

Current and experimental drug therapy for the treatment of polycystic ovarian syndrome

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Article Highlights

- Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder of reproductive-aged women globally;
- PCOS is a syndrome of ovarian dysfunction. Its cardinal features are hyperandrogenism and polycystic ovary morphology;
- The revised diagnostic criteria of PCOS suggested that the diagnosis of PCOS should include two of the following three criteria: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, polycystic ovaries; it is necessary to exclude other etiologies (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome);
- The current options employed in PCOS treatment aim to treat infertility, regulate menstrual disturbances, alleviate symptoms of hyperandrogenism, reduce weight and manage the metabolic disorder

- A recent goal of the research is to understand the molecular mechanisms involved in the pathogenesis of PCOS; data on the pathogenetic role of chronic inflammation are growing.
- Antioxidant and anti-inflammatory therapies could be the future options of treatment for patients with PCOS.

Introduction

- Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in the female population
- the diagnosis of PCOS should include two of the following three criteria: oligo- or anovulation; clinical and/or biochemical signs of hyperandrogenism; polycystic ovaries on ultrasonography [5]
- According to the new evidence on the pathogenesis of PCOS, chronic inflammation [6,7] and epigenetics alteration [8] may play a crucial role in the behavior and development of this syndrome

- Hyperandrogenism and IR, the two main hormonal profile abnormalities of women with PCOS
- Nowadays, therapeutic strategies for treating PCOS are various and can act on the different biological characteristics of the disease. Initiate treatment as soon as possible may decrease the risk of potential long-term complications
- early interventions would be of critical relevance to prevent the growing expression of the syndrome that has irreversible and self-perpetuating mechanisms
- Aims of therapy are to allow a good quality of life of patients and ensure long-term fitness and health

Current pharmacological options

- Treatment of PCOS does not include a single gold-standard agent, but it depends on the clinical presentation of each patient. For this reason, the options employed in PCOS treatment aim to improve fertility, to regulate menstrual disturbances, to alleviate the symptoms of hyperandrogenism, to manage the metabolic disorder

Infertility treatment

- In PCOS women, the ovulatory disturbance may lead to infertility and adverse pregnancy outcomes. The treatment of infertility in PCOS includes lifestyle changes (diet, exercise, and behavioral strategies), pharmacological therapies (oral agents such as clomiphene citrate, letrozole or metformin or injectable agents, such as gonadotrophins), surgical therapy (laparoscopic ovarian surgery) or in vitro fertilization (IVF)
- letrozole should be considered a firstline pharmacological treatment for ovulation induction in PCOS women

Regulation of menstrual disturbances

- OCP seems to be the best option to restore the rhythm of bleeding, to reduce HA, and to decrease the risk of endometrial hyperplasia. These effects depend on the ability of OCP to suppress pituitary LH, increasing the levels of SHBG, and decreasing the levels of free androgens
- In 2019 an extensive systematic review with meta-analyses confirmed that OCP therapy improves hyperandrogenism and menstrual regulation in women with PCOS

Alleviation of the symptoms of hyperandrogenism

- Frequently, the leading cause that leads women with PCOS to request a medical consultation is hirsutism, acne, androgenetic alopecia and acanthosis nigricans due to excessive androgen synthesis; these symptoms can deeply worsen patient's quality of life
- as evaluated by Thuzar et al., spironolactone could be effective
- As a recent study suggests, treatment with SPIOMET, a low-dose combination of spironolactone, pioglitazone and metformin
- Topical minoxidil is the first-line treatment for female androgenetic alopecia approved by FDA

Obesity treatment

- Another goal of therapy in PCOS is to reduce obesity, primarily through lifestyle modification, diet, and pharmacological therapy with metformin; secondary, surgical methods can be performed with this aim. Exercise therapy can reduce the long-term cost to healthcare systems for people at risk of chronic metabolic diseases like pre-diabetes
- Finally, bariatric surgery has been suggested as a potential method of weight loss
- Bariatric surgery is only recommended in patients with a BMI of 40 kg/m^2 or greater or 35 kg/m^2 or greater with comorbidities

New pharmacological approach

- A new therapeutic approach is based on the use of glucagon-like peptide-1 receptor agonists (GLP-1 RA). These anti-diabetic medications are incretin mimetics that offer a unique opportunity to address both excess body weight and glycemic control in one medical therapy
- Vitamin D deficiency may have an impact on the pathogenesis of IR in patients with PCOS, thus suggesting the evaluation of vitamin D supplementation in this setting
- Supplementation with omega-3, α -lipoic acid, and N-acetyl cysteine (NAC) has an antioxidant, anti-inflammatory effect, suggesting a hypothetical role in improving the insulin sensitivity and lipid profile of women with PCOS

Inflammation: role in the pathogenesis and therapeutical consequences

- Chronic inflammation may have an essential role in the pathogenesis of PCOS, and oxidative stress may influence the evolution of the disease [97]. Increased pro-inflammatory cytokines production, such as TNF- α and IL- 1β [10], seems to facilitate cell apoptosis [12] and chronic anovulation [13]. The higher level of IL- β can also downregulate SHBG, subsequently leading to HA [98].

Conclusion

- It is necessary to consider that PCOS has a multifactorial etiology and numerous clinical manifestations. Currently, the therapeutic strategies for treating PCOS are various and act on the different clinical manifestations of the disease. Future researches are yet required to understand the role of chronic inflammation in this disease to explore innovative anti-inflammatory treatments [119]. Statins, antioxidants, antiinflammatory drugs can be used as concomitant medication in the treatment of PCOS [113, 114], but we need more drugs to be considered in the treatment of PCOS which should have a profound effect on insulin resistance, ameliorating the hyperandrogenemia, infertility and overall metabolic milieu of women having PCOS.

Expert Opinion

- PCOS should be considered as a heterogeneous and evolving condition associated not only to the gynecological manifestation but also to significant systemic clinical or subclinical implications (such as hypertension and diabetes)
- PCOS women may also have an altered capacity to store fat properly. The abnormal fat deposition causes ectopic lipid accumulation in non-adipose tissue, including the ovaries, where it can perpetuate insulin resistance and inflammation and harm the oocyte, leading to adverse metabolic and reproductive implications

- When choosing a treatment regimen for PCOS, physicians should consider patients' comorbidities (e.g., cardiovascular risk factors, endocrinologic alterations) and desire for pregnancy. Lifestyle modifications should be used as a first step strategy; besides, medical treatments can be considered for treating various clinical manifestations