is a powerful inducer of epigenetic modifications that results in PCOS models. [15, 16] The actual cause of PCOS is still unknown, but it is thought to be a combination of various hormonal, environmental and genetic variables. Some of the factors involved are given below: [17]

- Genetic factors - PCOS is more common in women who have a family history of the disorder. The onset of PCOS may be influenced by certain genes linked to inflammation, hormone synthesis, and insulin control. [18]

- Disproportions in Hormones:

Insulin Resistance: It happens when increased insulin levels result from the body's cells losing their sensitivity to the effects of insulin. This may encourage the production of more androgens or male hormones, by the ovaries.

Hyperandrogenism: The elevated amounts of androgens not only interfere with regular menstrual cycle but the hormonal imbalance can also cause ovarian cysts. Elevated LH (luteinizing hormone): This causes the abnormal formation of ovarian follicles. [19]

- Environmental Elements:

Lifestyle and Diet: Lazy lifestyle and heavy diet lead to insulin resistance, obesity and hormonal imbalances which in turn causes PCOS.

Environmental Endocrine Disruptors: Environment pollutants like the endocrine disrupting chemicals alter the hormones and thus they contribute towards PCOS. [20]

- Inflammatory response: Inflammation leads to insulin resistance and thus it can also interfere with the normal ovarian function

- Ovarian deficiency and follicular development: PCOS causes a disturbance in the regular process of follicular development, which results in formation of several small sized cysts on the ovaries. [17,21]

- Anovulation: Menstrual abnormalities and fertility issues can arise from irregular or absence of ovulation, which is a common in women with PCOS. [22]

PCOS is a heterogeneous disorder, i.e. different people suffering from this disease will have different types and combinations of symptoms. Due to this complicated nature of the disease, individualized methods are required for diagnosis and treatment because each patient differs in genetic predisposition, hormonal abnormalities and environmental factors. [23] Formation of cysts is a sign of ovarian dysfunction which is caused by the interruption of follicular development. [25]

PCOS is often linked to chronic low-grade inflammation, which is known to worsen ovarian dysfunction and insulin resistance. [26] The combination and interaction of environmental, hormonal, metabolic and hereditary factors influence the occurrence of PCOS and this also decides its treatment. Drugs that target hormonal imbalances are often targeted during PCOS in addition to exercise and dietary changes so that symptoms can be cured because there is no full cure

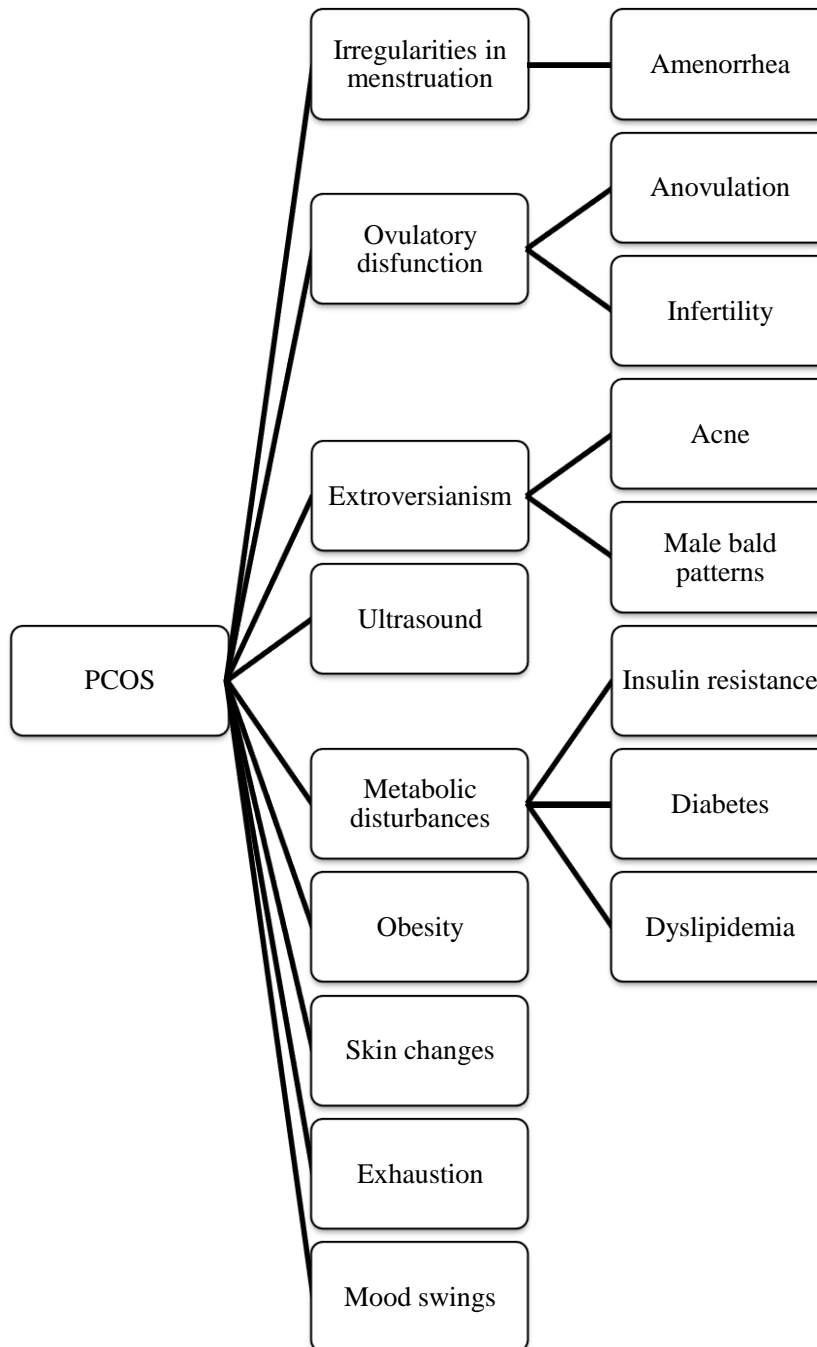
of PCOS yet.^[27] It is essential to study and understand the complex pathophysiology of PCOS in order to create individualized and efficacious treatment plans.^[28, 29]

V. CLINICAL FEATURES

PCOS is not same for all. As we have discussed previously that the symptoms of PCOS are not shared by all the patients, they differ individually patient to patient and thus require customized care.^[30] Usually, a combination of clinical, biochemical, and imaging results are used to diagnose PCOS. The most typical clinical features of PCOS are mentioned in Fig. 1.

- Irregularities in menstruation: PCOS may cause irregularity in menstrual cycles or amenorrhea i.e. a few months without menstrual cycle.^[31]
- Ovulatory Dysfunction: Infertility or anovulation i.e. inconsistent ovulation may occur.^[32]
- Extroversionism: Excessive hair growth on the back, chest, abdomen, or face is known as hirsutism. Acne or male pattern baldness is also seen in women with PCOS.
- Polycystic Ovaries on Imaging: PCOS can be diagnosed with the help of ultrasonography where cyst are small sized and can be seen on imaging.^[33]
- Disturbances in Metabolism: PCOS accompanies insulin resistance, high risk of type-2 diabetes and excessive blood lipid levels.^[34]
- Obesity: Abnormal weight gain is the primary symptom of PCOS.^[35]
- Other Symptoms: Skin changes like darkening of the skin in body folds, fatigue, mood swings like anxiety or depression are also associated with this disease.^[36]

PCOS increases the risk of chronic conditions such type 2 diabetes, cardiovascular disease, and endometrial cancer.^[37] As soon as any symptom is visible, one should immediately consult a physician so as to take proper advice and control it on an earlier stage. Late diagnosis means no cure.^[38]

FIGURE 1 CLINICAL FEATURE OF PCOS

VI. DIAGNOSIS

A combination of clinical, laboratory, and imaging evaluations are used to diagnose polycystic ovarian syndrome. PCOS diagnosis usually includes the following:

Clinical Assessment:

Medical History: Menstrual history, androgen excess symptoms (e.g., acne, hirsutism), and other pertinent medical issues will be questioned by the healthcare practitioner. ^[39]

Physical examination: This involves evaluating the symptoms of excess androgen, such as acne, hirsutism, and male-pattern baldness.

Laboratory Examinations:

Hormone Levels: Blood tests are used to determine the levels of certain hormones, such as testosterone, FSH, LH, SHBG, Estradiol, and Prolactin. ^[40]

Insulin Resistance: Insulin resistance can be evaluated by measuring insulin and fasting glucose levels.

Lipid Profile: Triglycerides and cholesterol levels in the blood may be measured. ^[41]

Imaging Research:

Pelvic Ultrasound: To see the ovaries, transvaginal ultrasonography is frequently used. ^[42]

Diagnostic Standards:

Meeting certain criteria is often the basis for PCOS diagnosis. For instance, the Rotterdam requirements demand that at least two of these must be present- anovulation or oligoovulation, signs of hyperandrogenism or ultrasound of polycystic ovaries. ^[43, 44]

Only early diagnosis and treatment can help to reverse the long term health issues associated with PCOS, so necessary test and examination must be carried out once symptoms are noticed. ^[45]

VII. SUBTYPES AND VARIABILITY

As PCOS presents itself in wide variety of ways from person to person, different subtypes of PCOS have been identified. ^[46] The two broad subtypes of PCOS are given below:

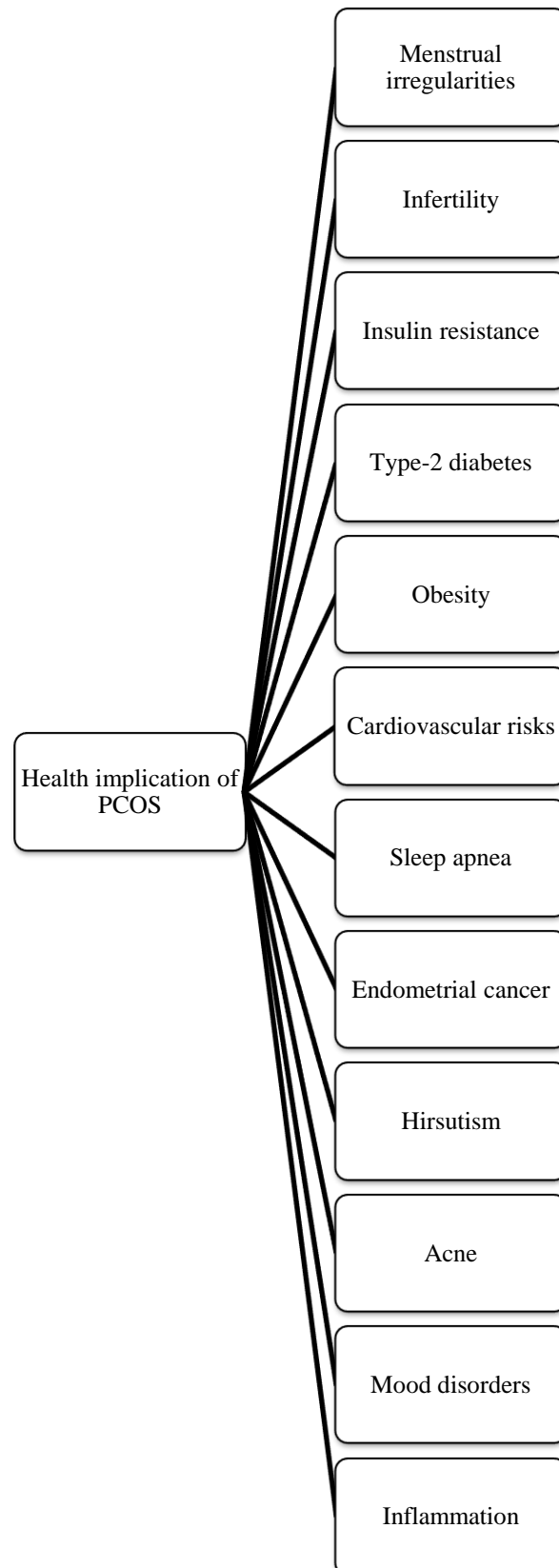
Classical PCOS: Major characteristic features of this subtype are anovulation and hyperandrogenism. Examples of such characteristics include acne, irregular menstruation, hirsutism and polycystic ovaries on ultrasonography. ^[47] The level of LH is higher than the level of FSH in those women who are suffering from classical PCOS. Classical PCOS is also interlinked with insulin resistance. ^[48]

Non-classical or Ovulatory PCOS: In this subtype, menstrual abnormalities do not show noticeable symptoms. Women experience regular menstruation but simultaneously they suffer from acne and hirsutism. ^[49]

Symptoms of PCOS depend on the genetics, lifestyle and environment. As the age of women increases, the symptoms and physical characteristics also changes. ^[50, 51] PCOS is very complex and unpredictable. Simple lifestyle changes like having low fat diet, yoga, exercise, less oily food and less junk food can help to treat and control certain symptoms like obesity. It also helps in managing the hormonal abnormalities. ^[52, 53] Medical help should be seek to have an accurate diagnosis and an endocrinologist or gynecologist must be consulted ^[54]

VIII. HEALTH IMPLICATIONS

Polycystic Ovary Syndrome (PCOS) is associated with both physical and psychological health implications. ^[55] The health implications of PCOS are provided in Fig.2.

FIGURE 2 HEALTH IMPLICATIONS OF PCOS

Menstrual Irregularities: PCOS causes infrequent periods to heavy and prolonged bleeding. Sometimes, it also causes amenorrhea. ^[56]

Infertility: PCOS causes irregular ovulation or lack of ovulation because it interferes with menstrual cycle and the release of eggs from the ovaries. ^[57]

Insulin Resistance and Type 2 Diabetes: PCOS cause insulin resistance and thus body cells are not able to respond to insulin. Thus, the insulin levels are elevated and diabetes occurs. ^[58]

Obesity: PCOS causes obesity which further leads to metabolic abnormalities and cardiovascular problems. ^[59]

Cardiovascular Risks: PCOS increases the risk of cardiovascular diseases such as hypertension, dyslipidemia (abnormal levels of cholesterol and triglycerides), and atherosclerosis (hardening of the arteries).

Sleep Apnea: Sleep apnea refers to the interruption of breathing during sleep, which is also caused by PCOS.

Endometrial Cancer: Prolonged exposure to unopposed estrogen (due to anovulation and irregular menstrual cycles) may increase the risk of endometrial hyperplasia and, subsequently, endometrial cancer. ^[60]

Hirsutism and Acne: Elevated androgen levels in PCOS can lead to symptoms such as hirsutism (excessive hair growth, often in areas where men typically grow hair) and acne.

Mood Disorders: PCOS increases the risk of mood disorders, including depression and anxiety. The hormonal fluctuations and the impact of symptoms on body image can contribute to these mental health concerns.

Inflammation: Chronic low-grade inflammation is often present in individuals with PCOS, and it may contribute to various health issues, including cardiovascular problems and insulin resistance. ^[61]

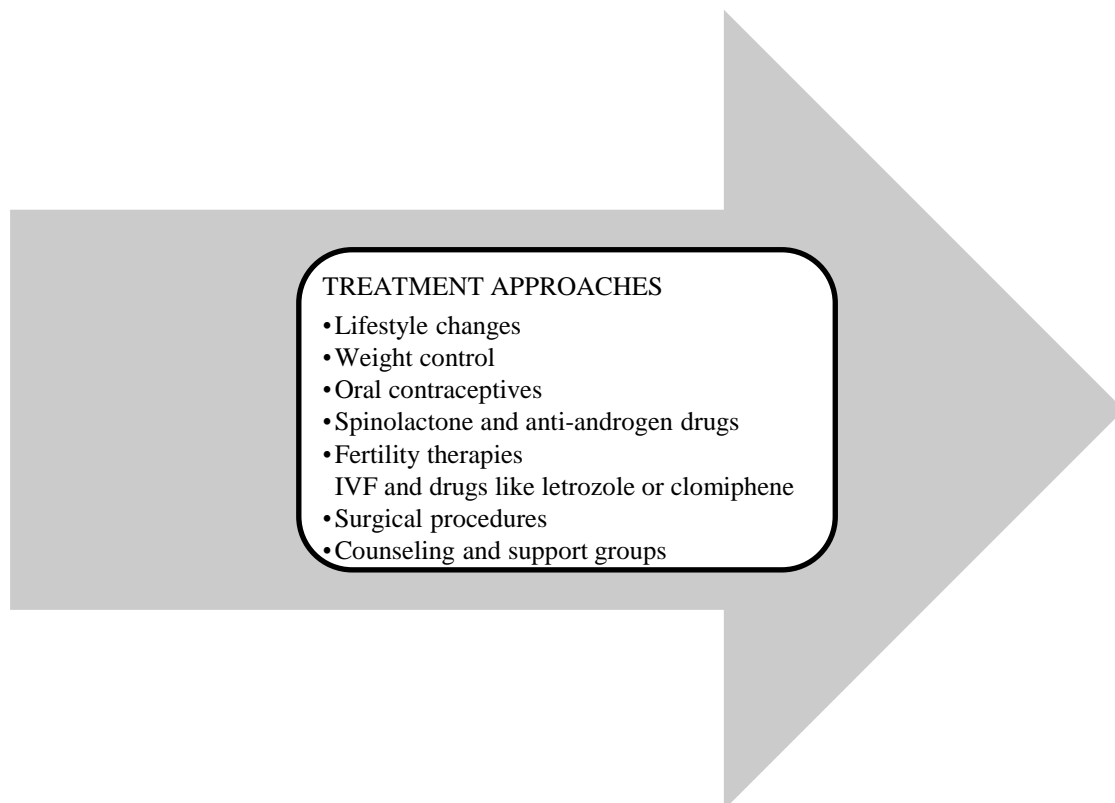
Management of PCOS typically involves a combination of lifestyle modifications, such as healthy eating and regular exercise, along with medications to address specific symptoms. ^[62]

IX. TREATMENT APPROACHES

As we have discussed previously that PCOS requires early diagnosis and customized treatment therapy for each individual. One important element is changing lifestyle such as food, so as to improve hormone regulation and insulin resistance and exercising frequently to control obesity and promote general well being. Main and primacy emphasis should be on weight control so that reproductive health could be maintained. ^[63]

Medications are essential for treating the various PCOS symptoms. Oral contraceptives are frequently recommended to control menstrual periods, lower testosterone levels, and treat conditions including hirsutism and acne. Spironolactone and other anti-androgen drugs focus on particular symptoms, and metformin is used to increase insulin sensitivity, particularly in patients with insulin resistance. Various treatment approaches are provided in Fig.3. ^[64]

FIGURE 3 TREATMENT APPROACHES FOR PCOS



Fertility therapies are specifically designed to trigger ovulation in those who want to become pregnant. Ovulation is stimulated by drugs like letrozole or clomiphene citrate, and when necessary, more sophisticated procedures like in vitro fertilization (IVF) may be taken into consideration. When medicine becomes ineffective, surgical procedures such as ovarian drilling may be considered. ^[65]

Alternative therapies are being researched like acupuncture and certain herbal supplements like inositol and spearmint tea. Mental health issues are serious. Support groups and counseling are great resources for treating anxiety, despair, and body image issues related to PCOS. Healthcare professionals should adopt a holistic approach to meet the requirements of the patients. Frequent health monitoring activities must take place so as to keep a check on long term health consequences occurring due to PCOS. ^[66]

X. PCOS & PREGNANCY

PCOS has a very negative impact on reproductive health and makes it difficult for people to conceive. Anovulation is one of the causes for infertility. But with right treatment and care, one can conceive.^[67] Fertility treatment are a good option for women to become pregnant, doctors can also prescribe ovulation inducing drugs like letrozole or clomiphene to promote the release of eggs. Assisted reproductive methods like IVF can also be considered. To enhance fertility, certain measures can be taken like maintaining a healthy lifestyle, in taking balanced diet, regular exercise, yoga, weight control etc. Coordination with medical professionals is very necessary so as to undergo a healthy pregnancy and child birth along with PCOS.^[68] Proper routine monitoring, management and personalized care will lead to successful outcome for PCOS patients and a healthy parenthood.^[69]

XI. IMPACT ON MENTAL HEALTH

Mental health is a topic that needs urgent attention. Besides the physical symptoms, PCOS accompanies very negative impact of mental health of women. Psychological pain is something which no one talks about, but PCOS accompanies high risk of mood disorders such as depression and anxiety. Prolonged nature of PCOS leads to feeling of frustration, stress and despair. Due to hirsutism and acne, women suffer from body image issues, feelings of self-consciousness and low self-esteem.^[70] This is further complicated by weight gain and eating disorders, societal pressures and feeling of shame.^[71]

Infertility also leads to emotional distress such as feelings of loss, guilt, sadness and negativity. It also disrupts the relationship of patients with their partners. Care and understanding is required in such cases so that women could live stress free and happy.^[72] Both physical and emotional needs should be considered equally important and thus women should seek counseling and therapy sessions to manage their mental health status.^[73]

XII. EMERGING THERAPIES AND RESEARCH DIRECTIONS

Polycystic Ovary Syndrome (PCOS) research and emerging therapeutics are moving forward to offer more specialized and efficient treatments to women. Novel drugs are being developed that target androgen excess, insulin resistance and hormonal abnormalities and they are currently in ongoing clinical trials.^[74] A class of molecules known as isositols exhibits insulin-sensitizing qualities and may be able to enhance reproductive and metabolic results. Furthermore, studies are looking at the function of gut microbiota modulation, highlighting the relationship between PCOS and metabolic health.^[75]

Precision medicine approaches are becoming more and more popular, with the goal of customizing therapies according to the unique features and subtypes of PCOS. The potential of lifestyle modifications, such individualized exercise and nutrition plans, to supplement conventional medications is also being investigated. These new treatments and research directions give hope for more specialized and customized management approaches down the road as our understanding of PCOS develops.^[76]

XIII. CONCLUSION

This review concludes by highlighting the complexity of Polycystic Ovary Syndrome (PCOS) and all the major symptoms, clinical features, treatment approaches and therapies available today so as to control it. Major functional treatments include fertility treatments, drugs and medications, lifestyle adjustments, exercise and counseling. Mental health should also be focused along with physical issues. Personalized care must be provided which include a holistic strategy for disease management. New researches are also taking place with the hope of helping the patients and enhancing their physical and emotional health.

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CONFLICT OF INTEREST

The author has no conflict of interest in this article.

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