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PCOS and Women's Health: An Integrated Review of Gynecology, Endocrinology, and Mental Health

By

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Abstract

The complex endocrine and metabolic disorder known as PCOS (Polycystic Ovarian Syndrome) is frequently characterized by infertility, polycystic ovaries, obesity, insulin resistance, and anovulation. Obesity, gut dysbiosis, genetics, environmental contaminants, lifestyle or nutrition, and neuroendocrine changes are some of the risk factors that make women more likely to develop PCOS. PCOS is a most common endocrine and metabolic condition that affects between 6–20% of women who are of reproductive age. Early puberty is when the majority of PCOS symptoms appear. Because PCOS manifests as a variety of symptoms, it is regarded as a heterogeneous illness. The development of numerous little antral follicles and an irregular menstrual cycle are the results of the ongoing hormonal imbalance, which finally results in infertility in females. The last three characteristics—hyperandrogenism, oligo- or an-ovulation, and polycystic ovaries are included in the most widely recognized diagnostic criteria, the Rotterdam criteria. Prebiotics and probiotics or a gastrointestinal microbiota transplant (FMT) to restore gut microbiota may be a novel, effective, and noninvasive strategy to prevent and lessen PCOS. Predisposing risk factors for PCOS development include genetics, neuroendocrine, lifestyle/environment, and obesity. Insulin resistance, hyperandrogenism, and hormonal dysfunction are the main pathophysiological factors of PCOS. These factors reduce folliculogenesis and raise the risk of associated comorbidities such as type II diabetes and endometrial cancer. This study summarizes the pathophysiology and risk management of drugs that impact PCOS clinical symptoms, anovulation, and infertility.

Keywords: *Polycystic Ovarian syndrome, Insulin resistance, Anovulation, Treatment, Hyperandrogenism*

Introduction

An endocrine and metabolic illness that significantly affects a woman's life, polycystic ovarian syndrome (PCOS) is characterized by anovulation, ovarian cysts, and variance in hormones [1]. A disruption in the normal menstrual cycle caused by a disruption in the important reproductive hormones, such as FSH, LH, estrogen, and testosterone, can result in anomalies such as oligomenorrhea and amenorrhea [2]. The World Health Organization, also known as the WHO, estimates that PCOS affects about 100 million females globally, or 4% of the population [3]. The main pathophysiological factors of PCOS include insulin resistance, hyperandrogenism, chronic low-grade inflammation, and hormonal imbalance. These variables increase the risk of related comorbidities such as type II diabetes and endometrial cancer and impede folliculogenesis [4]. According to worldwide recommendations, the three main criteria used to diagnose PCOS are ovarian morphology, hyperandrogenism, and anovulation. Geographical location, nutrition and food, socioeconomic level, and environmental contaminants are some of the environmental factors that may be influencing the

onset, prevalence, and treatment of PCOS. Although there are significant individual variances, hyperandrogenism, irregular menstruation, and varied ovarian cyst sizes are the hallmarks of PCOS [5]. This complicated syndrome first appears in adolescents who are at high risk for several comorbidities, including obesity, type II diabetes, infertility, endometrial dysplasia, cardiovascular issues, and mental disorders. Because PCOS is a complicated condition, multiple sets of diagnostic criteria have been developed to prove its presence. Along with the three diagnostic criteria, anti-Mullerian hormone (AMH) is an important hormonal indicator that affects how ovarian follicles mature and expand in women with PCOS [6]. Excessive AMH secretion inhibits follicular growth, leading to ovarian dysfunction. The microbiome and PCOS have been linked in recent years, and this is thought to have had a role in the development of the condition. A pathogenic component in the development and progression of PCOS could be gut microbial dysbiosis caused by environmental risk factors. Different pathogenic features of PCOS are caused by different microbiota, and important pathways linking their involvement in the onset of various PCOS clinical manifestations open up new treatment options for the disorder. Prebiotics, probiotics, synbiotics, and gastrointestinal microbiota transplants (FMTs) help manage the variety of phenotypes associated with PCOS by promoting eubiosis and reducing the effects of altered microbial profiles [7]. Women with PCOS may benefit from microbiota-mediated treatments that address their hormonal, inflammatory, and metabolic issues. The risk factors for PCOS's onset, prevalence, and modulation are compiled in this article, along with information on potential treatments such as IL-22 and miRNA therapy. We also examine various microbiota-focused therapeutic strategies that may aid in the management of PCOS and talk about the significance of gut dysbiosis in the disease's pathophysiology [1].

Definition

There has been a considerable misunderstanding about its definition among women who experience it and among medical professionals who are unfamiliar with it since Stein and Leventhal's original description[8]. The word "polycystic," which refers to one of the syndrome's effects on the radiological appearance of the gonads, where follicles are stopped at the various phases of maturation but are not cysts, is mostly to blame for the mistake. This nomenclature obscures the fact that the sickness is a metabolic endocrinopathy with post-reproduction repercussions [9]. Characteristics of the syndrome, now defined as typical PCOS, include elevated androgen levels and clinical and biochemical ovulatory failure. The Rotterdam criteria were published in 2003 by the American Society of Reproductive Medicine and the European Society of Human Reproduction in an attempt to develop a broader definition that would include women with polycystic ovarian morphology (POM) and ovulatory dysfunction without hyperandrogenism [10]. According to this definition, if no other medical condition may mimic the clinical signs and characteristics of polycystic ovarian syndrome (PCOS), then at least two of the following criteria must be met for PCOS to be diagnosed: In transvaginal ultrasound, biochemical hyperandrogenism, ovulatory dysfunction, and POM are listed in order of precedence. more likely to experience related metabolic side effects, including non-alcoholic steatohepatitis, insulin resistance, glucose intolerance, obstructive sleep apnea, diabetes mellitus (DM), and dyslipidemia [10]. Regardless of POM, phenotypes that link ovulatory failure to hyperandrogenism—particularly biochemical ones—have more detrimental clinical and metabolic effects. The ovulatory phenotype is the next most severe from a metabolic standpoint, whereas the non-hyperandrogenic phenotype is the less severe. Therefore, addressing the cardiometabolic risk that these women face is made easier with a good diagnosis and patient phenotyping [11].

Physiopathology and Risk Considerations

The trait that distinguishes PCOS is the preponderance of androgen in those who have it. Hyperandrogenism is characterized by elevated blood levels of free (unbound) testosterone, a key hormone implicated in the pathophysiology of PCOS. This complex disorder's main pathophysiological elements are dissected [12]. Predisposing risk factors for polycystic syndrome include genetics, neuroendocrine disorders, lifestyle/environmental variables, and obesity. Some women are at a higher risk of developing PCOS because of dominant genes. To determine the PCOS phenotype, specific loci and alleles are identified by a multitude of genome-wide association data. Depending on the population, environmental factors like diet, lifestyle, and physical activity may vary significantly [13]. Examples of environmental variables that might cause genetic variation and disruption of the biochemical and reproductive processes that can result in PCOS phenotypes and related challenges include endocrine-disrupting chemicals and glycotoxins. Androgen exposure can modify the ratio of LH to FSH, increase high pulse levels of GnRH, and cause follicle arrest and dysplasia [14].

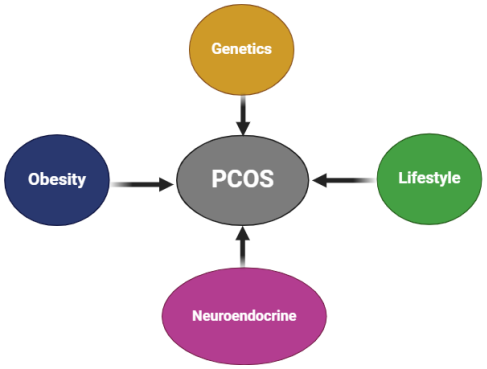

Figure: 1.1 PCOS risk change factors.

Aggregation of families

Families of women with PCOS are known to exhibit family aggregation, suggesting a possible genetic basis for the etiology of the disorder [15]. Environment and genotype may interact to produce variation in the disease's behavioral

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manifestations. There has been no success in finding the genes that cause polycystic ovarian syndrome because just a few genetic differences have been replicated in people with the illness from different populations. Insufficient clinic characterizing of the clients, the use of distinct diagnostic standards that make it difficult to compare data across different groups, and the possibility that the engaged genetic variants differ depending on ethnic substrate are the main reasons for this failure [16]. Furthermore, as Table 1 illustrates, non-genotypic lifestyle dissemination may be the primary cause of this family aggregation rather than genetic causes. This produces a toxic environment that begins in the womb and results in metabolic reprogramming, which induces insulin resistance (IR) and excess testosterone [14].

Table 1. Phenotypic Classification of PCOS.

Phenotypes	**Diagnostic Criteria**	References
Phenotype 1	POM+Hyperandrogenism+ Oligoovulation	[17]
Phenotype 2	Hyperandrogenism + Oligo-ovulation	[16]
Phenotype 3	POM+ Oligo-ovulation	[18]
Phenotype 4	Oligo-ovulation + POM	[17]

A. Abnormal ovarian morphology

The number of pre-antral and small antral follicles in a polycystic ovary is around 6–8 times that of a normal ovary. At a size of 2 to 9 mm, these follicles stop developing, have a slow rate of atresia, and are sensitive to external follicle-stimulating hormone (FSH). A stromal volume increase is always seen, and it is common to have a total volume of ovaries larger than 10 ml. As seen in Figure 1.2, the aberrant ovarian morphology is probably mostly caused by an excess of androgens [19]. Primary follicle development is aided by androgens through the pre-antral and tiny antral follicle stages. This process happens faster in an ovary with extra androgens than in one that is in good health. Along with a host of other variables that hinder the endogenous function of FSH, the growth arrest may also be brought on by an overabundance of androgens. Furthermore, PCOS is associated with an excess of anti-apoptotic molecules, which slow down the turnover of these stopped follicles. These factors can be the reason for the growth arrest. A variety of variables combine to give polycystic ovaries their unique appearance [20].

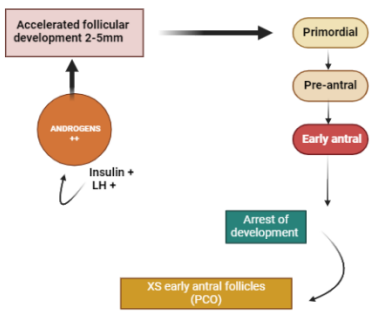

Figure: 1.2 Pathophysiology of Polycystic Ovarian Syndrome.

A. PCOS and Hyperandrogenism

Deteriorated folliculogenesis results from excess androgens interfering with normal androgen production. Excess androgens during the early gonadotropin stage cause the antral follicles to expand and promote the growth of primordial follicles. When GnRH is secreted by the hypothalamus, the pituitary will release the gonadotropin hormone. Luteinizing hormone causes the LH receptor in ovarian theca cells to become more active, which in turn increases the synthesis of androgen [21]. Follicle growth is promoted by the simultaneous conversion of androgens into estrogens by follicular stimulating hormone acting on the FSH receptor in ovarian granulosa cells. It is believed that instability of the neuroendocrine system leads to an imbalance in the hypothalamic-pituitary-ovarian axis, which in turn results in an overabundance of gonadotropin. A discernible hormonal rise in the LH: FSH ratio results from PCOS, where the increase in GnRH promotes the synthesis of more LH than FSH [22].

B. Insulin resistance and Type 2 diabetes

Hyperinsulinemia is the primary cause of excessive androgens because insulin enhances GnRH indirectly and directly mimics the actions of LH. In insulin, sex hormone-binding globulin (SHBG), a vital circulation protein that controls testosterone levels, is decreased. As a result, decreased SHBG would elevate free androgen levels, which would lead to clinical signs such as acne, hirsutism, and alopecia [23]. Insulin resistance can lead to dyslipidemia, and patients with PCOS are more likely to develop diabetes and cardiovascular disease. PCOS prevalence in females with type 1 diabetes is 19%, 37%, and 41%, respectively, according to the ESHRE/ASRM criteria, the NIH criteria, and the AE-PCOS definition. Following a cross-sectional study, up to 35% of American women have IGT, and up to 10% have T2D. Controlling insulin resistance has been shown in several studies to finally reduce excess androgens and ameliorate the condition [24].

C. Obesity and POCS

Obesity and abnormal hypothalamic-pituitary-ovarian axis activity have been connected to the development of PCOS. In PCOS patients, hyperinsulinemia, which is linked to obesity, increases glucose intolerance and the lipid profile. Obesity raises androgen production via stimulating LH, which eventually leads to hyperandrogenism. PCOS obesity Leptin, an adipokine that controls hunger, has a direct effect on women's neuroendocrine and reproductive systems [25]. Additionally, hyperleptinemia may inhibit the growth of ovarian follicles. Therefore, reducing visceral fat would regulate the ovary's androgen action via controlling hunger, sugar levels, lipolysis, and SHBG [26].

Diagnosis and Differential Diagnosis

According to earlier observations, hyperandrogenism or prolonged anovulation serves as the basis for the diagnosis of PCOS, which is made when there is no discernible pituitary or

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adrenal tumor. Table 3 lists the tests required to fully assess these options in addition to PCOS differential diagnosis [27]. These illnesses seem to have some symptoms with PCOS, but not all of them. The following disorders should be checked out: pregnancy, hypothyroidism, and hyperprolactinemia. These conditions can cause secondary amenorrhea, but not hirsutism. Finding any additional signs of illnesses unrelated to PCOS requires a thorough history and physical examination. Hypothyroidism may be indicated by goiter and symptoms like dry skin, increased fatigue, and cold intolerance [28]. A woman may or may not have galactorrhea if she has hyperprolactinemia. An ovarian tumor may be the cause of Virilization symptoms, which show noticeably greater levels of testosterone than those observed in PCOS. Cushing's syndrome individuals may be more likely to have a rounded, plethoric face, purple abdomen striae, hypertension, and large dorsal cervical fat pads. Although late-onset illness congenital adrenal hyperplasia is uncommon, it is noteworthy because it can clinically mimic PCOS in every way. Congenital adrenal hyperplasia is caused by enzyme abnormalities in adrenal steroidogenesis, one of numerous possible reasons [29]. Complete enzymatic abnormalities and ambiguous genitalia are features of the typical forms of these disorders in newborn girls. These disorders are conclusively detected by measuring the hormone that accompanies the enzymatic block. PCOS differential diagnosis tests frequently solely look at 21-hydroxylase deficiency because it is the most prevalent cause of late-onset congenital adrenal hyperplasia [30].

LABORATORY EVALUATION

Biochemical evaluations should look into signs of PCOS and rule out the previously stated disorders. Every patient should get every test listed in Table 2. It is crucial to remember that there are several strategies for dealing with the difficulties that come with direct testing, such as Insulin resistance(IR) [31]. Only the simplest fasting glucose-to-insulin ratio is given for simplicity's sake. Notably, the fasting blood glucose-to-insulin proportion has been mainly examined in mature white women who are fat and lean and euglycemic but are not Hispanic teenagers, as well as in mature white women who are obese and thin and euglycemic but are not Hispanic. Screening for Insulin resistance in non-euglycemic adults may be pointless because it may not be a valid signal in people with reduced glucose tolerance [30]. Furthermore, one could argue that none of the IR tests are particularly sensitive or specific, raising doubts about their usefulness. But it might be enough to measure lipids and glucose when fasting. Last but not least, a 2-hour oral glucose tolerance test is very helpful in determining a patient's risk of developing diabetes mellitus, which can affect treatment choices. Table 3 contains a collection of differential diagnostic tests. Additionally, it might predict IR more accurately than fasting glucose. There are several subtleties involved in interpreting these lab tests, and they can have a big influence on judgments made later [32].

Table 2: lists the diagnostic criteria for insulin resistance syndrome in females.

HDL-cholesterol	Less than 50 mg/dL	**[33]**
Fasting glucose	Greater or equal to 110 mg/dL	**[31]**
Triglycerides	Greater or equal to 150 mg/dL	**[30]**
Blood pressure	Greater or equal to 135/85	**[32]**

Table 3: Screening procedures and the distinction between PCOS and other gynecological conditions.

Diagnosis	Laboratory test
Hyperprolactinemia	Prolactin
Hypothyroidism	TSH(thyroid stimulating hormone)
Pregnancy	Pregnancy test
Late-onset CAH	17-hydroxyprogesterone
Ovarian tumor	Total testosterone

1. **Prolactin**

There are claims that mild hyperprolactinemia affects 6% to 30% of women with PCOS. In general, prolactin levels are just 50% above the top limit of normal. It should be mentioned that hyperprolactinemia is usually a transient syndrome; between 4% and 6% of patients with hyperprolactinemic PCOS have continuously elevated prolactin levels. Because of this, some now think that PCOS and hyperprolactinemia are two different diseases. If there is no normalization upon resampling, more research into other factors should be done. Ultrasonography may reveal polycystic ovaries in prolactinoma patients [34].

2. **Luteinizinghormone/follicle-stimulating hormone ratio**

A ratio higher than 3.0 is indicative of PCOS, yet it is neither extremely sensitive nor specific. Gonadotropin levels are impacted by oral contraceptives [35].

3. **Testosterone**

A total androgen measurement is probably more precise than the free testosterone level because of the problems with many assays used to detect free testosterone. Testosterone levels may be normal in PCOS. The majority of PCOS patients will have testosterone levels below 150 ng/dL [36].

4. **Dehydroepiandrosterone-sulfate (DHEA-S)**

DHEA-S levels in PCOS may be normal or slightly elevated. It is important to consider an adrenal tumor when DHEA-S levels surpass 800 µg/dL [37].

5. **Pelvic ultrasonography**

In the evaluation phase, pelvic ultrasonography can also be very helpful; nevertheless, polycystic ovaries are present in over 20% of normal women, indicating that the disease is not exclusive to PCOS. Both the ovarian volume and the number of follicles are important factors in the ultrasonography evaluation. Polycystic ovaries syndrome is confirmed by the

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existence of more than 12 follicles with a diameter of two to nine mm each or numerous cysts with a diameter of about 03 to 09 mm, together with an increased amount of stroma and an enhanced ovarian area or volume. When it came to diagnosing PCOS, these criteria showed an 80% sensitivity and 99.0% specificity[38].

Treatment

To improve fertility in women who want children, avoid endometrial hyperplasia in those with severe ovulatory failure, prevent or treat metabolic problems, and reduce the psycho-emotional impact of transdermal symptoms of androgen excess. All patients who want to combat or prevent smoking, obesity, and sedentary behavior are often advised to follow hygienic-dietetic therapy. In moderate cases, patients might simply need clinical monitoring to make sure they have more than four to six menstrual cycles each year, which effectively protects the endometrium. On the other hand, to ensure proper management, moderate to severe symptoms and signs will require long-term drug therapy [28].

6. Treatment of androgen excess

In general, depending on the patient's psychological reaction and the severity of their symptoms, several dermatology cosmetic techniques may be recommended in addition to medication treatment. Treatment options for excessive facial hair include the process of electrolysis waxing, shaving, laser photodepilation, bleaching, and tweezing [39]. Baldness and hirsutism may be treated with topical minoxidil, while acne may be treated with antibiotics or retinoids. The best systemic therapies are birth control pills that contain progestagens with a lower affinity for androgen receptors or anti-androgenic characteristics (such as cyproterone or drospirenone). In this group, progestogens such as norgestimate and dienogest decreased the risk of clotting. An adolescent who has not reached their maximal bone mass should take 32–40 μg of ethyl estradiol each day [40].

7. Treatment of ovulatory dysfunction

Treatment for oligo-anovulation symptoms should be individualized for each patient, taking into account menstrual disruption and subfertility. Women who experience acute ovulatory issues without gestational desire are more likely to develop endometrial cancer and hyperplasia [41]. Females who have fewer than typical cycles each year are especially in danger. People with modest menstruation issues can be checked once a year, while people with severe menstrual issues need to take medication. If imminent pregnancy is not sought and psychological or emotional symptoms occur, combining oral contraceptives (OC) is advised for sexually active women who are not contraindicated or who refuse alternative therapies [42]. Levonorgestrel-releasing intrauterine devices, continuous progestogen usage, or cyclical progestogen use to induce menstruation by deprivation are further choices, particularly for patients without excess androgens who do not desire OC treatment. Weight loss is one of the first things overweight women with pregnancy cravings should do. Furthermore, it is advised to perform a semen analysis as the initial step in evaluating fertility [43].

1. Management of Infertility: Treatment by using medicines

In 75 percent of instances, PCOS is a contributing factor to anovulatory infertility. Furthermore, among pregnancies that do occur, the rate of miscarriages in the first trimester can vary from 30% to 50%. Patients and healthcare professionals can both be greatly satisfied when infertility in these people is effectively managed medically [44]. However, treating infertility can be difficult, which emphasizes the value of collaboration between gynecologists, endocrinologists, and potentially reproductive endocrinologists. The complexities of treating infertility in PCOS individuals won't be covered in detail in this review. Instead, a quick examination of PCOS patients' relative resistance to clomiphene treatment will be covered, followed by a more thorough examination of the possible advantages of methods meant to improve insulin sensitivity [45].

a. Clomiphene citrate

Obese females with PCOS typically do not respond well to low dosages of clomiphene; in women weighing more than 90 kilograms, their ovulation percentage at 50 mg is only about 20%. There is a correlation between the degree of obesity and the dose of clomiphene required to achieve ovulation. Because multiple gestations typically require greater dosages of clomiphene, they may occur more often and have negative effects [46].

b. Metformin

The biguanide metformin, which is used to treat insulin resistance and irregular menstruation in PCOS, is produced in large quantities. Because metformin increases the absorption and use of glucose, it helps PCOS patients with their insulin resistance [47]. Unlike other insulin-regulating drugs that have the potential to cause either hyperglycemia or hypoglycemia as a side effect, it regulates the amount of glucose. Metformin lowers insulin levels indirectly via increasing SHBG, which lowers free testosterone, and decreases CYP17 cytochrome activity, which is associated with androgen production [48]. Another effect of metformin on PCOS patients is a little improvement in their lipid profile. Metformin does not have any teratogenic effects during pregnancy and also lowers pregnancy-related inflammation and problems. Infertile PCOS patients showed an increase in ovulation and pregnancy rate when clomiphene citrate was added. Despite flutamide's lack of safety in experimental animals, metformin and antiandrogens like it have a synergistic impact on obese PCOS women. Dexamethasone treatment improved hyperandrogenism in PCOS women, which was a positive outcome [49].

c. Laparoscopic Ovarian Drilling (LOD): An operative therapeutic technique

The main method for diagnosing and treating PCOS used to be bilateral wedge ovarian resection. Despite its effectiveness in reviving ovulation and promoting conception for many women, its usage was terminated because of a high risk of

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pelvic adhesion formation. Since then, laparoscopic ovarian drilling, or LOD, has brought the surgical therapy concept back to life, most likely by lowering ovarian bulk [50]. The laparoscopic procedure known as LOD involves puncturing each ovary's cortex between four and ten times at a depth of 2 to 4 millimeters. While lasers are an alternative, bipolar or unipolar electrocautery usually recommends 40 W for 4 seconds per puncture [51]. Because of its better results and slower rate of adhesion formation, electrocautery is recommended. After a year of LOD, the ovulation rate is 84% and the rate of gestation is 56%, according to preliminary findings. The almost exclusive development of mono-follicular ovulation, which reduces the risk of multiple pregnancies and eradicates ovarian hyperstimulation syndrome (OHSS), is a major benefit of LOD for ovulation in PCOS patients. Moreover, the miscarriage rate after LOD is lower than with other ovulation induction techniques for PCOS [52].

Lifestyle Intervention

For women with PCOS, altering one's lifestyle is a crucial and simple tactic because PCOS is a chronic disorder that is more likely to be linked to other comorbidities, such as type II diabetes. A recent study has shown that changes in nutrition, exercise, and attitude improve insulin resistance, testosterone levels, and body mass index[53] .

Conclusion

The most common endocrine disorder that affects women before menopause is PCOS. Numerous elements, including epigenetic, genetic, and environmental influences, contribute to its complex etiology. The diagnosis is based on ruling out other possible causes of oligo-anovulation and excessive androgen symptoms while verifying ovulatory failure, biochemical a condition called hyper or polycystic ovary morphology (POM). The goals of treatment are to prevent or treat early metabolic problems, ovulatory dysfunction, and symptoms of androgen excess. It should be long-lasting, customized, and tailored to the specific requirements of every patient for their lifetime. Type 2 diabetes is a serious condition and the risk of coronary artery disease can be postponed or even prevented with prompt diagnosis and adequate treatment, such as lifestyle changes and/or insulin sensitizers. It is clear from the review that PCOS is a complex condition. The basic mechanism is difficult to understand and explain. No treatment can be heralded as a cure since it addresses the clinical symptoms rather than the underlying cause of the disease. Alternative treatments, such as herbal or medicinal plants, should be considered by knowing their mode of action. To forecast the long-term impacts on the patient's health, more investigation is required into the pathophysiology and drugs that influence it. The symptoms of PCOS may be lessened by changing one's lifestyle.

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