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Relationship between Polycystic Ovary Syndrome and Metabolic Syndrome.

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous, complex, and widely misunderstood endocrine disorder that affects intermediate metabolism, the cardiovascular and reproductive systems, and has social and psychological consequences. The prevalence and incidence of PCOS is high among women with Metabolic Syndrome (MetS). In Mexico, the hyperandrogenic subtype is the most prevalent of the characterized subtypes and is characterized by hyperandrogenism, insulin resistance, and ovulatory dysfunction. Central obesity plays a role in the development of the hyperandrogenic subtype as adipositopathy can cause a syndrome of insulin resistance and androgen excess, both of which contribute to cardiovascular comorbidities. These two syndromes share similar pathophysiological mechanisms, suggesting that PCOS could be a complication of MetS or vice versa. The purpose of this article is to explore the relationship between MetS and PCOS, with a focus on pathogenesis, infertility, microbiota, comorbidities, and treatment.

KEYWORDS: Metabolic syndrome, Polycystic Ovary Syndrome, fertility, insulin resistance, microbiome.

1 INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in reproductive-aged women, characterized by polycystic ovaries, hyperandrogenism, anovulation, menstrual irregularities, and weight gain. It is estimated to affect approximately 7% of reproductive-aged women and is one of the most common causes of infertility.[1]

Metabolic syndrome (MetS) is a group of medical disorders, including central obesity, high blood pressure, insulin resistance, hyperglycemia, and hyperlipidemia, that are associated with an increased risk of cardiovascular disease and type 2 diabetes. Women with PCOS have been shown to have a higher prevalence of MetS compared to women without PCOS. In addition to its association with MetS, PCOS is also associated with a higher incidence of infertility. Anovulation and hyperandrogenism are key factors in infertility associated with PCOS. Insulin resistance and weight gain may also contribute to infertility in women with PCOS, as these factors can affect ovulation and ovarian function. PCOS is the most common endocrine disorder that leads to infertility in women. Despite its name, the "cysts" seen in the ovaries are accumulations of follicles in varying stages of

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maturation and atresia, which only represent one aspect of this complex syndrome.[2-4]

Attempts have been made to rename this condition, but international expert societies and academies in the field have not yet agreed on a more accurate name, due to the different phenotypes that the disease can take. For example, the Rotterdam definition requires 2 of the following 3 criteria for a diagnosis of PCOS:

1) hyperandrogenism,
2) ovulatory dysfunction, and
3) oligoovulation and polycystic ovarian morphology (PCOM).

The Androgen Excess and PCOS Society (AE-PCOS), on the other hand, requires the presence of hyperandrogenism with ovarian dysfunction and PCOM. The National Institute of Child Health and Human Development, meanwhile, does not consider PCOM, but mandates hyperandrogenism and ovarian dysfunction.[5-7]

Given the heterogeneity of PCOS in terms of both pathophysiology and severity, it's possible that we are dealing with multiple entities that are being grouped under one name. Some women have hyperandrogenism without insulin resistance and a normal weight, while others have clear insulin resistance, metabolic and reproductive dysfunction, are overweight/obese, and have hyperandrogenism and PCOM. There is currently no solid basis for categorizing each group. However, in Mexico, we have observed that the prevailing PCOS phenotype is linked to cardiometabolic disorders, insulin resistance, hyperandrogenism, and PCOM, which is associated with the increase in the incidence and prevalence of MetS in our country.[8-9]

MetS is defined by central obesity, high blood pressure, insulin resistance, and dyslipidemia, and its long-term complications include the development of type 2 diabetes, cardiovascular disease (coronary heart disease, stroke), cancer, obstructive sleep apnea, psychological/psychiatric problems, infertility, and reproductive system disorders. It's important to note that the pathophysiology and long-term consequences of hyperandrogenic PCOS are like MetS, as if they were the same entity and PCOS was just another complication (Figure 1). Some authors argue that PCOS is the cause of the development of MetS, but evidence shows that hyperandrogenism is not the cause of insulin resistance, as the pharmacological suppression of androgens does not improve insulin resistance. It's not yet clear if PCOS is a manifestation of MetS or vice versa.[10-11] This review examines the current relationship between PCOS and MetS, highlighting their similarities and offering a critical perspective for medical professionals when dealing with patients with both syndromes.

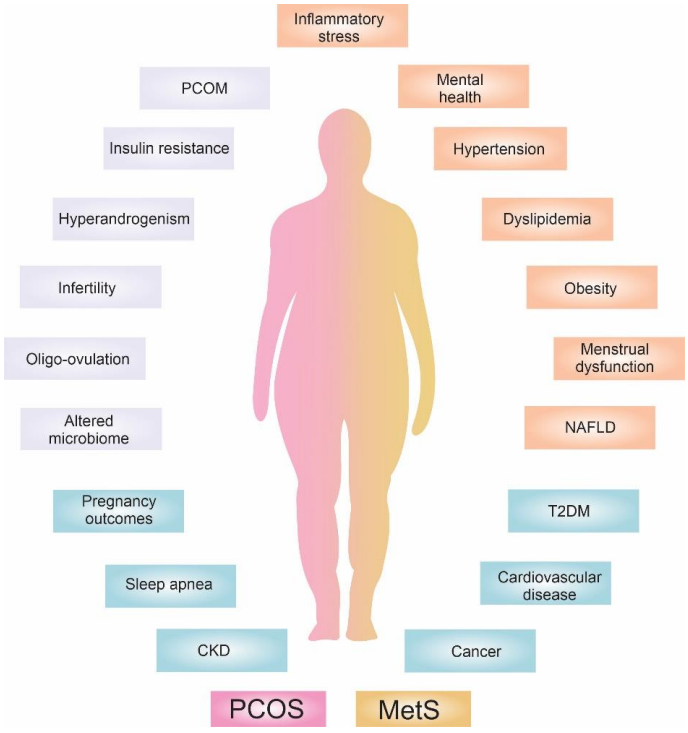

Figure 1. Interrelationship between PCOS and MetS. The interrelation between PCOS and MetS is a result of a vicious circle where excessive visceral adipose tissue increases androgen production, which in turn can trigger PCOS. However, women with PCOS also have a higher risk of developing obesity due to insulin resistance. As a result, MetS and PCOS feed each other. This potentiates the presence of short-term comorbidities such as mental health problems, menstrual disorders, infertility, acanthosis nigricans, etc., and in the long term: type 2 diabetes (T2DM), chronic kidney disease (CKD), increased risk of cancer, cardiovascular diseases, obstructive sleep apnea, non-alcoholic fatty liver disease and liver cirrhosis, leading to patient death. It is important to identify and refer both syndromes to address these comorbidities and prevent any long-term health problems.

2 Pathogenesis

PCOS is a heterogeneous syndrome characterized by an excess of androgens (hirsutism and/or hyperandrogenemia) and ovarian dysfunction (oligoovulation and polycystic ovarian morphology). The etiology remains unknown, but there is evidence of it being a multigenic and epigenetic disease with influences from the external environment, especially lifestyle factors. Different phenotypes of PCOS have been described:

1) hyperandrogenism with ovulatory dysfunction,
2) hyperandrogenism with PCOM,
3) oligo-ovulation with PCOM,
4) hyperandrogenism, oligo-ovulation, and PCOM.[8, 12]

In terms of pathophysiology, insulin resistance and hyperinsulinemia are the most important mechanisms in the development of PCOS. This is because in a state of overweight/obesity, adipositopathy promotes a state of peripheral insulin resistance and compensatory hyperinsulinemia that contributes to excessive androgen production. Furthermore, insulin acts as a gonadotropin in the ovary, facilitating the secretion of suprarenal androgens and modulating the pulsatile secretion of LH. In turn, androgens contribute to dysfunction of the adipose organ, generating a vicious circle of excess androgens that favors the deposit of abdominal fat tissue and visceral adiposity by inducing insulin resistance and compensatory hyperinsulinemia, which further facilitates androgen secretion by the ovaries and suprarenal glands. From this perspective, the most important factor is obesity, abdominal adiposity, and insulin resistance, elements that are fundamental to the development of MetS. Because apparently the heterogeneity and severity of PCOS is due to a possible MetS, genetic and epigenetic factors would play an important role in the development of different phenotypes and subphenotypes reported. When the environmental factors related to the development of PCOS and MetS are analyzed, we observe that they share the same etiopathogenesis. Briefly, intrauterine growth delay and insulin resistance induce a thrifty phenotype that leads to overweight problems in childhood, which can progress to obesity, hypertension, insulin resistance, dyslipidemia, and PCOS, as if PCOS were a lost milestone in the natural history of MetS. Many answers to the multiple questions of the origin and complexity of PCOS are still outstanding.[13-16]

3 Infertility

PCOS is the most common causa of infertility in women. This is because PCOS can cause irregular menstrual cycles and the formation of cysts on the ovaries, which can prevent ovulation from occurring. As a result, women with PCOS may have trouble getting pregnant without medical intervention. Treatment options for infertility in women with PCOS may include medications to induce ovulation, such as clomiphene citrate or letrozole, or assisted reproductive technologies like in vitro fertilization (IVF). Maintaining a healthy lifestyle, including a balanced diet and regular exercise, can also help improve fertility in women with PCOS.

Due to a poor understanding of the mechanisms involved, there are limited options in the specific etiological treatment for infertility, however, once pregnancy is achieved, PCOS predisposes to the development of gestational diabetes, spontaneous abortion, hypertension in pregnancy, preeclampsia, pregnancy preterm which increases the risk of neonatal death, complications shared in women with MetS in the fertile stage[17].

3.1 Miscarriage

Although the main causes of spontaneous abortion are associated with chromosomal abnormalities, it is also linked to metabolic disorders such as obesity, MetS, diabetes mellitus, and PCOS Several studies have found that PCOS is not a direct cause of spontaneous abortion, as the rates of spontaneous abortion among women with PCOS were similar to those among women without PCOS. However, when PCOS is present in women with high Body Mass Index (BMI), a strong association has been observed, suggesting that BMI may be a confounding variable, as obesity is a known cause of spontaneous abortion. Given that both PCOS and MetS are prevalent in Mexico, it is possible that the presence of both conditions could contribute to the high rate of spontaneous abortions among women with both syndromes. The mechanism by which PCOS may lead to spontaneous abortion is not yet clear, but potential mechanisms include insulin resistance, hyperhomocysteinemia, hyperandrogenemia, PAI1, vitamin D binding protein, and MetS. Further studies are needed to fully understand the association between these syndromes and spontaneous abortion.[18-22]

3.2 Gestational Diabetes Mellitus.

Gestational Diabetes Mellitus (GDM) is characterized by a state of glucose intolerance that develops in the second trimester of pregnancy and is linked to insulin resistance, hyperglycemia, oxidative stress, and chronic inflammation. The connection between MetS and GDM is widely acknowledged, and it is crucial to identify patients who may be at risk for developing GDM. However, the relationship between GDM and PCOS is unclear. Several studies have not yet confirmed the extent to which the relationship between GDM and PCOS is independent of MetS.

Some authors suggest that PCOS is not a standalone risk factor for the development of GDM, as pregnancies that occur with PCOS often come with additional risk factors, such as high Body Mass Index (BMI). To date, there is no study that clarifies the relationship between GDM and PCOS without the influence of obesity as a confounding factor. This could be due to the fact that the attempt to separate PCOS from MetS is misguided, as PCOS could actually be considered a bi-syndrome.[23-26]

3.3 Preeclampsia

Pregnancy-induced hypertension is defined as a systolic blood pressure >140 mmHg and/or a diastolic blood pressure >90 mmHg on two separate occasions with at least 2 hours difference, that occurred either before pregnancy or after 20 weeks of gestation. MetS is a risk factor for preeclampsia, and similarly to gestational diabetes mellitus (GDM), there is a confounding factor between obesity and PCOS and preeclampsia. Several meta-analyses have tried to clarify the role of PCOS in the development of pregnancy-induced hypertension and although the results are polarized, it seems that there are a number of mechanisms that potentially support the association between PCOS and preeclampsia, many of which are shared with MetS. Some of these mechanisms include insulin resistance and hyperinsulinemia, hyperhomocysteinemia, restriction of coenzyme A, peripheral vascular resistance, hyperlipidemia, chronic inflammation, among others. Again, more clinical studies are needed to decipher the interaction between MetS, PCOS, and preeclampsia.[27-30]

3.4 Preterm birth

PCOS has been associated with preterm birth (Preterm birth is defined as birth before 37 weeks of gestation) in several studies, although the exact mechanisms linking the two are not well understood. The association between PCOS and preterm birth is partly due to the history of assisted reproduction, as previously it increased the risk of multiple births and hypertensive diseases, which are associated with the development of preterm birth. With regards to the proposed mechanisms, these include obesity, MetS, nulliparity, hyper-estrogenemia, hyperinsulinemia, GDM, meta-inflammation, and hyperandrogenism. Although there appears to be an association between PCOS and preterm birth, the reported risk factors are mainly associated with MetS, which highlights the need for further research to fully understand the link between PCOS and preterm birth.[31-33]

4 Microbiome

The intestinal microbiome is a collection of microorganisms that reside the gastrointestinal tract, with the majority belonging to four phyla: Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria and others. These microorganisms maintain a stable relationship with the intestinal epithelium and form a stable community that performs complementary functions and interacts with the host.

Changes in the gut microbiome have been linked to the development of metabolic disorders such as type 2 diabetes and obesity. There is evidence that the gut microbiome differs between people with metabolic disorders and those who are healthy. Intestinal dysbiosis is associated with chronic inflammation, insulin resistance, excessive androgen secretion, dyslipidemia, and obesity, conditions that are common in PCOS and MetS.[34]

In a recent study, Saturina et al. observed that it was possible to distinguish significant differences in the microbiome of PCOS patients and those without PCOS. These findings are controversial compared to previous reports that found no significant differences. This discrepancy may be due to the fact that Saturina et al. classified PCOS patients based on phenotypes. On the other hand, Lull et al. reported a negative correlation between the Shannon index and body mass index, fasting insulin, and free androgen index, and a positive correlation with sex-hormone-binding globulin, Matsuda index, and disposition index. While some studies have not found clear changes in the microbiome related to hyperandrogenism, a pathological metabolic state may reveal that changes in the microbiome are influenced by MetS rather than hyperandrogenism. There is ample evidence to support that MetS patients have a distinct gut microbiome compared to healthy individuals. The gut microbiota affects women with PCOS by promoting insulin resistance and increasing gut permeability, leading to chronic inflammation and subsequent excessive androgen secretion. Further research is needed to determine if there is a difference in the microbiome of Mexican women with PCOS and PCOS/MetS compared to healthy women.[35-37]

5 Comorbidities

PCOS and MetS share several comorbidities, including:

1) Obesity: Both PCOS and MetS are often linked to obesity, which can exacerbate the symptoms and comorbidities associated with the conditions,
2) Insulin resistance: Women with PCOS are at an increased risk of insulin resistance, while MetS is characterized by elevated insulin levels,
3) Cardiovascular disease: PCOS and MetS both increase the risk of heart disease, high blood pressure, and stroke,
4) Type 2 diabetes: PCOS and MetS both increase the risk of developing type 2 diabetes,

5) Dyslipidemia: Both PCOS and MetS are associated with alterations in cholesterol and triglyceride levels, which can increase the risk of cardiovascular disease,
6) Sleep apnea: PCOS and MetS both increase the risk of obstructive sleep apnea,
7) Mental health issues: Women with PCOS and MetS may experience depression, anxiety, and other mood disorders.

It's important for women with PCOS and MetS to be evaluated and monitored regularly by a healthcare provider to address these comorbidities and prevent any long-term health issues. For a more detailed review, consult the review article by Emily W. Gilbert et. al.[38]

5.1 PCOS and COVID-19

PCOS and SARS-CoV-2 (COVID-19) infection are two different medical conditions that affect different bodily systems. However, there is some evidence that women with PCOS may have an increased risk of serious complications from COVID-19. The relationship between PCOS and COVID-19 is discussed, with evidence suggesting that women with PCOS have a significant risk of hospital complications and mortality during the COVID-19 pandemic due to factors such as insulin resistance, central obesity, and hyperandrogenemia. Additionally, epidemiological data suggests that women with PCOS have a 28% to 50% higher risk of contracting SARS-CoV-2 and that COVID-19 is associated with higher rates of hospitalization, morbidity, and mortality in these women. It has also been seen that obesity worsens the COVID-19 situation due to the increase in proinflammatory cytokines, and that insulin resistance and hyperinsulinemia, which are common in PCOS, explain the association between PCOS and a more prevalent infection with SARS-CoV-2. PCOS is a common endocrine disorder that affects approximately 5-10% of women of reproductive age. It is characterized by irregular ovulation, increased production of androgen hormones, and the formation of ovarian cysts. Many women with PCOS have obesity, hyperinsulinemia, and insulin resistance, which makes them more prone to developing metabolic diseases such as type 2 diabetes and cardiovascular disease. On the other hand, COVID-19 is an infectious disease caused by the SARS-CoV-2 virus that spreads through contact with respiratory droplets from an infected person. COVID-19 can cause mild to severe symptoms, including fever, cough, difficulty breathing, and in severe cases, respiratory failure and death. PCOS is a different clinical entity from the MetS, but both can be related. Many women with PCOS have risk factors for the MetS, such as obesity, insulin resistance, and hyperinsulinemia. However, there are also women with the MetS who do not have PCOS. Therefore, it can be said that PCOS and the MetS are two distinct, but related conditions.

In recent studies, it has been demonstrated that women with PCOS have a higher risk of developing serious complications from COVID-19, including hospitalization and the need for mechanical ventilation. This may be due to a combination of factors such as obesity, insulin resistance, and hyperandrogenemia, which are known to increase the risk of serious COVID-19 illnesses. Obesity can trigger PCOS because excess body fat can increase the production of androgen hormones, which in turn can trigger PCOS. However, women with PCOS also have an increased risk of developing obesity due to insulin resistance and other health problems related to PCOS. Therefore, it can be a vicious circle, where obesity and PCOS feed into each other. Insulin acts as a gonadotropin in women with PCOS due to insulin resistance that characterizes the disease. Insulin resistance causes insulin levels to increase in the body, which in turn stimulates the production of androgens in the ovaries. These excessive androgens can trigger the growth of ovarian cysts, which are a distinctive feature of PCOS. Furthermore, high insulin levels can also interfere with normal ovulation, which can contribute to the development of PCOS. It has been seen that women with PCOS have a higher risk of contracting COVID-19 due to the presence of comorbidities associated with PCOS, such as insulin resistance, central obesity and hyperandrogenemia. These factors, along with age and other metabolic diseases, can increase vulnerability to infection with the SARS-CoV-2 virus. In addition, it has been demonstrated that obesity exacerbates the course of COVID-19 disease, which explains the association between PCOS and a higher prevalence of SARS-CoV-2 infection. In conclusion, although PCOS and COVID-19 are two different medical conditions, there is some evidence that women with PCOS may have a higher risk of serious complications from COVID-19.[39-41]

6 Recent advances in emerging PCOS therapies.

The current treatment for PCOS with metabolic features depends on the patient's goals. For women not seeking fertility assistance, combined oral contraceptive pills (OCs) are commonly prescribed to treat menstrual irregularities and physical manifestations of hyperandrogenism such as hirsutism, acne, and alopecia. These pills contain both estrogen and progestin and reduce gonadotropin release and androgen production. Anti-androgen medications may also be used if needed. For metabolic symptoms, weight loss and dietary changes, as well as oral insulin sensitizers like metformin, are recommended. For women seeking fertility treatment, weight loss and ovulation induction agents such as letrozole or

clomiphene citrate with metformin may be advised, but these treatments increase the risk of ovarian hyperstimulation syndrome.[42]

6.1 Novel treatments for PCOS.

Although current treatment strategies for the endocrine, metabolic, and reproductive aspects of PCOS are effective, there is still a need for improvement. Firstly, many current therapies are associated with adverse side effects, such as weight gain associated with oral contraceptive use, gastrointestinal problems related to metformin and an increased risk of ovarian hyperstimulation syndrome (OHSS) in fertility treatments. Secondly, hormonal treatments are not always appropriate, for example in individuals where estrogen therapy is contraindicated, such as breast cancer, venous thrombosis, and stroke. Fortunately, there are several novel treatments for the management of PCOS that are demonstrating their potential in preclinical animal models and early clinical trials.[43-45]

6.2 New treatments targeting excess androgens.

Hyperandrogenism contributes to the central pathogenesis of PCOS and underlies many of the obvious and problematic symptoms for patients with PCOS. According to this, animal models replicating the metabolic and reproductive features of PCOS are often generated by prenatal or peripubertal exposure to excess androgens. Therefore, therapeutic reduction of androgens or androgen receptor (AR) blockade are important strategies in the treatment of PCOS. Early antiandrogenic intervention may also be critical for improving fertility outcomes. A population-based retrospective study in Sweden found that women with PCOS who had early antiandrogenic intervention (before the age of 18) had improved fertility rates compared to those with later interventions. Furthermore, studies in mice indicate that excess androgens can have long-term impacts on follicle and oocyte quality that may continue to affect fertility even after restoring hyperandrogenism. Direct antagonists of androgen receptors may interact with GABA-A receptors in the brain, increasing the risk of seizures.[46-48]

6.3 New treatments targeting neuroendocrine dysfunction.

Clinical targeting of neuroendocrine dysfunction involves the modulation of GnRH and its inputs within the GnRH neuronal network to treat conditions such as PCOS GnRH antagonists, such as cetrorelix, have shown promise in treating PCOS in animal models. Modulation of kisspeptin through a kisspeptin receptor agonist, MVT-602, has been investigated as a therapeutic strategy in a small clinical trial, with promising results. Modulation of neurokinin B through its antagonist fezolinetant has also been studied in clinical trials and has shown reduction in LH and testosterone levels in women with PCOS. Another avenue of therapy is to target the dynorphin receptor kappa opioid to enhance dynorphin-mediated inhibition of kisspeptin secretion. Overall, the modulation of GnRH inputs within the GnRH neuronal network offers promising avenues for the treatment of PCOS.[49-51]

6.4 New treatments targeting insulin resistance.

Treatments targeting insulin resistance in PCOS aim to reduce hyperinsulinemia and insulin resistance that commonly occur in both obese and non-obese women with PCOS. This reduction helps to reduce hyperandrogenism, which exacerbates ovarian androgen production and reduces SHBG (Sex Hormone Binding Globulin), leading to increased testosterone levels. Due to limitations and adverse effects of metformin, alternative insulin sensitizing agents are being researched, including humanin analogues, sodium glucose co-transporter inhibitors, and incretin mimetics. Humanin is a peptide with protective effects under stress conditions in various cell types, including gonadal cells. Decreased humanin expression has been found in PCOS patients with insulin resistance. Studies in DHEA-induced PCOS rats showed humanin supplementation improved fasting glucose and insulin levels and decreased body weight gain. Sodium glucose co-transporter inhibitors, such as SGLT2 inhibitors, are anti-diabetic drugs used in treating type 2 diabetes. They improve insulin sensitivity and blood glucose levels and can cause weight loss. Clinical trials comparing SGLT2 inhibitors to metformin in overweight/obese PCOS patients showed benefits including decreased body weight, serum DHEAS, and fewer adverse effects. A dual SGLT1/2 inhibitor (LIK066) showed promising results in reducing insulin and androgen levels in a 2-week Phase 2 trial in PCOS women. Incretin mimetics, such as GLP-1 receptor (GLP-1R) agonists, have shown promising results in treating PCOS. Clinical trials found that GLP-1R agonists, such as Liraglutide and Semaglutide, reduced free androgens and body weight, and improved insulin sensitivity compared to placebo or metformin. There is some evidence that GLP-1R analogues modulate GnRH release and LH surge in rats. Although the results of these treatments are promising, further studies with larger sample sizes and direct comparisons are needed to fully establish their efficacy and safety for use in treating PCOS.[52-54]

6.5 PCOS and clinical trials.

Although there are multiple treatments aimed at treating the symptoms of PCOS, there is no specific treatment approved by either the FDA or the European Medicines Agency. Currently, there are 749 records of clinical trials on ClinicalTrials.gov addressing PCOS

and 223 addressing the relationship between PCOS and MetS, however, the number of studies involving a treatment is limited. In the pharmaceutical industry, there are only 12 studies addressing PCOS and obesity, including low-dose contraceptive treatments, exenatide, dapagliflozin, exenatide plus dapagliflozin, dapagliflozin plus metformin, liraglutide, D-chiro-inositol, metformin, and orlistat, and phentermine with topiramate. And only 25 records by NIH that include low-carbohydrate dietary intervention, flutamide, oral contraceptives, stress management-focused psychological treatment, iDPP4, adrenergic receptor agonists, leuprolide acetate, and spironolactone. Therefore, from a pharmacological treatment perspective, PCOS may currently be considered the most prevalent orphan disorder among adolescent and adult women.

7 Conclusion

In conclusion, PCOS is a common endocrine disorder in reproductive-aged women that is characterized by polycystic ovaries, hyperandrogenism, anovulation, menstrual irregularities, and weight gain. PCOS is also associated with a higher prevalence of MetS, which is defined by central obesity, high blood pressure, insulin resistance, and dyslipidemia. The exact pathogenesis of PCOS remains unknown, but there is evidence that it is a multigenic and epigenetic disease that is influenced by lifestyle factors, particularly obesity and insulin resistance. PCOS and MetS have similarities in terms of pathophysiology and long-term consequences, and it's not yet clear if PCOS is a manifestation of MetS or vice versa. Further research is needed to better understand the relationship between PCOS and MetS.

This syndrome is one of the most poorly understood by both patients and physicians. It has been wrongly perceived as a temporary condition with limited impacts on fertility, but the lack of understanding about its long-term consequences has led to deaths in our country. One reason for this misunderstanding may be due to the incorrect terminology; Polycystic Ovary Syndrome (Hyperandrogenic) should more accurately be referred to as a MetS affecting the female reproductive system and its associated consequences. By adopting this proper terminology, we can better address and prevent cardiovascular and metabolic complications.

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CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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