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Comprehensive Management of Polycystic Ovary Syndrome: The Role of Metformin in Addressing Metabolic and Endocrine Dysregulation

Martyna Kaźmierczak,

Central Clinical Hospital of Medical University of Lodz,

ul. Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0007-7798-0069

Jakub Parys,

Central Clinical Hospital of Medical University of Lodz,

ul. Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0009-1955-7865

Agnieszka Mikosińska,

Central Clinical Hospital of Medical University of Lodz,

ul. Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0003-0891-9089

Patrycja Kałuziak,

Charles Jonscher Medical Center,

ul. Milionowa 14, 93-113 Łódź, Poland

https://orcid.org/0009-0008-0976-1523

Marta Jajczak,

University Clinical Hospital No.2 of Medical University of Lodz,

ul. Żeromskiego 113, 90-549 Łódź, Poland

https://orcid.org/0009-0009-6000-7769

Maciej Mossakowski,

Central Clinical Hospital of Medical University of Lodz,

ul. Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0008-0423-2083

Aleksandra Witek,

Central Clinical Hospital of Medical University of Lodz,

ul. Pomorska 251, 92-213 Łódź, Poland

https://orcid.org/0009-0002-1214-2199

Mateusz Litwin,

University Clinical Hospital No.2 of Medical University of Lodz,

ul. Żeromskiego 113, 90-549 Łódź, Poland

https://orcid.org/0009-0006-5131-1863

Stanisław Jesionek,

Pabianice Medical Center Sp. o.o.,

ul. Jana Pawła II 68, 95-200 Pabianice, Poland

https://orcid.org/0009-0004-6026-702X

Abstract

Background: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine and metabolic disorder that affects women of reproductive age, characterized by hormonal imbalances, insulin resistance, and a range of clinical manifestations, including infertility and metabolic disturbances. Effective management of PCOS remains a challenge due to its multifaceted nature, necessitating a comprehensive understanding of therapeutic options.

Aim of the Study: This paper aims to explore the role of various treatment modalities for PCOS, with a particular emphasis on the use of metformin, an antidiabetic medication increasingly recognized for its benefits in managing insulin resistance and other associated conditions in PCOS patients.

Conclusion: The findings highlight metformin's three primary mechanisms of action: enhancing insulin sensitivity, inhibiting hepatic gluconeogenesis, and influencing lipid metabolism. Metformin is effective in improving metabolic parameters and restoring ovulatory function in women with PCOS. While it is a cornerstone of therapy, the management of PCOS requires a tailored approach that considers individual clinical

symptoms and phenotypes. Additional therapeutic strategies, including non-pharmacological measures and other pharmacological agents, play a vital role in a comprehensive treatment plan for PCOS.

Key words: Polycystic Ovary Syndrome (PCOS), insulin resistance, hyperandrogenism, Rotterdam criteria, metformin, lifestyle interventions

INTRODUCTION

Polycystic Ovary Syndrome (PCOS), also known as the Stein-Leventhal syndrome, is a multifaceted endocrine and metabolic disorder, often presenting during puberty. It is characterized by a range of clinical and biochemical abnormalities, including hormonal imbalances that lead to antral follicle formation, irregular menstruation, and infertility. PCOS is further linked to insulin resistance**,** cardiovascular disease**,** abdominal obesity**,** psychological conditions, and an elevated risk of certain cancers. (1)

Epidemiology

Polycystic ovary syndrome affects **7%** to 15**%** of women of reproductive age. Accurate prevalence data is difficult to obtain due to inconsistent definitions of the syndrome and its subphenotypes, as well as variations among study populations and recruitment methods. (2)

Diagnostic Criteria

Over recent decades, efforts have been made to standardize the diagnosis of polycystic ovary syndrome. European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) introduced the Rotterdam criteria, which mandate the presence of at least two of the following: oligo-anovulation, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasonography. (3) Despite these criteria, significant variability persists in reported

prevalence across epidemiological studies, largely due to differences in study populations, sampling methods, protocols, and inconsistent definitions of PCOS phenotypes.(4)

The Rotterdam criteria define four PCOS phenotypes: Type A (Classic PCOS) includes hyperandrogenism (HA), ovulatory dysfunction (OD), and polycystic ovary morphology (PCOM); Type B includes HA and OD; Type C includes HA and PCOM; and Type D includes OD and PCOM. With advancements in three-dimensional ovarian imaging and standardized anti-Müllerian hormone (AMH) assays, Type B may eventually be reclassified as Type A due to improved follicle population assessment.(5)(6)

Etiology

Etiology of PCOS remains uncertain, and effective treatment guidelines are lacking. A dysfunction in ovarian theca cells is believed to lead to excessive androgen production and associated clinical manifestations. A key feature of PCOS is the increased ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH). The relationship between causative factors and effects in PCOS pathogenesis is often unclear. Furthermore, obesity tends to worsen menstrual irregularities and hyperandrogenism, while weight loss may improve these symptoms. Insulin resistance is a major concern women with PCOS.(7)

In women, androgens are primarily produced by the adrenal glands and ovaries during reproductive years. Approximately 33% of circulating testosterone originates from ovarian theca cells, while the remainder is derived from androstenedione (A4)**,** produced by both glands and converted to testosterone in peripheral tissues. Testosterone is further metabolized to dihydrotestosterone (DHT) via 5-alpha reductase in ovarian granulosa cells and peripheral tissues like the skin.

The ovaries and adrenal glands also secrete dehydroepiandrosterone (DHEA) and A4, while dehydroepiandrosterone sulfate (DHEA-S) is exclusively produced in the adrenal zona reticularis under ACTH regulation. In contrast, ovarian androgen production is controlled by luteinizing hormone (LH)**.** Except for DHEA-S, circulating androgen levels fluctuate with the menstrual cycle phase. (8)

TREATMENT

Non-pharmacological measures

Several studies(9) have shown that a 5 to 10% weight loss in overweight and obese women may be sufficient to restore regular ovulation A 2013 study(10) found that women with polycystic ovary syndrome had a higher mean BMI compared to those without the condition (29.3 ± 7.5 vs. 25.6 ± 5.8 kg/m², $P < 0.001$). Although women with PCOS reported better dietary quality—higher micronutrient intake and lower saturated fat and glycemic index—their total energy intake was also elevated, along with increased sedentary behavior, while total physical activity levels were similar to non-PCOS women. Factors such as PCOS status, increased energy intake, higher glycemic index, and lower physical activity, along with age, smoking, alcohol consumption, occupation, education, and country of birth, were independently associated with BMI. Various elements, including poor dietary habits, lifestyle choices, inadequate care, late diagnosis, and lack of awareness, contribute to the prevalence of PCOS. A balanced diet consisting of 40% carbohydrates, 30% fats, and 30% proteins, coupled with regular physical activity, is recommended to alleviate severe PCOS symptoms and enhance metabolic health.(11). A meta-analysis indicates that obese women with diagnosed PCOS with bariatric surgery presented a decrease in testosterone levels. (12)

Pharmacological measures

The management of PCOS primarily targets three key areas:

1. **reducing hyperandrogenism,**
2. **improving metabolic parameters,**
3. **normalizing menstrual cycles.**

These objectives are interdependent and closely interconnected, with improvements in one domain often influencing outcomes in the others. Medications used in PCOS management frequently target one or more of these key areas, addressing specific symptoms or exerting broader effects on the syndrome as a whole. Therefore, the approach to treatment is tailored to

the clinical symptoms and phenotypes outlined in the introduction, ensuring a more personalized and effective management strategy.

This represents a simplified approach, as other additional factors, such as infertility, also play a critical role in PCOS management. However, infertility is closely linked to the key areas mentioned above, and while addressing it is essential, the treatment of infertility is beyond the scope of this paper.

Furthermore, emerging research suggests that beyond pharmacological interventions, supplements, including herbal remedies, may positively impact symptoms and overall well-being. However, these studies remain controversial, and the scientific community has not yet reached a consensus on their efficacy or safety. As such, these complementary approaches are also not addressed in this paper. (13) (14)

Additionally, the medications discussed below represent only some of the available options, highlighting the diverse and individualized approaches to managing this complex syndrome.

- **Combined oral contraceptive pills**

  Combined oral contraceptive pills (COCPs), containing both estrogen and progestogen, are among the most common treatments for PCOS. By suppressing the hypothalamus–pituitary axis, COCPs regulate menstrual cycles and act as hormone replacement therapy. They are particularly suitable for women with PCOS not seeking pregnancy. A systematic review confirmed their effectiveness in improving menstrual regularity and reducing hirsutism, with COCPs containing cyproterone acetate showing greater efficacy in managing hirsutism compared to standard formulations.(15)(16)

- **Myo-inositol**

  Myo-inositol, a stereoisomer of a C6 sugar alcohol in the inositol family, serves as a precursor to inositol triphosphate, an intracellular second messenger regulating hormones like thyroid-stimulating hormone, follicle-stimulating hormone (FSH), and insulin. It plays a crucial role in the follicular microenvironment, supporting oocyte development, maturation, and FSH signaling in PCOS treatment. Myo-inositol

effectively regulates plasma insulin levels, the homeostasis model assessment (HOMA) index, and hormones such as LH, LH/FSH ratio, testosterone, and prolactin.(17) (18)

- **Spironolactone**

  Spironolactone, an androgen receptor antagonist, is significant in treating hyperandrogenism. When prescribed for acne in women, it may reduce the reliance on antibiotics and potentially isotretinoin. Additionally, it may benefit conditions such as hidradenitis suppurativa and female androgenetic alopecia. As a monotherapy, spironolactone is as effective as cyproterone acetate combined with estradiol for the long-term management of idiopathic hirsutism. In patients with PCOS, spironolactone effectively reduces hirsutism; however, to address the hormonal or metabolic aspects of PCOS, it may need to be combined with either an antigonadotrophic agent or a drug that enhances peripheral insulin sensitivity. (19) (20)

METFORMIN

N,N'-Dimethylbiguanide, commonly known as Metformin, is an antidiabetic medication that enhances glucose utilization in insulin-sensitive tissues. Given that polycystic ovary syndrome (PCOS) and diabetes share several altered parameters, including abnormal glucose-to-insulin ratios, disrupted lipid metabolism, and insulin resistance, the use of Metformin has gained significant acceptance and is increasingly widespread in the management of PCOS.

Metformin primarily exerts its effects through three key mechanisms. First, it enhances insulin sensitivity, allowing for improved glucose uptake by the body's cells. Second, it inhibits gluconeogenesis in the liver, reducing glucose production and helping to maintain normal blood sugar levels. Third, metformin influences lipid metabolism, which can lead to lower levels of cholesterol and triglycerides(21)

Insuline sensitivity

Metformin is the most commonly prescribed medication for the management of type 2

diabetes (T2D) and is recognized as an "essential medicine" by the World Health Organization. (22) Numerous studies in both animal models and humans have identified impaired GLUT4-mediated glucose uptake as a key mechanism underlying insulin resistance (IR). While Metformin is primarily known for its ability to lower plasma glucose levels, research into its additional properties and effects is ongoing. In terms of glucose homeostasis, Metformin primarily functions by enhancing insulin-mediated suppression of hepatic glucose production and improving insulin-stimulated glucose uptake in peripheral tissues. (23) (24)

Experimental studies have demonstrated that the improvements in insulin sensitivity associated with Metformin may involve several mechanisms. These include increased insulin receptor tyrosine kinase activity, enhanced glycogen synthesis, and, at the most downstream level, increased recruitment and activity of GLUT4.(25)

Findings emerged from studies examining GLUT4 expression in the endometria of patients with polycystic ovary syndrome (PCOS). Researchers observed that GLUT4 mRNA and protein levels were significantly higher in the endometria of PCOS patients who had been on Metformin for at least three months compared to those not receiving Metformin, with levels reaching similar values to those found in the control group.(26)

Inhibition of gluconeogenesis

Hepatic glucose production (HGP) constitutes approximately 90% of endogenous glucose production and is essential for systemic glucose homeostasis. (27)The regulation of HGP involves the suppression of both hepatic glycogenolysis and gluconeogenesis. The liver plays a critical role in maintaining normal glucose levels; it produces glucose during fasting periods and stores it postprandially. However, these hepatic processes can become dysregulated, leading to impaired glucose homeostasis.(28)

One of the most thoroughly investigated mechanisms of metformin is its activation of the signaling kinase AMP-activated protein kinase (AMPK). Recent studies indicate that metformin activates AMPK by decreasing hepatic energy charge, which increases the ratios of [AMP]:[ADP] and/or [ADP]:[ATP].(29) Additionally, metformin may activate AMPK through the upstream kinase LKB1, resulting in the downregulation of gluconeogenic gene transcription. Metformin has a milder effect compared to other related guanidine and

biguanide compounds, such as galegine and phenformin. However, phenformin was removed from clinical use due to its adverse effects, particularly the heightened risk of lactic acidosis. (30)

Metformin, similar to other biguanide-class medications, elevates plasma lactate levels in a concentration-dependent manner by inhibiting mitochondrial respiration predominantly in the liver. Metformin-associated lactic acidosis (MALA) generally arises when high plasma metformin concentrations—often observed in patients with renal impairment—coexist with additional factors that hinder lactate production or clearance, such as cirrhosis, sepsis, or hypoperfusion.(31)

The impact of metformin on plasma lactate levels in bariatric surgery patients remains unexplored; however, these individuals may be at a heightened risk for metformin-associated lactic acidosis (MALA) due to enhanced absorption and bioavailability of the drug.

Many individuals with diabetes continue to take metformin even when they have conditions that increase their risk for lactic acidosis. Some estimates indicate that approximately 25% of patients prescribed metformin have one or more contraindications to its use.(32)

Renal dialysis is recommended for the treatment of metformin-associated lactic acidosis (MALA) to facilitate the removal of metformin and correct metabolic acidosis. This approach underscores the relationship between elevated plasma metformin concentrations and increased plasma lactate levels.(33) (34)

CONCLUSION

Polycystic Ovary Syndrome is a complex endocrine and metabolic disorder affecting 7% to 15% of women of reproductive age. Characterized by hormonal imbalances, including hyperandrogenism, irregular menstruation, and insulin resistance, PCOS is associated with a variety of health issues such as infertility, cardiovascular disease, and an increased risk of certain cancers. The diagnosis of PCOS is guided by the Rotterdam criteria, which require the

presence of at least two of the following: oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology.

Treatment strategies for PCOS focus on three key areas: reducing hyperandrogenism, improving metabolic health, and normalizing menstrual cycles. Both pharmacological and non-pharmacological measures are employed, with lifestyle modifications such as weight loss and a balanced diet being critical. Among pharmacological options, combined oral contraceptives, spironolactone, and myo-inositol are commonly used. Metformin, an antidiabetic medication, is increasingly recognized for its role in managing PCOS due to its effects on insulin sensitivity, gluconeogenesis inhibition, and lipid metabolism.

Metformin enhances glucose utilization in insulin-sensitive tissues and helps regulate metabolic parameters in women with PCOS, making it a valuable treatment option. However, the management of PCOS should be individualized, taking into account the specific symptoms and phenotypes of each patient. While metformin is a cornerstone of therapy, other therapeutic strategies and complementary approaches, such as herbal supplements, are also emerging, although their efficacy requires further investigation. Overall, a multifaceted and personalized approach to treatment is essential for effectively managing the complexities of PCOS.

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Authors' contribution:

Conceptualization: Marta Jajczak, Martyna Kaźmierczak;

Methodology: Mateusz Litwin, Jakub Parys

Investigation:, Jakub Parys, Stanisław Jesionek

Sources: Maciej Mossakowski, Aleksandra Witek

Formal analysis: Agnieszka Mikosińska, Marta Jajczak

Visualization: Jakub Parys, Agnieszka Mikosińska

Validation: Maciej Mossakowski, Stanisław Jesionek

Supervision: Patrycja Kałuziak,

Writing - original draft: Martyna Kaźmierczak

Writing - review and editing: Aleksandra Witek, Mateusz Litwin

Project administration: Patrycja Kałuziak,

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