A Review of the Current Understanding of Polycystic Ovarian Syndrome and its Therapeutic Alternatives for Female Fertility and Well-being

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Abstract

Female reproductive disorders are increasing with changes in the environment and lifestyle. Polycystic ovarian syndrome (PCOS) is one such female reproductive disorder that has several metabolic implications on the health of a female. Not only is this concern increasing in number but also putting up newer challenges for fertility management. There is a need for newer approaches to be developed for the treatment and management of this disorder. In this review, we attempt to give an overview of polycystic ovarian syndrome (PCOS) and its pathophysiological implications along with its impact on female fertility. This paper also reviews the available treatment options for polycystic ovarian syndrome (PCOS) and its relative impact on the health management of female patients.

Keywords

PCOS, Fertility, Hyperandrogenism, Insulin, and Neuroendocrine disorder

Introduction

Women's health is a matter of concern in recent times. Several illnesses are gender-specific, out of all the gynecological trouble involving distress is a reproductive organ of a female. Some of these feminine disorders are curable, others are chronic, and some are fatal.[1] Some of these disorders are the leading cause of infertility. With the increasing exposure to endocrine-disrupting chemicals, the instance of hormonal imbalances is on the surge. Several common hormonal anomalies are endometriosis, amenorrhea, fibroids, polycystic ovarian syndrome (PCOS), ectopic pregnancy, miscarriage, ovarian cancer, etc.[2]

Polycystic ovarian syndrome (PCOS) is a disorder that is heterogeneous affecting the regulation of endocrine system functioning, which includes ovulatory dysfunctions, ovarian cysts, and endocrine variations that irreversibly affect the life of a woman.[3] Although the actual cause of PCOS is unknown it is considered multifactorial disarray with various genetic, endocrine, metabolic, and environmental deformities. There is rising evidence suggesting that PCOS affects the whole of a woman's life starting from *in* utero in genetically predisposed elements, its patients clinically at puberty and continues during the reproductive years.[4] Features linked with PCOS are menstrual irregularity, hyperandrogenism, and polycystic ovarian morphology, which have significant reproductive implications for females, with an elevated risk of pregnancy-related complications. Also, in addition, women suffering from PCOS have a higher risk of getting type 2 diabetes and possible cardiovascular diseases.[5] Due to a lack of awareness and knowledge PCOS has a high percentage of individuals who remain undiagnosed while consulted by doctors, estimated as high as 75%.[6] In present years, the geographic variations of PCOS prevalence have been studied globally and the percentage of PCOS is routinely derived between 6% to 26%.[7] Age ranged from 18 to 45 years mostly suffer from this disorder. Almost one out of ten women are found affected by PCOS (Fig. 1)[8]

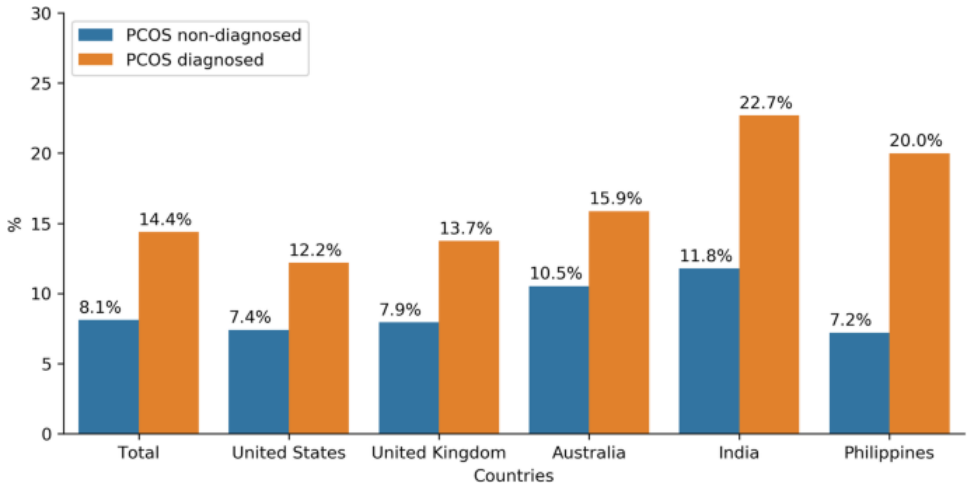

Figure 1: Global prevalence of PCOS patients non-diagnosed vs diagnosed[8]

Though the root cause behind this syndrome is unknown and the prevalence of the disorder also differs because of several varying criteria being used for the detection of PCOS by different investigators.

Phenotypic variants in PCOS			
Sr. No.	**Type**	**Symptoms**	**Hormonal Levels**
1.	PCOS Type A (Classic PCOS)	• Irregular periods, delayed ovulation, or anovulation • Hyperandrogenism: acne, hirsutism, alopecia • Polycystic ovaries on ultrasound	• High testosterone and AMH (anti-mullerian hormone), low progesterone • High LH/FSH ratio
2.	PCOS Type B (Classic PCOS, without cysts)	• Irregular periods, delayed ovulation, or anovulation	• Lower AMH level compared

		• Hyperandrogenism: acne, hirsutism, alopecia • **Normal ovaries on ultrasound**	to Type A PCOS
3.	PCOS Type C (Non-Classic, Ovulatory PCOS)	• **Bleeding that occurs at regular intervals, with or without ovulation** • Hyperandrogenism: acne, hirsutism, alopecia • Polycystic ovaries on ultrasound	• Lower LH/FSH ratio (slightly elevated levels than Type A and B PCOS)
4.	PCOS Type D (Mild PCOS)	• Irregular periods, delayed ovulation, or anovulation • **Normal androgen levels, no hyperandrogenism** • Polycystic ovaries on ultrasound	• Slightly elevated LH/FSH ratio compared to normal women

Table 1: Phenotypic variants in PCOS[9]

Owing to the complexity of this condition, diagnostic criteria have been set for the confirmation of PCOS out of which Rotterdam criteria is clinically approved (Fig. 2)[10]

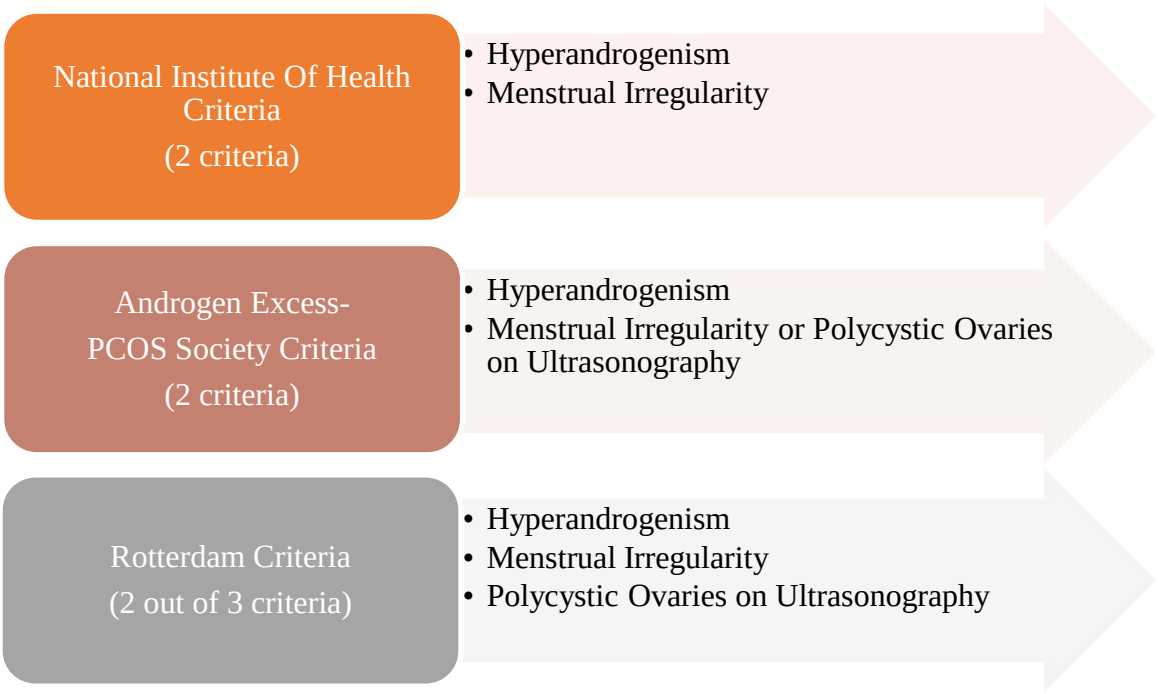

Figure 2: Diagnostic criteria currently accepted for the confirmation of PCOS-Rotterdam criteria[11]

This study approaches to understand the current development of personalized and precision medicine approaches for PCOS. There is a critical necessity for in-depth investigations into the genetic, epigenetic, and environmental factors contributing to PCOS. This review focuses on current risk factors, implications related to PCOS, and therapeutic approaches for the management of PCOS.

Methodology

A comprehensive literature search was carried out in electronic databases such as PubMed, Web of Science, Research Gate, Google Scholar, and Scopus. Studies were incorporated if the information provided insights into pathophysiology, etiology, or PCOS management. Both interventional and observational learning were considered. Articles centered on well-defined aspects of PCOS such as diagnostic criteria, genetic factors, lifestyle interventions, and hormonal profiles were included while articles not directly related to recent management or understanding of PCOS were excluded.

Pathophysiology And Risk Considerations

The pathophysiology of polycystic ovary syndrome incorporates hereditary ovarian dysfunction which can be detected by an ample number of androgens found in PCOS patients. The susceptible risk factors include lifestyle, genetics, obesity, nutrition, and neuroendocrine disorders that lead to PCOS development.[12] Hyperandrogenism is denoted by raised levels of unbound testosterone in the bloodstream, a chief hormone donating to the pathophysiology of PCOS. This complex state is interpreted into its main pathophysiological elements.[13] The predisposing risk elements include neuroendocrine, genetics, obesity, and lifestyle/environment which contribute to the growth of PCOS. These factors lead to the principal cause of hyperandrogenism, hyperinsulinemia, oxidative stress, and oligomenorrhea eventually rising metabolic syndrome. Some women have an elevated risk of developing PCOS because of predominant genes.[14] Environmental agents including lifestyle, exercise, and diet may differ widely according to the community.[15] Environmental factors also count for endocrine disruptors and glycotoxins which may affect genetic variance and disarrangements of metabolic and reproductive pathways, which can evolve PCOS phenotypes and related issues.[16] Some risk factors that are involved in PCOS are insulin resistance, hyperandrogenism, obesity, and environmental toxins. Women associated with PCOS usually have profound insulin resistance which is a root cause of this condition.[17] Hyperandrogenism is one of the distinctive features of PCOS which is clinically expressed as acne, hirsutism, and male pattern baldness. Obesity or Adiposity is known to increase the rigors of the clinical symptoms of PCOS.[18] Exposure to environmental toxins, i.e. chemical pollutants present in the environment (smoke, lead, pesticides, mercury, and BPA) affects human health and reproduction.[19]

(a) Insulin Resistance in PCOS

Hyperinsulinemia is the main ground of excess androgens as insulin straightly stimulates the action of LH and increases the GnRH indirectly.[20] Insulin drops the sex hormone-binding globulin (SHBG), a chief circulatory protein in charge of testosterone levels. So deceased SHBG results in an elevated level of free[21] Dyslipidemia can be caused by insulin resistance and patients with PCOS are at peak risk for diabetes and cardiovascular disease.[22] In women with diabetes, the generality of PCOS is 19%, 37%, and 41% by NIH criteria, ESHRE/ASRM criteria, and AE-PCOS definition respectively.[23] Various studies revealed that managing insulin resistance in time would decrease the excess androgens and ameliorate the condition.[24]

(b) Hyperandrogenism in PCOS

Weakened folliculogenesis is the outcome of excess androgen that disturbs normal androgen synthesis. The surplus androgen stimulates the development of primordial follicles and rises in the antral follicles at the initial gonadotropin stage.[25] The production of GnRH from the hypothalamus will initiate the gonadotropin hormone liberated from the pituitary. Luteinizing hormone initiates the LH receptor to assist androgen-making in ovarian theca cells, and follicular stimulating hormone (FSH) follows on the FSH receptor altogether in granulosa cells to modify the androgens to estrogens, which nurture the follicle growth.[23] It has been assumed that chronic inflammation in the neuroendocrine system results in a variation of the hypothalamic-pituitary-ovarian axis guiding to an excess level of gonadotropin. Arise in the GnRH encourages the production of LH over FSH, developing a noticeable hormonal increase in the LH: FSH proportion in PCOS.[25,26]

(c) Obesity and PCOS

Obesity has been linked with unusual hypothalamic-pituitary-ovarian axis function directed to PCOS symptoms.[27] Obesity is associated with hyperinsulinemia which additionally increases glucose intolerance and lipid profiles in PCOS patients. Obesity increases the production of androgens by stimulating LH, which in succession leads to hyperandrogenism.[28] An appetite-controlling adipokine leptin has a direct impact on the reproductive function and neuroendocrine of obese PCOS women.[29,30] Moreover, hyperleptinemia may hamper ovarian follicular growth.[30] So, diminishing the visceral fat would command the appetite, lipolysis, and glucose levels which expands the SHBG so that balancing the androgen action in the ovary.

(d) Environmental Toxins and PCOS

There is a growing amount of evidence that environmental toxins have a notable impression on human health and reproduction.[31,32] Environmental toxins are determined to be chemical pollutants in the environment that have unfavorable effects on biological organisms. Research-based evidence suggests the lasting and significant effects of environmental toxins on human reproductive well-being.[33,34] Although pollutants such as lead, pesticides, tobacco smoke, and chromium are harmful to the general population of particular interest to reproductive health are endocrine-disrupting chemicals (EDCs), including polycystic ovarian syndrome (PCOS) and their associated symptoms. Demonstrated Endocrine-disrupting chemicals (EDCs) present in

organic wastewater are first found in the form of human byproducts, which include potent pharmaceutical products, phytosterols such as beta-blockers, antiepileptic drugs, lipid-regulating agents, and estrogens.[35] Evidence suggesting elevated serum levels of Bisphenol A (BPA) a synthetic amalgam with lenient estrogenic activity found in the usual plastic consumer items, among women with polycystic ovarian syndrome compared to control subjects.[35] Given the confirmed existence of these environmental pollutants in soil, groundwater, air, food, and habitual household products[35] and the confirmed association of PCOS,[36,37] further research is required to assess the role that endocrine disruptors may play a role in disrupting the reproductive health between women and perhaps triggering PCOS and its associated symptoms.

(e) Gut-Microbiome and PCOS

There is a link between gut microbiota of PCOS and insulin resistance, hyperandrogenism, metabolic syndrome, and environmental factors.[38] Research proposes that variation in the composition and function of the gut microbiota may contribute to the key features of PCOS including hyperandrogenism, inflammation, and metabolic dysfunctions.[39] Dysbiosis in the gut- microbiota is characterized by lowered microbial diversity and alteration in specific bacterial taxa which may amplify adipose tissue dysfunction and insulin resistance observed in PCOS patients.[40] Moreover, the gut- microbiome affects hormonal signaling pathways and the precursors involved in androgen production, possibly contributing to excess androgens in PCOS.[41] Lifestyle and dietary factors also add to the alteration in gut-microbial structure, emphasizing their potential to minimize PCOS symptoms and improve overall metabolic health.[42]

Therapeutic Alternatives for PCOS

Currently, there is no pharmacological treatment that can heal the syndrome, but some intermediate medications are used to serve the clinical symptoms of PCOS.[43] Pharmacological therapies along with modification in the lifestyle may improve the overall condition. The therapeutic strategy varies according to the clinical symptoms which include hirsutism, acne, infertility, menstrual problems, and fundamental causes such as hyperandrogenism, ovulatory dysregulation, improving insulin resistance, and infertility.[44] The treatment approaches are

categorized according to the first-line, second-line, and third-line therapies according to the individual's symptoms.[45] The first-line therapy includes lifestyle interventions which include dietary patterns and physical regimes and oral contraceptives such as insulin sensitizers, metformin, and antiandrogens. The second-line therapy includes ovulation-inducing agents and laparoscopy surgery while the third-line therapy includes in vitro fertilization. (Figure 3)

(a) First-Line Therapy

(i) Lifestyle Interventions

Lifestyle interventions include diet patterns, workout regimes, and behavioral interventions which are a part of the primary treatment for infertility management and complications which are associated with PCOS.[47] PCOS is a deep-rooted disease with a considerable chance of other comorbidities like type 2 diabetes connected with it, so lifestyle modification is a pivotal and simple proposal for application in women with PCOS.[53] Studies have shown that rigorous modifications in lifestyle and reducing weight can lead to a reduction in circulating insulin and has been known to improve FSH and lipid levels which ultimately could result in regulating menstrual cycles, ovulation induction, and overall improvement of reproductive health.[48] Research revealed that changes in lifestyle, including exercise, diet, and daily routine have a positive influence on body weight, testosterone levels, and insulin resistance as well.[54] There is insufficient research data related to dietary compositions for PCOS individuals because of problems in methodology curations and clinical trials.[49] Women with PCOS are found to have a deficiency of Vitamin D and supplementation of the same might improve women's fertility and insulin efficiency.[50]

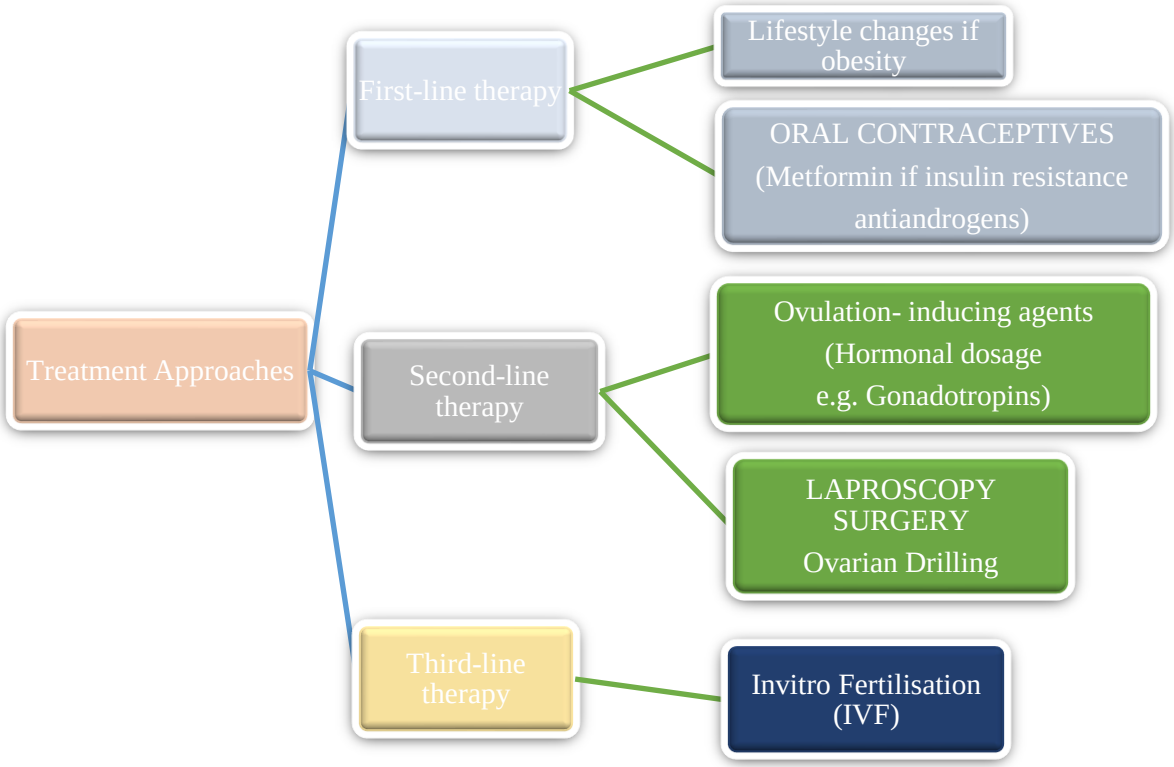

Figure 3: Different treatment approaches for the management of PCOS[46]

PCOS women are also known to have mood swings, behavioral patterns, and anxiety disorders where regular physical activities can help in reducing these stress-related behaviors and overeating patterns which also helps in improving mood and body language associated with it.[51] Hyperandrogenism is one of the traits in PCOS women and smoking is known to increase hyperandrogenism in PCOS women with significantly increased levels of fasting insulin, testosterone, and free androgen index. However, the clinical parameters are yet to be studied in detail.[52] In addition, regular health and counseling sessions might aid in reducing the risk of complications associated with PCOS and help in better overall health (Figure 4).[53]

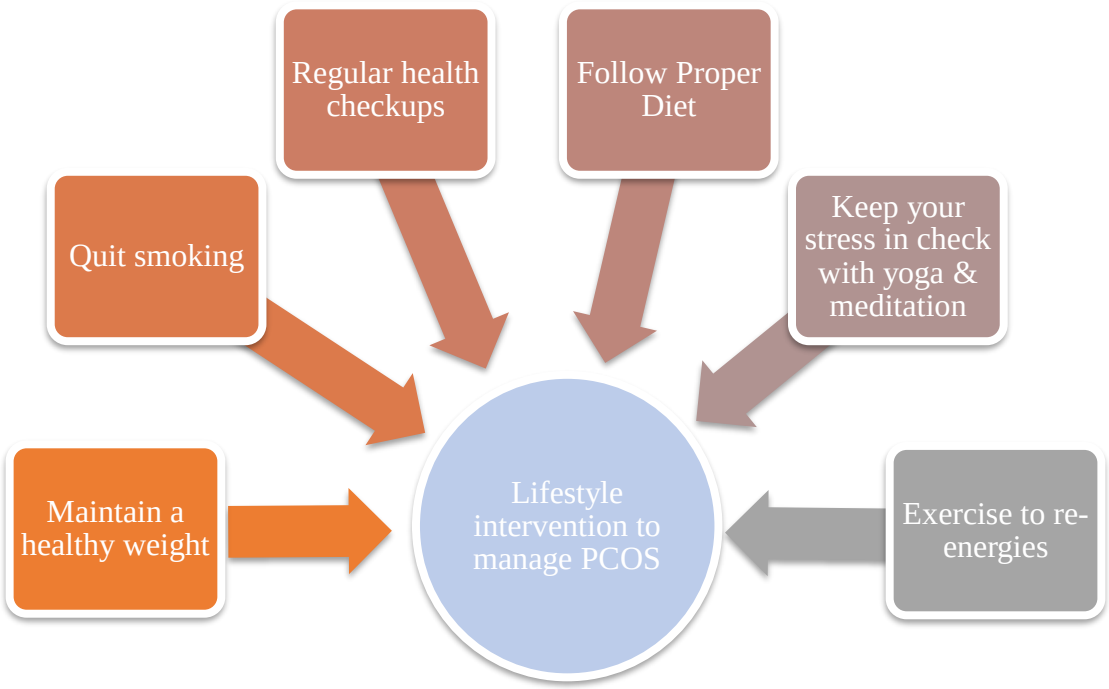

Figure 4: Overview of Lifestyle Strategies for PCOS Management[54]

(ii) Oral Contraceptives (OCPs)

The OCPs are split into combined pills and progesterone-only pills containing both progesterone and estrogen.[55] OCPs are the first preferred therapy for women who are facing menstrual irregularities and who do not want to ovulate. Oral contraceptives decrease the flowing androgens by raising SHBG.[56] The use of oral contraceptives (OCPs) does not affect insulin resistance but shows a change in lipid profiles which can lead to metabolic disruptions.[56] Thus the usage of oral contraceptives should be in accordance with the risk grade and immediately stopped if any confutation occurs.

Insulin sensitizers are generally used to heal PCOS-related metabolic comorbidities by depleting insulin resistance and normalizing insulin levels. By decreasing insulin resistance (IR), the related androgen level will lower resulting in the enhancement of the menstrual cycle.[56]

Metformin is a biguanide manufactured extensively that is used to treat insulin resistance (IR) and restore irregular menstrual cycles in PCOS patients.[56] Metformin raises the glucose uptake and its application which in return improves the insulin resistance in PCOS patients.[56,57] Metformin works indirectly by decreasing the insulin level with a drop in CYP17 cytochrome activity which is involved in the production of androgen and raises the SHBG further lowering

in the free testosterone.[58,59] Combining metformin with clomiphene citrate, the ovulation, and rates of pregnancy were found to be improved in infertile PCOS women.[60] Moreover, including metformin in the ovulation-stimulating procedure for IVF, PCOS patients showed good oocyte quality.[61]

Antiandrogens include flutamide, spironolactone, and cyproterone acetate which lowers androgen secretion by receptor inhibition and is favored as first-line medicine for hirsutism.[57] Flutamide is an anti-androgen used to cure prostate cancer. It is effective in managing hirsutism.[58,59] Flutamide is taken in combination with metformin as it brings about hepatotoxicity when used alone.[60] Spironolactone, an aldosterone antagonist when taken in high doses produces an antiandrogenic effect. Spironolactone when taken alone causes frequent menstrual cycles, so it is normally taken in combination with OCPs to produce a synergistic effect and overcome the problem.[58] Cyproterone acetate is also an antiandrogen with strong progestogenic activity.[57,58] Cyproterone acetate when taken in combination with ethinylestradiol is used as a remedy for hirsutism and acne.[61]

(b) Second-Line Therapy

(i) Ovulation-Inducing Agents

Clomiphene citrate (CC) is the main alternative drug for treating anovulatory sterile women.[62] Clomiphene citrate (CC) raises the FSH level by hindering the estrogen receptor via a negative feedback mechanism.[53,63] It is recommended for the management of anovulatory PCOS patients, though the pregnancy rates may vary significantly according to BMI, for BMI (Body mass index) less than 30 grows the rate of pregnancy and vice-versa.[64]

Letrozole, an aromatase inhibitor is an off-label drug, that chokes the androgen-to-estrogen conversion pathway and supports folliculogenesis by stimulating FSH.[65] Letrozole is more powerful than clomiphene citrate as estrogen receptors is not depleted and the antiestrogenic effect on the endometrium is not discovered.[66] Thus, letrozole is a recommended drug option in ovulation induction used as an alternative drug to clomiphene showing similar effects.[67] Recent studies suggest that letrozole is likely to be more effective in anovulatory infertility than clomiphene citrate in PCOS patients.[68]

Gonadotropins such as recombinant follicle-stimulating hormone (FSH), and human menopausal gonadotropins (HMG) are the second choice of treatment for anovulatory infertile

PCOS patients.[69] Gonadotropins can be too expensive for timely intercourse management, so instead of that intrauterine insemination (IUI) or in vitro fertilization (IVF) is done.[69,70] Low-dose follicle-stimulating hormone (FSH) therapy is accepted for ovulation induction and enhancing pregnancy rates in PCOS patients.[62,71]

(ii) Laparoscopy Surgery

Laparoscopic surgery is a secondary surgical method for ovulation in clomiphene-resistant PCOS patients or non-answerers of clomiphene.[71] Laparoscopic ovarian drilling (LOD) is puncturing the ovary multiple times by diathermy or laser.[72] The risk of hyperstimulation of the ovary and multiple pregnancies is lowered by LOD.[73] Ovarian drilling leads to a reduction in the size and volume of ovarian tissue, additionally damaging the ovary but it is assumed through studies that exhaustion in the ovarian size designates normal functioning of the PCOS ovaries.[74]

(c) Third-Line Therapy

(i) In Vitro Fertilization (IVF)

In-vitro fertilization (IVF) is endorsed as a third-line treatment for managing infertility in PCOS patients without any linked complications.[75,68] Assisting metformin therapy for a short period boosts pregnancy rates in polycystic ovarian syndrome women undergoing IVF [76] which involves complex procedures with side effects, mostly hyperstimulation of the ovary and expensive treatment.[77]

Conclusion

It is evident from the review that polycystic ovarian syndrome is a multifactorial complex disorder. The etiology of PCOS is difficult to state and understand. As a result, no therapy can be claimed as an exact method as it targets the clinical symptoms instead of curing the syndrome. Alternative drugs such as medicinal or herbal plants should be contemplated by finding their mechanism of action. Investigating the pathophysiology and drugs acting on it should be done to improve the survival consequences on patients' health. Lifestyle modifications could ease polycystic ovarian syndrome-related symptoms.

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Glossary

Pathophysiology- The disordered physiological process associated with disease or injury.

Endometriosis- A condition resulting from the appearance of endometrial tissue outside the uterus which causes pelvic pain during menstruation.

Amenorrhea- Absence of menstrual periods.

Fibroids- A benign tumor of muscular and fibrous tissues, typically developing in the wall of the uterus.

Rotterdam criteria- According to the Rotterdam consensus, polycystic ovarian syndrome (PCOS) is defined by the presence of two of three of the following criteria: oligo-anovulation, hyperandrogenism and polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary).

Hyperandrogenism- Condition in which there is excess production of androgens.

Hyperinsulinemia- Excess amount of insulin in the blood which is considered unhealthy.

Oligomenorrhea- Irregular and inconsistent menstrual blood flow in women.

Hirsutism- Abnormal growth of hair on women's face and body.

Dyslipidemia- Imbalance of lipids such as cholesterol, low-density lipoprotein cholesterol, (LDL-C), triglycerides, and high-density lipoprotein (HDL).

Hyperleptinemia- The presence of a higher number of leptins than the normal range in the bloodstream.