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How to control Polycystic Ovary Syndrome's symptoms through pharmacological and non-pharmacological approaches

Ana Sofia da Silva Marques

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Orientador: Dr. Renato Alessandre Silva Martins
Coorientadora: Dr.ª Marlene Marques Morgado

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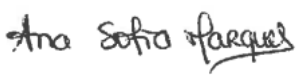

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Resumo

A Síndrome de Ovários Poliquísticos (SOP) é uma doença multissistémica com elevada prevalência, até 20% de mulheres em idade fértil (1), com grandes consequências em saúde, a longo prazo. Apesar destes dados pouco animadores, a fisiopatologia desta doença permanece pouco esclarecida, sendo que o hiperandrogenismo, hiperinsulinemia, disfunção ovariana e obesidade parecem ser fatores importantes no seu desenvolvimento.

O tratamento desta síndrome continua por estabelecer e depende de vários fatores, incluindo o fenótipo da doente, as suas preocupações e os seus objetivos, abordando os sintomas mais importantes para cada doente e a busca, ou não, de conceção. Inclui alterações do estilo de vida, prática de exercício físico, suplementação e medidas farmacológicas.

A infertilidade é uma das consequências com maior impacto na vida destas mulheres e dos/das respetivos companheiros/as e que, muitas vezes, leva estes casais a recorrer a métodos de reprodução medicamente assistida (RMA). Mesmo após a conceção, os riscos obstétricos associados à SOP, permanecem elevados, tais como o risco de abortamento precoce e pré-eclampsia (73).

A informação sobre o tratamento da SOP é vasta e mostra evidências para a utilização de duas abordagens, a farmacológica e não farmacológica. Os estudos realizados levam-nos a acreditar que é premente a adoção de um tratamento individualizado e multidisciplinar. Este deve ser baseado nos sinais e sintomas mais prevalentes, incluindo uma abordagem holística destas mulheres, sem descartar a utilização de nenhuma das terapêuticas. Ainda assim, é necessária uma aposta na prevenção e literacia da população, para a adoção de estilos de vida mais saudáveis.

Palavras-chave

polycystic ovary syndrome; drug therap*; diet* therap*; lifestyle; insulin resistance; amenorrhea; oligomenorrhea; ovulation; inositol; hyperandrogenism; pathophysiology; infertility; fertility

Abstract

Polycystic Ovary Syndrome (PCOS) is a multisystemic disease highly prevalent in reproductive age women, with a prevalence of 20% (1), with many long-term health consequences. Even though these data are not very cheering, its pathophysiology remains poorly stablished. It seems that hyperandrogenism, hyperinsulinemia, ovarian disfunction, and obesity are involved in its development.

The treatment of Polycystic Ovary Syndrome is not fully stablished yet and it depends on a variety of factors, including the patient's phenotype, concerns, and main goals, approaching the most important symptoms for each patient and its will for pregnancy. Taking this into a count, the treatment includes lifestyle interventions, exercise, supplementation, and pharmacological treatment.

Infertility is one of the consequences with the most impact on these women's lives and their partners. Because of that, more often, these couples feel the need to seek help from Artificial Reproductive Techniques (ART). Even though they can achieve conception, the obstetric risks associated with PCOS remain high, such as early pregnancy loss and preeclampsia (73).

There is a vast base of information on PCOS's treatment which shows evidence for the usage of both pharmacological and non-pharmacological approaches. The reviewed studies lead us to believe that the adoption of an individualized and multidisciplinary treatment based on prevailing signs and symptoms is a pressing issue, including a holistic approach of each case, without discarding any kind of approach. Beside this, it is also necessary to bet on prevention and society's literacy for the adoption of healthier lifestyles.

Keywords

polycystic ovary syndrome; drug therap*; diet* therap*; lifestyle; insulin resistance; amenorrhea; oligomenorrhea; ovulation; inositol; hyperandrogenism; pathophysiology; infertility; fertility

Index

List of Tables

List of Acronyms

AIs	Aromatase Inhibitors
AMH	Antimüllerian Hormone
ART	Artificial Reproduction Techniques
BBB	Berberine
BMI	Body Mass Index
CC	Clomiphene Citrate
COC	Combinationed Oral Contraceptives
CoQ10	Co-enzyme Q10
CVD	Cardiovascular Disease
DCI	D-Chiro Inositol
DPP4-i	Dipeptidyl Peptidase-4 inhibitors
FMT	Fecal Microbiota Transplantation
FSH	Follicle Stimulant Hormone
GDM	Gestational Diabetes Mellitus
GLP-1	Glucagon like Peptide 1
GnRH	Gonadotropin hormone-releasing hormone
HA	Hyperandrogenemia
HDL	High-Density Lipoprotein
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
IR	Insulin Resistance
IVF	In-Vitro Fertilization
IVM	In-Vitro Maturation
LDL	Low-Density Lipoprotein
LGI	Low Glycemic Index
LH	Luteinizing Hormone
LOD	Laparoscopic Ovarian Drilling
LPS	Lipopolysaccharides
LSM	Lifestyle Modifications
MetS	Metabolic Syndrome
MI	Myoinositol
NAC	N-Acetyl Cysteine
OHSS	Ovarian Hyperstimulation Syndrome
PCOS	Polycystic Ovary Syndrome
PUFAs	Polyunsaturated Fatty Acids
QOL	Quality of Life
QUR	Quercetin
RMA	Reprodução Medicamente Assistida
ROS	Reactive Oxygen Species
SGLT-2	Sodium-Glucose Cotransporter 2
SHBG	Sex Hormone Binding Globulin
SOP	Síndrome de Ovários Poliquísticos
TCM	Traditional Chinese Medicine
TG	Triglycerides
TZDs	Thiazolidinediones
WHO	World Health Organization

1. Introduction

Polycystic ovary syndrome (PCOS), also known as Hyperandrogenic Anovulation or Stein-Leventhal syndrome, is a multifactorial lifelong disorder that affects many women worldwide (1).

Usually, it is diagnosed when complications are developed, which significantly reduces the patient's quality of life (QOL) (e.g., hair loss, alopecia, acne, and infertility-related problems) and underscores PCOS' significant financial burden. PCOS is not only a gynecological disease, rather it is an endocrine and metabolic disorder that has many comorbidities, including metabolic disfunction and obstetric complications (1).

According to the World Health Organization (WHO), PCOS is the major cause of anovulatory infertility and eugonadotrophic hypogonadism, however its pathogenesis has not been fully elucidated yet (2). Thereby, the most critical factor in the diagnosis of PCOS is the physician awareness, knowledge, and attentiveness to possibility of the diagnosis (1).

PCOS' treatment has not been stablished yet and there are a lot of questions regarding alternative medicine techniques and drugs that can help these women. As such, it is important to review the major treatment approaches for this syndrome.

In this review, the pharmacological and non-pharmacological approaches to treat PCOS are reviewed, as well as its epidemiology, pathogenesis, and clinical presentation.

2. Methodology

To write this literature review, it was conducted a search throughout different databases, including PubMed, Biblioteca do conhecimento online and EBSCO host, using this combination of keywords: "polycystic ovary syndrome"; "drug therap*"; "diet* therap*"; "lifestyle"; "insulin resistance"; "amenorrhea"; "oligomenorrhea"; "ovulation"; "inositol"; "hyperandrogenism"; "pathophysiology"; "infertility"; "fertility".

Only reviews, systematic reviews and meta-analysis written in English from the past 5 years were included in this paper.

Later, only full-text articles were included, excluding articles based on animal studies, articles regarding studies about molecular basis of pathogenesis and articles which subject deviates from the objective of this work.

3. Polycystic Ovary Syndrome

3.1. Definition

PCOS, also known as Hyperandrogenic Anovulation or Stein-Leventhal syndrome, is a multifactorial lifelong disorder that affects many women worldwide (1).

It is characterized by the presence of hyperandrogenism, irregular ovulation and/or polycystic ovarian morphology (3).

3.2. Diagnostic criteria

Using the Rotterdam 2003 criteria, health professionals can identify a broader population of PCOS women (1). In May 2003, this consensus workshop held in Rotterdam dictated that the diagnosis of PCOS was made by the presence of, at least, two of the following features: irregular or failed ovulation, clinical symptoms and/or laboratory findings of hyperandrogenism and the presence of polycystic ovarian morphology confirmed by ultrasonography (3, 4).

According to the Rotterdam criteria (5, 6), four phenotypes could be determined:

- Oligo/Anovulation + Hyperandrogenism + Polycystic ovaries;
- Oligo/Anovulation + Hyperandrogenism;
- Hyperandrogenism + Polycystic ovaries;
- Oligo/Anovulation + Polycystic ovaries.

Table 1: Clinical phenotypes of PCOS. Adapted from Azziz R (1). The symbols * represent the signs/symptoms present in each PCOS phenotype.

Feature	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Hyperandrogenism	*	*	*	
Chronic anovulation	*	*		*
Polycystic ovaries	*		*	*

There are other diagnostic criteria, such as National Institutes of Health 1990 and AE-PCOS Society 2006. However, the Rotterdam 2003 criteria are the most consensual among physicians and the ones used more often (1).

PCOS is a diagnostic of exclusion, so other possible etiologies should be discarded, such as thyroid dysfunction, androgen secreting tumors, and hyperprolactinemia. In the present of

the criteria above, if all these disorders are excluded, the diagnosis of PCOS can be made (7).

In adolescent girls, multicystic ovaries morphology, as well as oligo-anovulation are more frequent, independently of the diagnosis of PCOS. Because multicystic ovaries are too prevalent in adolescence, this characteristic should not be used for the diagnosis of PCOS in this age group (1).

Given the normal physiological changes that occur during pregnancy, diagnostic criteria for PCOS are not applicable and a diagnosis of PCOS is not possible in pregnancy (8).

4. Epidemiology

In the last decade, the prevalence of PCOS increased and it is known as a 20th century phenomenon (9, 10).

Several studies have reported a prevalence of PCOS affecting between 5% and 20% of reproductive-aged women, depending on the definition used (1, 11). The prevalence of different PCOS phenotypes is also variable (12).

In the past few years, it was demonstrated that there are global differences in PCOS phenotypes of women with different racial and ethnic origins. There are, also, global differences in prevalence of adverse outcomes (13).

In the studies reviewed by K. VanHise et al., black women showed increased fasting insulin levels, homeostatic model assessment of insulin resistance (HOMA-IR) scores, and systolic blood pressure, when compared with white women. On the other hand, these women had lower triglycerides (TG) levels. Such findings suggest that black women diagnosed with PCOS have an increased risk of metabolic dysfunction. Although, there is a high degree of heterogeneity between studies which can be correlated with differences in Body Mass Index (BMI) (13, 14).

Black women also showed an increased risk of psychological comorbidities, such as lower QOL, in the infertility domain. However, the prevalence of depression between black and white women was not significantly different (13, 15). In contrast, E. A. Greenwood et al., observed, in a longitudinal study, that black women with PCOS had a higher depression burden than that of white women with PCOS, after accounting for age, BMI, race, education, and exercise output (13, 16).

Hispanic women were more likely to have an elevated fasting insulin level and higher HOMA-IR scores than those of non-hispanic white origin. These results suggest an impaired glucoregulatory response in hispanic women with PCOS, which may put these women at increased risk of metabolic consequences, such as type 2 diabetes mellitus (13, 17).

Asian women with PCOS were much less likely to be obese than those from other racial groups, but more likely to have diabetes mellitus, when compared with white women, after adjustment for age and BMI (48). Unfortunately, there were no studies regarding asian women's mental health. Higher BMI results are correlated with higher rates of mental health problems, such as depression. With this lack of studies, we cannot conclude if their lower BMI translates in a lower rate of depression (13, 18).

According to these results, we can conclude that different ethnic and racial origins are related to different PCOS comorbidities, which represents a difficult in assessing incidence and prevalence (13).

5. Pathogenesis and Clinical Presentation

The pathophysiology of PCOS is multifactorial and influenced by alterations in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors, and sympathetic nerve function (7, 19).

This, in turn, leads to different clinical manifestations. As seen in Table 1., different PCOS' phenotypes are presented by different signs and symptoms, which can difficult the recognition and diagnosis of the disease.

5.1. Hypothalamus-Pituitary Axis

Patients with PCOS demonstrate gonadotropin secretory abnormalities, including increased Luteinizing Hormone (LH) pulse amplitude and frequency, and increased circulating levels of LH, most evident in patients who are not obese. The LH increased levels aim to stimulate androgen secretion by the ovarian theca cells (1).

The hypothalamic–pituitary axis appears to be somewhat resistant to the suppressive effects of progesterone on gonadotropin-releasing hormone (GnRH) pulse frequency (1, 20).

The neuroendocrine dysregulation is thought to cause an imbalance in the hypothalamic–pituitary–ovarian axis, which leads to an excess of gonadotropin. The increased levels of gonadotropin promote the production of LH over Follicle Stimulating Hormone (FSH), causing an elevation in the LH/FSH ratio and resulting in a substantial hormonal surge. The overproduction of LH leads to alterations in these patients' ovaries (7).

5.2. Ovaries Alterations

On the ovarian level, these women's follicles demonstrate relative resistance to FSH. This either can be intrinsic to the disorder or secondary to the high levels of Anti-müllerian Hormone (AMH), which modulates follicular recruitment and growth. Other factors that may also contribute to the abnormal follicular development seen in this condition include hyperinsulinemia and hyperandrogenism (1).

The growing follicles are exposed to an atypical environment, with increased levels of LH, insulin, androgen, and AMH, accompanied by insufficient levels of FSH (19). The excessive production of LH causes theca cells to undergo hyperplasia, which forms cystic structures along the ovary's periphery, also known as polycystic ovaries morphology. On the ultrasound, the ovaries have an appearance of a string of pearls (7).

Otherwise, many women with PCOS seem to have oligo-ovulation. Oligo-ovulation is generally detected by the length of the menstrual cycle, and it can be defined as menstrual cycles greater than 35 days, which, in turn, translates into 10 or less cycles per year (1).

Despite the aforementioned alterations, these women's abundance of ovarian follicles seems to be translated in a longer fertile life span, which may allow them to compensate for their oligo-ovulation, later in life (19, 21).

Stating this, fertility may improve naturally. With age, the number of ovarian follicles start to diminish which leads to lower AMH levels and a concomitant rise in FSH levels, leading to a more normal menstrual cycle (19, 22).

5.3. Insulin Resistance

The majority of patients with PCOS demonstrate chronic insulin resistance (IR) beyond that dictated by body mass only (1, 23). According to this, patients with PCOS produce less insulin than they would, determined by the degree of their IR. As a result of their IR and suboptimal compensatory hyperinsulinemia, patients with PCOS are at increased risk for impaired glucose tolerance and type 2 diabetes mellitus (1).

Hyperinsulinemia acts synergistically with LH, stimulating androgen production. Along with hyperandrogenism, it suppresses the hepatic production of Sex Hormone-binding Globulin (SHBG) (1). So, we can say that hyperinsulinemia is the primary cause of excessive androgen production, in these women, causing a never-ending cycle of IR and hyperandrogenemia (HA) (7).

Khomami et al. (52) suggested that the combination of hyperandrogenism and IR and/or hyperinsulinemia may lead to adverse pregnancy outcomes, in women with PCOS (24, 25). Patients with PCOS may reduce the spontaneous abortion rate by losing weight while preparing for pregnancy, and the ideal target of weight control should be within the normal BMI range (24).

5.4. Hyperandrogenemia

The biochemical hallmark of PCOS is HA and it is present in all three diagnostic criteria, as a central facet.

Clinically, HA manifests itself as hirsutism or the presence of excess terminal hairs in a male-like pattern, acne, or alopecia (1, 7). Biochemically, increased free testosterone levels are also indicative of hyperandrogenism (7).

Initially, excess androgens disrupt normal androgen synthesis, impairing folliculogenesis, encouraging the growth of primordial follicles and elevating the antral follicles count (7, 26).

An altered cortisol metabolism is another proposed mechanism that contributes to excess androgens, in PCOS patients. The enhanced inactivation of cortisol may cause increased peripheral cortisol metabolism. This results in less negative feedback suppression of adrenocorticotropic hormone secretion. With these alterations, the excessive concentrations of androgens enable the maintenance of normal plasma cortisol levels (7, 27).

Additionally, HA also interferes with the immune system, causing its activation and low-grade chronic inflammation. HA affects the immune cell subtypes in different ways, but in general, excess androgen levels in the body stimulate neutrophils, while inhibiting dendritic cells. These alterations in immune cells, in turn, produce a wide range of cytokines that contribute to many of the features of PCOS, such as infertility since it induces ovarian dysfunction (28).

5.5. Dysbiosis

Recently, investigations revealed a significant difference in the composition of the gut microbiome between healthy controls and PCOS patients. Studies indicate that the diversity and structure of the gut microbiota in PCOS women may be impacted by IR, sex hormone levels, and obesity (7, 29).

It has been hypothesized that, in women with PCOS, a poor-diet-induced dysbiosis may lead to an increase in the permeability of the gut mucosa, which in turn increases the passage of lipopolysaccharides (LPS). The resulting immune system activity elevates serum insulin levels, increasing the production of androgens in the ovaries and interfering with normal follicle formation (7, 30).

5.6. Diet and Lifestyle

High-calorie diets and sedentary lifestyles might be possible causes for PCOS exacerbations. High-sugar diets may contribute to PCOS by changing gut flora, inducing chronic inflammation, and increasing IR and HA. Obesity and weight gain worsen defining features of this syndrome (7).

In the study of Gonzales et al., they reported that consumption of high saturated fat promotes LPS mediated inflammation and IR, which worsens PCOS symptoms (7, 31).

Obesity, associated with hyperinsulinemia and consequent IR, worsens the patients' glucose intolerance and lipid profile, which can lead to dyslipidemia and type 2 diabetes mellitus. Obesity also stimulates LH, increasing androgen production and causing HA (7, 32). Obesity is also known to promote oxidative stress and low-grade inflammation, which, in turn, promotes the biological activity of androgens and, consequently, leads to HA (19).

After reaching the limit of overweight, BMI ≥ 25 kg/m^2, the spontaneous abortion rate of these patients increases. However, the same is not seen in patients who reach the standard of obesity, BMI ≥ 30 kg/m^2 (24). High BMI, ≥ 25 kg/m^2, may have a profound effect on the secretion and metabolism of sex hormones, resulting in changes in the bioavailability of estrogen and androgens and thereby affecting the normal development of follicles (24, 33).

The relationship between PCOS and obesity seems to be bilateral. On the one hand, weight gain and adiposity may contribute to PCOS, while on the other, disturbances found in this syndrome drive further weight gain and adiposity (34-36). It was suggested that women

with PCOS manifest global adiposity, rather than a dominance of visceral fat (34, 37). Obesity promotes the development of oxidative stress and low-grade inflammation. Further, the abnormal lipid metabolism leads to an increase in the free fatty acid levels, causing IR and HA's vicious cycle (19).

In contrast, fermentable fibers offer metabolic benefits for the gut flora, resulting in the release of short-chain fatty acids and consequent restoration of gut microbiome, which is usually altered in PCOS patients (7, 38).

Regarding micronutrients, vitamin D can alter AMH signaling, FSH sensitivity, progesterone production and release in human granulosa cells, indicating a possible physiologic role for vitamin D in ovarian follicular development and luteinization (39-41). Vitamin D also has an essential antioxidant function, controlling systemic inflammation and oxidative stress (39, 42).

It has been shown that low vitamin D levels may worsen PCOS symptoms. In other words, it was reported an inverse correlation between serum Vitamin D levels and metabolic and hormonal disturbances of PCOS (39, 43, 44).

Vitamin D deficiency is a contributing factor to IR, obesity, and metabolic syndrome (MetS), all of which are commonly associated with ovulatory dysfunction and PCOS (39).

5.7. Oxidative Stress

Oxidative stress refers to the imbalance between oxidation and antioxidation in the human body. The excessive accumulation of oxidative active substances leads to tissue cell dysfunction, essential in the regulation of the occurrence and development of various diseases, especially PCOS (45).

As an important pathophysiological basis of PCOS, HA and IR can be induced or aggravated under oxidative stress imbalance (45).

In PCOS, a glucose-based diet can induce an increase in oxidative stress levels, causing the body to be in a state of chronic low-grade inflammation and promoting the expression of various inflammatory factors which, in turn, increase the biological activity of androgen and, eventually, leads to HA (45, 46).

Insulin also plays a role in oxidative stress state. Hyperinsulinemia stimulates the proliferation of theca-interstitial cells, increases the production and secretion of

testosterone, reduces the serum SHBG levels, improves the bioavailability of serum androgen, and further aggravates HA. All these mechanisms promote the production of reactive oxygen species (ROS), and further aggravate oxidative stress imbalance (45).

5.8. Cardiovascular risk

PCOS is associated with multiple cardiovascular risk factors, such as obesity, hypertension, IR, and dyslipidemia. Although it is not clear if these risk factors represent an increased risk of cardiovascular disease (CVD) (47). In 2015, a study conducted by D. Glintborg et al. (48) showed no increased risk of CVD. However, when this population was reanalyzed broadening the definition of CVD to include hypertension and dyslipidemia, women with PCOS showed a ~2-fold increased risk of CVD events (35, 47).

The prevalent IR, hyperinsulinemia, and chronic low-grade inflammation result in an increased risk for abnormal vascular function. Taking this into a count, patients with PCOS are at greater risk for hypertension, cerebrovascular accidents, and deep vein thrombosis (1, 49).

5.9. Metabolic Disfunction

The term MetS refers to a group of endocrine and metabolic abnormalities that often occur together, including obesity, high blood pressure, increased TG, elevated fasting blood glucose, decreased high-density lipoprotein (HDL) cholesterol, and higher low-density lipoprotein (LDL) levels (1).

It has been demonstrated that different PCOS phenotypes are associated with varying risk of metabolic complications. Women with both hyperandrogenism and ovulatory dysfunction are generally characterized by higher prevalence of MetS, central obesity, dyslipidemia, and prediabetes, in comparison to patients with ovulatory and normoandrogenic phenotypes (12, 50, 51). In general, normoandrogenic PCOS phenotypes present comparable metabolic profiles to healthy women (12).

Therefore, the influence of hyperandrogenism, IR, and obesity on metabolic features of PCOS cannot be reviewed separately, but rather as a complex of interrelated features (12).

Regarding the lipid profile, women with PCOS, even the lean ones, seem to present a more atherogenic lipoprotein pattern, which is closely associated with HA (12, 52). These observations indicate that patients with hyperandrogenic phenotypes should be considered at a higher risk of developing visceral obesity, IR, and their metabolic consequences (12).

5.10. Cancer Risk

The combination of oligo-anovulation and hyperinsulinemia places patients with PCOS at increased risk for endometrial hyperplasia and endometrial carcinoma (1, 49). The longstanding unopposed estrogen stimulation is the main hypothesis behind the potentially increased risk for endometrial cancer in women with PCOS (53).

Patients with PCOS may also be at increased risk for ovarian cancer. The same cannot be seen in the risk of breast cancer (1, 49).

5.11. Mental Health and Quality of life

PCOS is a chronic disease that causes patients to become vulnerable to mental health problems, such as depression, anxiety, and eating disorders (54).

Women with PCOS are at greater risk for anxiety and depression, whose risk appears to be most strongly correlated to androgen excess and hyperinsulinemia (1, 49, 55). Not surprisingly, patients with PCOS demonstrate reduced QOL. This fact is strongly determined by the low individual self-esteem and body image related to the presence of hirsutism and obesity. (1, 49) In a qualitative study on the subjective experience of PCOS, women reported that they felt less feminine and attractive, mentioning PCOS as the "thief of womanhood" (56, 57).

The clear-cut etiology of PCOS-associated depression has not been postulated yet, but these women have an 8 times higher prevalence of depression. This can be explained by the presence of pro-inflammatory markers and consequent activation of the immune system, during stress. Other factors leading to depression in PCOS are IR, HA, and hypothalamic-pituitary-ovarian axis dysregulation. At the bottom line, depression in PCOS has a multifactorial etiology (56).

In the study of Basirat et al., they concluded that women with PCOS are more stressed when it comes to infertility issues and their management. Stating this, these women need special attention and psychosocial care, compared to normal women with infertility (56, 58).

Excessive body hair in these patients is associated with decreased self-image evaluation. Infertility and alopecia are predictors for anxiety symptoms, while acne negatively influences the depression levels (54, 59, 60).

PCOS has been proposed to be associated with several mental health problems, including somatic symptoms, anxiety, depression, body image dissatisfaction, eating disorders, diminished sexual satisfaction, and lowered health related QOL, among other psychiatric issues (54, 61).

The worrisome situation of PCOS women's mental health addresses the urgency and necessity to develop psychological health care interventions for this patient's group (54).

5.12. Obstetric Complications

The metabolic characteristics of PCOS can extend into pregnancy and lead to increased risk of obstetric complications (62).

Women with PCOS appear to demonstrate an increased risk of miscarriages and other obstetric complications, such as pregnancy-induced hypertension, gestational diabetes mellitus (GDM) and macrosomia (1, 63, 64).

Hyperandrogenic phenotypes have an increased risk of pregnancy-induced hypertension (62). It is well known that GDM is related to IR, which can cause secondary hyperinsulinemia. A previous study confirmed that pregnant women with hyperinsulinemia are at increased risk of developing pregnancy-induced hypertension (62, 65).

In addition to PCOS, high BMI also correlates to obstetric complications. As stated before, overweight or obese women with PCOS have a higher risk of miscarriage and a lower chance to give a live birth (66). The risk of miscarriage related to obesity can be caused by altered glucose metabolism, which, in turn, causes defective decidualization and implantation abnormalities (66, 67). Abnormal implantation and placentation can lead to pregnancy-induced hypertension, preeclampsia, and intrauterine growth restriction (66).

The WHO defines GDM as "any level of the early or initial diagnosis of glucose intolerance in pregnancy" (2, 68). It is identified as glucose intolerance that manifests itself or is first recognized during pregnancy (2).

Obesity is not the only contributing factor for the increased risk of GDM. Pre-existing diabetes mellitus, high maternal age, history of previous GDM, family history of diabetes mellitus, hypertension, PCOS and smoking are also risk factors for GDM (2). According to multiple studies, PCOS relates to IR and GDM and it appears to be an independent predictor of GDM (2, 69).

In a healthy pregnancy, a phenomenon of IR manifests in order to ensure that the developing fetus receives an adequate supply of nutrients (70). As a direct consequence of this, not only maternal body produces more insulin, but also the levels of glucose and free fatty acids increase. Increased progesterone levels during pregnancy may induce a higher risk of developing IR (2, 71).

In GDM pregnant women, increased insulin secretion is insufficient to balance the increased IR, and as a result, abnormal glucose metabolism is clinically manifested (2, 72).

Despite the fact that GDM is a temporary disease (73), it is a frequent pregnancy complication that can have serious health consequences, for both the mother and the fetus. There are a variety of comorbidities that might arise in women who have GDM, including cesarean delivery and type 2 diabetes mellitus.

6. Pharmacological Treatment

In PCOS, the selection of therapeutic agents depends on the patient's phenotype, concerns, and main goals. Stating this, the therapy will be focused on suppressing and counteracting androgen secretion and action, protecting the endometrium, and improving menstrual dysfunction, metabolic status, and ovulatory fertility (1).

This treatment rarely is monotherapeutic, rather being personalized based on prevailing signs and symptoms (7).

6.1. Oral contraceptives

In those patients who are not pursuing conception and in whom hormonal contraception is not contraindicated, treatment with combined oral contraceptives (COC), oral contraceptives with both estrogen and progesterone, should be part of the initial therapy. COC suppress gonadotropin secretion and ovarian androgen production, regulate vaginal bleeding, and protect the endometrium from unopposed estrogen (1, 53). Even though women with PCOS can experience difficulties conceiving spontaneously, effective contraception is essential, whenever a pregnancy is not desired (53).

In those patients who cannot tolerate oral contraceptives, consideration may be given to transdermal combination contraceptives or progestin-only contraceptives. Alternatively, some patients may opt for cyclic progestogen administration, which will protect the

endometrium and minimize the risk of endometrial hyperplasia, but do not suppress androgen production (1).

COC function by encouraging negative feedback on LH secretion, leads to less androgen production in the ovaries and reduces HA. They raise liver produced SHBG, while lowering free androgens levels. They also work by inhibiting the peripheral conversion of testosterone and decreasing the release of adrenal androgens (7).

Most oral contraceptives preparations include estrogen and anti-androgens. Anti-androgens help with hirsutism and other androgen-related issues (7).

Third-generation COC, which contain antiandrogenic compounds, have been shown to improve metabolic phenotypes of PCOS, as well as lipid, and adipokine profiles (7).

In a large meta-analysis of healthy women, COC decreased total testosterone, increased SHBG, and decreased free testosterone levels. However, COC treatment is also associated with increased risk of venous thrombosis (53, 74).

So, we can state that COC are effective in improving subjective hirsutism, decreases testosterone and increases SHBG levels (53, 75).

6.2. Metformin

By reducing insulin secretion and stabilizing glucose tolerance, insulin sensitizers, like metformin, increase insulin sensitivity in target tissues and, consequently, trigger ovulation (7).

Metformin acts by reducing IR, increasing glucose absorption, and improving peripheral tissues' sensitivity to insulin (7).

Acne is a prevalent PCOS cutaneous manifestation, and it is related to a lower QOL and higher rate of depression. The treatment with metformin improved the acne score, whether as an adjuvant treatment or after other treatment alone. Both the presence of acne and acne score decreased significantly, after metformin treatment (76). By improving IR and decreasing androgen levels, metformin is able to ameliorate acne. It also has anti-inflammatory properties, targeting inflammation in acne pathogenesis (76-78).

As mentioned previously, COC agents can reduce androgen levels and regulate menstruation, but they increase the risk of venous thrombosis and metabolic abnormalities,

in long-term usage. With this premise, R. De Pirro et al. showed that metformin combined with COC and metformin combined with lifestyle modifications (LSM) both had better effects on overweight PCOS patients, reducing IR, total cholesterol, LDL cholesterol, and TG levels (79, 80). With these results, we can conclude that the association of metformin and LSM has less risks.

In a meta-analysis by A. Wang et al., the combination of metformin and LSM was the most effective in improving IR. Moreover, the combination of metformin and a hypocaloric diet was more effective in reducing TG levels. So, these combined therapies would be a better choice for metabolic disorders, in overweight PCOS patients (79).

Metformin is usually not used as an ovulation induction, however, there is a study conducted by Abu Hashim H. et al. (81), which showed that the combination of metformin and ovulation induction agents improved ovulation and pregnancy rates, reduced blood glucose and improved IR, in Clomiphene Citrate (CC) resistant women with PCOS (79).

In women with GDM, metformin administration, during pregnancy, has become increasingly popular, because of its efficacy, convenience, and safety (82). Metformin doesn't have a formal indication to be used during pregnancy. Although, given that metformin readily crosses the placenta and the insufficient data to support improvements on short-term pregnancy outcomes, in women with PCOS, its use beyond the first trimester should be limited to special circumstances (83).

During pregnancy, metformin is able to reduce the incidence of preterm delivery, but does not reduce the incidence of miscarriage, genetic metabolic diseases, pulmonary embolism, and cesarean section, in PCOS patients (82). High-quality randomized controlled trials and meta-analyses had shown the benefits of metformin on the treatment of GDM, even when compared to insulin (82, 84, 85).

In one case-control study (86), it was shown that metformin administration had benefits in lowering the incidence of GDM. This conclusion is different from other performed studies and can be explained by different methodologies (82).

As any other pharmacological agent, metformin can produce many side effects, such as nausea, stomach pain, and diarrhea (79). When prescribing it, professionals should be aware of these risks and inform the patient.

6.3. Anti-obesity drugs

Obesity characterizes 40% to 70% of patients with PCOS and plays a key role in the pathogenesis of both endocrine and metabolic abnormalities (87, 88). As it will be discussed later, diet and exercise are the mainstay management of obesity, in these patients. Moreover, anti-obesity drugs can be useful, in patients whose standard treatment has failed (87).

Pharmacological therapies should also be considered in this group of patients, to interrupt the vicious cycle of obesity-IR-HA (52).

Orlistat is a lipase inhibitor, resulting in a 30% reduction in the absorption of ingested fat and weight loss. Besides weight loss, orlistat also improves markers of IR and reduces circulating androgen levels, in PCOS patients (87, 89-91).

One randomized study compared orlistat with placebo, in patients with PCOS, and showed that orlistat reduced weight by 6,4% through decreasing testosterone levels, LDL cholesterol, TG and increasing HDL cholesterol levels (87, 92).

In a small study with 21 subjects, treatment with orlistat for 3 months induced a greater weight loss, when compared with metformin (87, 93).

Liraglutide is also an anti-obesity agent. One study evaluated the effects of the administration of liraglutide with the combination of liraglutide and metformin. Both treatment strategies induced similar weight loss and similar reductions in IR markers. However, the combination treatment induced a greater reduction in waist circumference, serum testosterone, and LDL cholesterol levels (87, 94). When compared to placebo, liraglutide induced a greater weight loss and reduction in waist circumference. The IR markers did not change, which leads us to believe that this reduction is more related to the effects of metformin than the effects of liraglutide. The levels of C-reactive Protein were similar, but there was a reduction in the plasma levels of hemoglobin A1c, glucose and leptin. (87, 95) Another study examined the effects of liraglutide on depression and QOL, in obese PCOS patients. The researchers found a significant improvement in QOL related to a dramatic weight loss, as well as an improvement in mental health (7, 96).

The combination of bupropion and naltrexone is an effective weight loss medication (34). Bupropion inhibits the reuptake of dopamine and noradrenaline, thus activating the pro-opiomelanocortin neurons, in the arcuate nucleus of the hypothalamus. Naltrexone is an opioid antagonist that blocks the effects of β-endorphin, which is released by pro-

opiomelanocortin neurons. There are some reports where the treatment with naltrexone, for 3 to 6 months, can reduce BMI (87, 97, 98). Naltrexone increases hepatic insulin removal but does not appear to have an effect in peripheral insulin sensitivity (87, 97). In a clinical trial, naltrexone also showed reduction in the severity of hirsutism and acne, besides improving menstrual cyclicity (87, 99).

However, there are no studies that assessed the effects of the combination of naltrexone and bupropion, in patients with PCOS. This combination is associated with several side effects, such as, renal, and hepatic impairment, headache, dizziness, insomnia, convulsions, neuropathic reactions, hypertension, tachycardia, elevation of intraocular pressure, warm waves, sweat, tremors, allergic reactions, and increased tendency for self-harm. There are no studies regarding reproductive toxicity (87).

Glucagon-like peptide-1 (GLP-1) analogues significantly reduce body weight and improve IR. They also can reduce appetite and delay gastric emptying (34, 100, 101). GLP-1 analogues are considered an anti-diabetic drug, so it will be discussed in the next section.

6.4. Anti-diabetic drugs

GLP-1 analogues improve insulin sensitivity. In a recent systematic review and meta-analysis, comparing GLP-1 with metformin, GLP-1 analogues showed a significant improvement in insulin sensitivity, besides reducing BMI, and abdominal girth (7, 103). These glucose-lowering agents are used to treat obese women with PCOS, once they reveal a greater weight loss, as well as an improvement in menstrual frequency, HA, and metabolic disorders, when compared with metformin (103-105).

A meta-analysis by A. Baranowska-Bik indicated that GLP-1 analogues have the same therapeutic effect as metformin, in decreasing testosterone (34). A study from Lyu et al. confirmed that the anti-obesity effect of GLP-1 analogues, alone or combined with metformin, was superior to metformin alone, in respect to reduction of body weight, waist circumference and BMI (34, 106).

Thiazolidinediones (TZDs) are insulin sensitizing agents and include pioglitazone and rosiglitazone. They increase insulin sensitivity, therefore, lowering insulin levels, which, in turn, reduces serum androgen levels (7).

By inhibiting sodium-glucose cotransporter-2 (SGLT2), SGLT2 inhibitors lower blood glucose, independently of insulin, via its glucosuric effect. Thus, they minimize the risk of

hypoglycemia observed with other antidiabetic agents (47). SGLT2 inhibitors also show cardiovascular and renal protection. These include canagliflozin and dapagliflozin (47).

SGLT2 inhibitors have demonstrated improvements in all disease states of PCOS, including IR, hypertension, obesity, and dyslipidemia, suggesting they may be a promising novel therapy to improve women's healthcare (47, 104).

SGLT2 inhibition decreases sodium reabsorption, in the proximal renal tubule, thus reducing renin release and reticular activating system activation (47). These drugs achieve a further reduction in blood glucose levels, by increasing insulin sensitivity and glucose uptake, in the muscle. They also decrease gluconeogenesis, in the liver, and improve insulin release from pancreatic β-cells (104).

Javed et al., in a randomized controlled trial, showed that empagliflozin decreased body weight, BMI, and fatty mass, in overweight women with PCOS. These results were better than those observed in the metformin treated group (47, 107). Elkind-Hirsch et al. explored the synergetic effect of SGLT2 inhibitors and GLP-1 analogues, using dapagliflozin and exenatide, in obese women with PCOS. They conclude that dual therapy was superior to either of them alone, with clinic and metabolic benefits (47, 108).

Selective SGLT2 inhibitors lower glucose levels through an insulin-independent mechanism, reducing hyperinsulinemia, and improving insulin sensitivity. They stimulate the excretion of glucose through the urine, producing glycosuria. This, in turn, reduces the level of glycemia in 1/3 of its value (109, 110). Many studies have shown that SGLT-2 inhibitors reduce the amount of fat tissue (by loss of calories and accelerated lipolysis through catabolism), lower blood pressure, improve glucose metabolism, reduce oxidative stress and inflammation, and protect the cardiovascular system (109, 111).

SLGT-2 inhibitors can also act on endothelial homeostasis. In a 2022 study, Pruett J.E. et al. came to the conclusion that SGLT2 inhibitors could be used in therapy, together with insulin sensitizers, by stating that lowering body weight with SGLT2 inhibitors therapy fixes the frequency of small adipocytes in visceral fat tissue (109, 112).

The role of SGLT2 inhibitors in the treatment of PCOS has not yet been fully studied. However, their method of action may be beneficial for several pathophysiological disorders related to PCOS, including the aforementioned IR, hypertension, obesity, and dyslipidemia. Besides these potential benefits, the use of SGLT2 inhibitors is not currently widespread in PCOS therapy (109).

Gliptins, also known as dipeptidyl peptidase-4 inhibitors (DPP-4i), are oral anti-diabetic medications. Performed studies have shown that sitagliptin, the most studied DPP-4i, improved insulin sensitivity and ovarian morphology and reduced fasting blood glucose and androgen levels, in PCOS women. The secondary effects of gliptins include headache, breathing problems, and pharyngitis (100, 109).

6.5. Statins

Statins include atorvastatin, pravastatin, rosuvastatin, fluvastatin and simvastatin. These drugs are helpful in treating PCOS patients because of their ability to lower sex steroid production, improve dyslipidemia and inflammation and lower ovarian androgen production (7).

There is a study stating that, in women with PCOS, the use of atorvastatin can augment the effects of metformin. In this study, women treated with a combination of atorvastatin and metformin had better outcomes in terms of HOMA-IR, free androgen index, total testosterone and SHBG levels, comparing with women who were administered a combination of metformin and placebo (7, 113). These results were confirmed by a meta-analysis conducted in 2021, where it was shown that statins could lower androgen levels and improve the cutaneous symptoms of HA, in PCOS patients (7, 114).

Keyan Miao et al. showed, in a systematic review and meta-analysis, that there was a difference in the response of hormone levels, when these women were treated with statins. The total testosterone, free testosterone, androstenedione, LH, LH/FSH ratio and prolactin levels were all reduced (115).

Stating that statins can lower the testosterone levels, it can be concluded that these drugs are able to improve clinical signs of HA, including hirsutism and acne. Moreover, these drugs lower cholesterol levels and provide an outstanding contribution for the prevention of CVD and stabilization of atherosclerotic plaques. The aforementioned meta-analysis showed that statins lower total cholesterol, LDL cholesterol and TG levels (115).

6.6. Ovulation Induction

For patients with fertility desire, medical professionals should consider treatment with an oral ovulatory agent, such as CC or letrozole (1, 116).

CC is the first-line treatment for ovulation induction. It is a partially selective estrogen receptor modulator, which is able to increase FSH availability and LH pulse frequency, in

normally cycling women, leading to ovulation. The increase in FSH levels is, most likely, the key to its success (7, 19, 117).

CC dosage required for ovulation induction is positively correlated with both body weight and obesity (118). That is to say that there is a reverse association between the likelihood of response to CC and an increased BMI. The same can be observed with the patient's age (118).

When using CC as an ovulation inductor, the patient's cycle should be monitored, using, for example, serum progesterone levels. When the ovulation does not occur, a progestin can be prescribed to induce menses, before the next cycle begins at a higher dose. On the other hand, an ultrasound sonography should be used to identify a successful ovulation, while avoiding the use of progestin (118, 119).

CC can be used alone, as a first-line pharmacological treatment in anovulatory women with PCOS and no other infertility factors, as it is superior to placebo or no treatment (120). Unfortunately, CC is associated with high rates of multiple pregnancies and risks of life-threatening complications, such as ovarian hyperstimulation syndrome (OHSS) (121-123).

OHSS may occur because of ovarian stimulation. It is characterized by ovaries' enlargement, increased vascular permeability, ascites, decreased intravascular volume, and hemoconcentration, with a varying degree of symptoms, from mild to severe. In some cases, hospitalization is required, and, in extreme occasions, OHSS can be fatal. To try and avoid this syndrome, several strategies have been evaluated, including stimulation and trigger protocols, as well as fresh or frozen embryo transfers (discussed in the next section) (19).

Other treatments for ovulation induction include low-dose gonadotropin therapy (discussed in "Infertility treatment" section) and aromatase inhibitors (AIs), such as letrozole (7).

Letrozole is a second-generation AI particularly effective in women with a higher BMI (19). Letrozole is being increasingly recommended as the first-line agent for ovulation induction, because of its higher pregnancy rates and lower rates of multiple pregnancies and OHHS (121, 124). In CC resistant women, letrozole can be considered as a second-line pharmacological treatment (125).

In a recent systematic review and meta-analysis, there was no evidence of increased fetal malformations related to the use of letrozole, when compared with CC, other fertility treatments and natural conception, in women undergoing fertility treatments (121).

When compared with CC, treatment with letrozole showed a significantly higher cumulative pregnancy and live birth rates. It also showed a significantly higher proportion of women who achieved ovulation and a significantly higher proportion of ovulations over total treatment (118, 126).

In CC resistant women, the use of prednisolone and dexamethasone has been described to increase the success rates of ovulation induction. Because these drugs are glucocorticoids, they should not be used for extended periods of time, once they are associated with several side effects, in long term usage (118).

As aforementioned, metformin can help the regularization of the menstrual cycles. It is not as effective as CC or letrozole, as a fertility treatment, but there is evidence that an association between metformin and CC has better results than CC alone (19, 127).

Pharmacological anti-obesity agents might be considered as an experimental therapy, with the purpose of improving fertility (125). As mentioned before, these drugs can lead to weight loss and, consequently, an elevation of ovulation rates, in PCOS women.

With the same purpose, bariatric surgery (discussed later) might also be considered as an experimental therapy, in anovulatory obese women with PCOS (125).

6.7. Infertility treatment

Infertility is a prevalent presenting feature of PCOS, with a 75% prevalence, making PCOS the most common cause of anovulatory infertility (120).

When standard ovulation induction medications are ineffective, exogenous gonadotropin therapy can be considered (19).

Recombinant FSH therapy results in a high rate of ovulation, but women with PCOS are especially prone to the complications of OHSS and higher-order multiple pregnancies. For this reason, prior to consideration of gonadotropin therapy or in vitro fertilization (IVF), laparoscopic ovarian drilling (LOD) has been proposed (19).

By surgically reducing the follicle burden, LOD leads to an increase in FSH levels, leading to ovulation. In women who underwent LOD, the maintenance of ovulation is frequent (19, 128). Being invasive operations, LOD and in vitro maturation (IVM) are often reserved for medication resistant cases (118).

More recently, transvaginal ultrasound assisted ovarian drilling has been recommended to avoid laparoscopy (19, 129).

Gonadotrophins could be used as a second-line pharmacological therapy, in cases where first-line pharmacological therapy has failed (125). During an Assisted Reproduction Treatment (ART) cycle, women with infertility/subfertility are treated with GnRH agonists or GnRH antagonists to desensitize the pituitary and stop the production of endogenous gonadotropins (130).

GnRH agonist protocol, also known as down-regulation protocol, includes starting with an GnRH agonist, such as leuprolide acetate, in the midluteal phase of the menstrual cycle. In the early follicular phase of the next menstrual cycle, a recombinant FSH agent should be started. This protocol results in a suppression of the LH and FSH secretion, thereby preventing the LH surge and consequent ovulation (19).

GnRH antagonist protocol has the same purpose as the previous one, but with the usage of an GnRH antagonist, such as cetrorelix or ganirelix. In this case, GnRH antagonists directly suppress gonadotropin release (19).

Regarding the fresh versus frozen embryo transfer, a recent multicenter randomized controlled trial was conducted. In this trial, Chen Z-J. et al. found out that frozen embryo transfer resulted in a higher live birth rate and lower rates of OHSS, but with a higher risk of preeclampsia (19, 131).

Based on the previously mentioned data, a reasonable approach to minimize OHSS while also improving live birth rates, in patients with PCOS, is to proceed with an antagonist protocol with GnRH agonist trigger and freeze all cycle, followed by frozen embryo transfer (19).

IVM consists in the generation of an embryo and posterior vitrification, thaw, and transfer, in a subsequent cycle. This treatment option can be offered to women with PCOS, in assisted reproduction units with sufficient expertise (125).

IVF is the process of stimulating the ovaries to produce multiple follicles, via exogenous gonadotropins. Once a patient has multiple follicles greater than 18 mm, a trigger shot of human chorionic gonadotropin and/or GnRH agonist is administered, to mimic the LH surge and stimulate oocyte maturation. After an average of 36 hours, oocytes are retrieved through transvaginal ultrasound with needle aspiration and, subsequently, fertilized in the

laboratory. A resulting embryo is then selected and transferred back inside the uterus, typically in the blastocyst stage (87).

6.8. Treatment during pregnancy

Pregnancy is often a motivating period for individuals and families. Optimizing health before pregnancy may improve pregnancy outcomes and maternal lifelong health. The preconception period provides a window of opportunity where pregnancy-related complications can be discussed, preventative screening and safe treatments can be initiated, and nutritional and lifestyle behaviors can be optimized to improve oocyte quality and potentially pregnancy outcomes (83, 132, 133).

Human studies suggest a higher prevalence of placental infarctions, villitis, and villous immaturity, in women with PCOS, even after adjusting for significant demographic and pregnancy complications associated with PCOS (83). Offsprings born to women with PCOS are associated with increased risks of higher childhood BMI, abnormal cardiometabolic markers, and neurodevelopmental disorders (83, 134).

To improve fertility and promote healthy pregnancies, optimizing health at preconception is of great importance. It is recommended that all women see their health practitioner for common preconception risk assessment, with enough time before conception to intervene (8).

Metformin use was recommended in nonpregnant women and in pre-pregnancy stage to assist the management of weight, IR, anovulation, and hirsutism (8). Given its positive effects, it seems rational to use metformin as a pre-pregnancy treatment (8, 135).

Anti-obesity medications are not recommended during pregnancy, and women should be advised to discontinue and implement other strategies, before getting pregnant (83, 136). Bariatric surgery has shown to decrease rates of GDM, hypertensive disorders, and macrosomia. On the other hand, it has a risk of potential postsurgical complications that need to be considered, such as fetal growth restriction, and nutritional challenges (83, 137).

As already mentioned, women with PCOS have an increased risk of GDM. Because of this higher risk, these women should be screened for diabetes mellitus and cardiovascular risk factors, before conception (83, 138, 139). During pregnancy, this risk should be reevaluated (83).

Beside GDM, women with PCOS have higher risk for adverse pregnancy outcomes and a closer surveillance, during the prenatal and postpartum period, is recommended (83, 140). Therefore, individualized fetal surveillance and perinatal management is advised (83).

The available data are insufficient to support metformin use to prevent miscarriage, preterm labor, GDM, preeclampsia or large-for-gestational-age infants. However, as aforementioned, its usage past the first trimester is not recommended (83).

Throughout the pregnancy, there is a recommendation to follow-up blood glucose levels, weight gain, blood pressure, smoking and alcohol habits, diet, exercise, sleep patterns, and mental, emotional, and sexual health, among women with PCOS (8).

As in all women, postpartum care should be viewed as an ongoing process with anticipatory guidance beginning in the prenatal period, with an individualized and comprehensive care plan which includes overall well-being, infant care, feeding, contraception, birth spacing, sleep patterns, delivery recovery, chronic health management, and goals for long-term health maintenance (83).

After birth, women should be encouraged to breastfeed and aim to achieve a healthy weight (8, 141, 142).

One of the strongest risk factors for later obesity, metabolic disease, and type 2 diabetes mellitus is postpartum weight retention (83, 143). With this in mind, targeted efforts to facilitate weight loss are critical. Encouraging the continuation of healthy lifestyles and resuming or initiating metformin, in the postpartum period, are important. Metformin can be resumed immediately postpartum, even if the mother is nursing. There is evidence that metformin excretion in breast milk is very low, less than 1%, with no reports of infant hypoglycemia (83, 144).

7. Bariatric Surgery

Bariatric surgery is an invasive method of treatment for morbidly obese patients (34).

It may be an option for women with PCOS and severe obesity with a high-risk of obesity complications, if standard weight loss strategies have failed (34, 102). With this surgery, patients will lose weight, improve their metabolic abnormalities, and ameliorate IR (34).

Despite these benefits, bariatric surgery is associated with high risk of perioperative and postoperative complications (34).

In what fertility is concerned, women who undergo bariatric surgery should be advised to avoid pregnancy within 1 year of the surgery or weight stabilization (83).

8. Non-pharmacological Treatment

Despite the high variety of pharmacological treatments, a significant portion of PCOS women prefer improving their health condition in a more natural way (145).

8.1. Diet

Diet and LSM are regarded as the cornerstone of PCOS management (7). A recent systematic review and meta-analysis on the effectiveness of LSM in PCOS patients with obesity indicated a beneficial role of healthy LSM, in the course of this particular endocrinopathy. In this review, the authors indicated a significant improvement in reproductive functions. Moreover, a combination of diet and exercise had better effects on metabolic and androgenic parameters than monotherapy (34, 146).

Obesity is the greatest challenge in PCOS management (9). The favorable results of diet interventions are supported by different clinical trials and include different types of diets, micronutrients, macronutrients, and nutritional supplementation (9, 147, 148). In PCOS patients disturbed by infertility, it is recommended that women with both PCOS and obesity delay infertility treatments and achieve weight modifications first (149).

As stated before, LSM, including diet and exercise, are recommended as the first-line approaches for weight management, in obese PCOS patients (9, 150). LSM counselling should be recommended for all the women with PCOS to better manage their signs and symptoms (9).

Macronutrients include fats, carbohydrates, and proteins. They supply the body with energy and their intake based on the subtypes acts as a modulator of the inflammation, oxidative stress, and IR (9). They also have a key role in weight regulation (9, 151). Based on macronutrient content, there are several types of diets, such as Ketogenic diet and Mediterranean diet (9, 152).

Recent evidence has shown that the quantity and quality of carbohydrates in diet are associated with ovulatory infertility. It is believed that, in terms of the quality of carbohydrates, the low glycemic index (LGI) ones are much better than the ones with high

glycemic index. In terms of quantity, limitation of carbohydrates ingestion has a key role in normal insulin sensitivity status, as well as ovulation regulation (9, 153, 154).

In 2016, Szczuko et al., demonstrated that the consumption of total fats, saturated fatty acids and cholesterol should also be reduced (9, 155).

The composition of the Mediterranean diet is based on the regular consumption of unsaturated fats, LGI carbohydrates, vitamins, fiber, antioxidants, and moderate consumption of animal protein (156, 157). Adherence to the mediterranean diet may act as a therapeutic approach, in women with PCOS, due to its anti-inflammatory and metabolic effects (9, 158). This diet might also contribute to women's fertility health, menstrual regularity, and overall QOL (9).

High-fiber diets (including but not limited to the mediterranean diet) have been found to have a positive effect on health (156, 159). It has been suggested that increased dietary fiber consumption reduces the risk of developing, among others, coronary artery disease, hypertension, diabetes mellitus, and obesity. Increasing the consumption of fiber reduces blood pressure and serum cholesterol levels and improves glycemia and insulin sensitivity. In obese patients, fiber supplementation significantly supports weight loss (156, 160).

Diets with LGI carbohydrates may improve cardio-metabolic and reproductive disturbances, in PCOS patients (9, 161). Moreover, reduced intake of carbohydrates improves insulin sensitivity and androgen levels (9, 162, 163).

Evidence has reported that hypocaloric diets among adolescents and young females with PCOS improve weight loss and reproductive parameters. The term "hypocaloric diet" refers to a reduction in 500 to 1000 kcal per day. One randomization study compared an hypocaloric diet with metformin, in women with excess body weight. After 12 weeks of intervention, the results showed a reduction of C-reactive protein, a marker of inflammation, and improved menstrual dysfunction. These authors also concluded that the effect of diet intervention on IR markers was superior to the metformin effect (42, 164). There was also evidence of improvement in HA and central adiposity (9). After weight reduction, several improvements are observed in what hirsutism, IR, and rate of circulating androgens are concerned (165, 166).

It has been suggested that ketogenic diets are an effective way to lose weight, if combined with caloric restriction. In addition, the adherence to these eating habits leads to an improvement in the lipid profile and reduction in blood pressure, as well as a reduction in

IR with an improvement in blood glucose and insulin levels, which is particularly important in the case of patients with PCOS (156, 167).

It is documented that the quality of dietary fat is much more important than its quantity, in ovulation disorders, once the high dietary fat intake disrupts the hypothalamic-pituitary-ovarian axis regulation and female fertility (9, 154, 168). Moreover, high-fat diets may cause intestinal dysbiosis by damaging the intestinal barrier and may also adversely affect body weight and metabolic variables (156, 169-171).

Additionally, the inflammatory effect of some nutrients, such as glucose or saturated fat, promotes atherosclerotic lesions (156, 172). In PCOS patients, glucose is found to induce oxidative stress, which stimulates an inflammatory response, even in the absence of obesity (156).

Regardless of diet composition, the adaptation of healthy eating habits and reduced caloric intake, especially in overweight PCOS women, improve the clinical picture through weight loss (156, 173).

Recent evidence has recommended omega-3 fatty acids to treat IR and lipid disturbances, in women with PCOS (9, 174). A monounsaturated fat-enriched diet significantly affects weight loss (9, 173). It was also showed that diets rich in monounsaturated and polyunsaturated fatty acids (PUFAs) are strongly linked to regular ovulation (9, 154).

Most women with PCOS, especially those with metabolic disturbances, suffer from one or more vitamins/minerals deficiency (9, 175-177). Poor intake of micronutrients and their deficiency result in impaired metabolic and hormonal profiles and it may worsen PCOS manifestations, including vitamin D, bioflavonoids, N-acetyl-L-cysteine (NAC), chromium, probiotics, magnesium, zinc, and selenium. Deficiencies of other micronutrients include inositol, vitamin A and omega-3 fatty acids. The latest might be associated with hyperandrogenism (9).

Zinc is a micronutrient which has been used to improve the clinical and biochemical profile of PCOS. It is essential for many vital functions, such as fertility, reproduction, inflammation, and oxidative stress (165).

Regarding dairy products, such as milk, cheese, butter, and yogurt, some bioactive compounds, including carotenoids, selenium, zinc, and vitamins A, and E, lead to antioxidant activity. This activity is higher in fermented dairy products, including cheese and yogurt (9, 178).

The use of spices was found to exhibit a beneficial effect on pancreatic lipase, amylase, and proteases activity, as well as on end digestive enzymes of the small intestine mucosa. Hence, apart from accelerated digestion, spices have an important role in the reduction of the time of food transport in the gastrointestinal tract. These beneficial effects are important in PCOS, once accelerated digestion is correlated with reduction in glucose surge levels and, consequently, a reduction in insulin levels (156).

Cinnamon can improve menstrual cycle and ovarian size and significantly reduce serum insulin, HOMA-IR, TG, and LDL cholesterol levels (259).

Aloe vera, also known as *Aloe arborescens*, contains vitamin A, vitamin C, and vitamin E. It also has antioxidant properties, nutrients and minerals, salicylic acid, enzymes, tannins, and a variety of LPS. These LPS are able to reduce and repair inflammation, with antibacterial and antimicrobial properties, reducing the state of chronic inflammation seen in PCOS patients (264).

Chamomile extract contains flavonoid compounds and antioxidants. It has anti-inflammatory and antispasmodic effects. The latter reduce menstrual cramps and the risk of preterm labor (264).

A specific customized diet for PCOS women has not been established yet, but the general rules are relatively clear: calorie restriction and reduced amount of carbohydrates (not exceeding 200 grams or no more than 30% of the total energy intake), preferring LGI ones (165).

The key element of diet therapy is, above all, following the recommendations of the developed eating patterns, as strictly as possible. Regarding this statement, the choice of diet and further nutritional behavior are influenced by individual and economic factors and by the availability of products, in such regions (156).

Besides the prescription of a specific diet therapy, patients with PCOS should have motivational support, control, and monitoring of implemented recommendations, to prevent relapses in unhealthy eating habits (156, 179).

8.2. Lifestyle

In recent years, LSM are gathering more and more importance in all interventions against PCOS. These interventions seem to draw the ovulation function and menstrual cycle into regular levels, which subsequently increases successful pregnancy rates. In addition, LSM

can alleviate anxiety and improve QOL, particularly in obese women with PCOS (149, 180, 181). This approach reflects many facets of the patient context, integrating care that addresses biological, psychological, social, spiritual, and ecological aspects (182).

In 2019, Lim SS, et al., conducted a meta-analysis to evaluate LSM in women with PCOS, defining LSM as a structured dietary, exercise, or behavioral intervention (designed, or not, to induce weight loss through an energy deficit). In terms of metabolic outcomes, LSM resulted in significant reductions in total cholesterol, LDL cholesterol and fasting insulin levels (182, 184).

Since sleep disorders impact PCOS symptoms, like metabolic abnormalities, relative sleep modifications are considered an integral part of the LSM approach. Practitioners should examine sleep health behaviors together as a multidimensional construct, rather than individually (149, 185).

Alcohol and cigarette use are considered as traditional lifestyle strategies. During the attendance of these women, it is important to assess alcohol consumption and cigarette smoking, when improving fertility and reproductive outcomes. Assessment of cigarette smoking is also important when assessing CVD risk factors and thromboembolism risk associated with COC (124, 182).

Regardless of the interventions above, the use of behavioral interventions should foster self-efficacy, including SMART (Specific, Measurement, Achievable, Realistic and Timely) goals, self-monitoring, stimulus control, problem solving and relapse prevention. Behavioral and cognitive interventions are required to improve sustainability of LSM, considering not only the specific behavior, but also their antecedents, consequences, and cognition (124, 182).

Research has supported a range of different psychological interventions, including counselling, cognitive behavioral therapy, and mindfulness meditation (182, 186-191).

8.3. Exercise

Physical exercise can be used as an independent treatment to appraise all PCOS phenotypic characteristics (192, 193). The WHO defines physical activity as "any body movement that needs more energy expenditure than rest", whereas exercise refers to "planned physical activity with a structural frequency, intensity, and duration" (194).

The QOL of women with PCOS can largely be affected by psychological problems, low self-esteem, and social isolation, not only, but also because the fact that they are at high risk for

rapid abdominal fat deposition (192, 195). Physical activity is able to reduce the risk of weight gain and improve reproductive functions, along with the promotion of QOL, among PCOS women (192, 196).

Despite the importance of exercise in improving metabolic status, the majority of PCOS patients lack regular physical activity (194, 197).

Various systematic reviews and meta-analysis reported the positive effects of regular exercise on PCOS symptoms management, regular menstruation, and fertility (194, 198, 199). Regular exercise can reduce total body fat, which stores estrogen and produces steroid hormones (194, 199).

Independently of weight change, exercise can help the improvement of metabolic indexes. The reduction of oxidative stress and systemic inflammation (200), improvement of hormonal balance and adipokines secreted from adipose tissue, and the efficiency of cellular metabolism are some of the mechanisms of exercise (194, 201, 202). A systemic review suggested that exercise can balance hormonal actions in PCOS women, especially in reducing HA and normalizing serum AMH levels (192).

The duration of the exercise seems to be related to the changes in lipid profile, raising HDL cholesterol levels and significantly reducing LDL cholesterol levels. These benefits can be achieved by increasing the frequency of training sessions per week or increasing the duration of each session (194).

Aerobic exercise can enhance glycemic control while providing a beneficial impact on sexual function and QOL (192, 203).

Resistance training has important physiological effect as it increases strength and muscle mass, improves insulin sensitivity, decreases visceral fat, and reduces the risk of MetS (194, 201).

For some authors, yoga is considered as the best complementary and alternative therapy, because of its help in weight loss, in relaxing the body and mind, in relieving stress, in regulating blood circulation, and in boosting metabolism. The practice of yoga can also reduce stress and fatigue. (204)

A study by Nidhi et al., showed that the practice of yoga, for 12 weeks, led to a significant increase in glucose metabolism, change in blood lipid levels, reduction of LH and testosterone levels, and improvement of menstrual frequency. These results concern

patients diagnosed with Rotterdam criteria, but researchers could not control over diet and medication used by the participants, which makes it harder to evaluate the real effects of yoga as a PCOS therapy (204, 205).

8.4. Inositol

Inositol is a carbocyclic sugar found in high concentrations in human and plant cells. It exists in nine different isomeric forms, the most common of which are Myoinositol (MI) and D-Chiro-inositol (DCI) (7). Inositols are present in greater quantities in fresh fruits and vegetables and in all foods containing seeds, such as beans, grains, and nuts (206).

The main inositol isomers are distributed throughout adipose tissue, liver, and skeletal muscle, and each organ requires a substantially higher proportion of DCI to maintain homeostasis (7, 207).

MI intake has been demonstrated to improve ovulation, oocyte maturation, as well as follicular development and raise in the likelihood of clinical pregnancies, in PCOS women. With MI therapy, ovulation induction time and FSH dosage requirements can be reduced, once MI increases the sensitivity of polycystic ovaries to gonadotropins (7, 208, 209). Regarding the fertility advantages, MI decreases estradiol levels on the day of ovulation triggers, reduces the number of intermediate-sized follicles, and increases the number of large follicles, thereby contributing to a reduction of OHSS risk (209, 210).

MI can also act as an important growth factor for human cells. In PCOS, the hormonal imbalance can result in an increased prevalence of osteoporosis. In this matter, MI, as well as DCI, both can enhance osteogenesis and bone mineral density, while inhibiting osteoclastogenesis (211-213).

The discovery of the insulin-sensitizing effect of MI proved its importance in the prevention of GDM, a highly prevalent disorder in women with PCOS (211).

DCI therapy has been shown to improve endocrine, metabolic, and reproductive parameters, by lowering blood pressure, and lipid, and insulin levels, as well as improving the maturity and quality of oocytes, while reducing oxidative stress in follicular fluid (7).

Even though these compounds can be administered individually, the best clinical results were achieved with the simultaneous use of MI and DCI (211, 214). Studies showed a change in LDL cholesterol, HDL cholesterol, and TG levels, after treatment with both MI and DCI. There was also a significant reduction in fasting insulin levels, which helps to assess insulin

sensitivity, in young obese women with PCOS (210, 211, 215). Studies showed that both MI and DCI, in a physiological plasma ratio of 40/1, can restore hormonal features, increasing progesterone and SHBG and decreasing LH, testosterone and insulin levels (209, 211). Therefore, this therapeutic approach can reduce the risk of MetS.

Low inositol level is a condition that characterizes several psychological issues. In fact, low MI levels in the frontal cortex may indicate depression and altered sleep symptoms (145). Considering pharmacological therapy normally used in psychiatry, some of them should be avoided in PCOS patients, due to their ability to induce modification in hormonal profile and increasing androgens production, in normal women's theca cells (145, 216). Inositols were shown to have positive effects in the management of panic disorder and premenstrual depressive disorder, thereby representing a novel approach able to restore normal physiology and helping in recovering from a severe psychiatric disorder (145, 217, 218).

8.5. Supplementation

Women with PCOS are reported to have imbalances in minerals and serum trace elements concentrations and, because of that, supplementation is usually recommended as a part of their treatment (9).

Antioxidants are a group of substances that help to capture and neutralize free radicals, thereby eliminating their damaging effects on the body. These substances include thiols, glutathione, vitamin E, vitamin C, selenium, vitamin A, thioredoxin and zinc (219, 220). Antioxidants can effectively reduce oxidative stress levels and inflammatory markers in PCOS, as well as improve antioxidant capacity and lipid metabolism of PCOS patients (28, 219).

Selenium supplementation is suggested because of its antioxidant properties and its ability to reduce ROS formation, which may benefit IR, lipid disturbances, and reproductive outcomes, in women with PCOS (28, 221).

Other antioxidants also can inhibit oxidative stress and ROS production. They include lipoic acid, vitamin C, vitamin E, Coenzyme Q10 (CoQ10), NAC, resveratrol, melatonin, and carnitine (28).

NAC is a nutritional supplement of non-essential amino acid which enhances the biosynthesis of reduced glutathione. The latter directly preserves the competency of other exogenous antioxidants. Evidence suggests that NAC improves insulin sensitivity and reduces ROS production. Some studies reported that the adjuvant therapy with NAC

improves ovulation induction efficacy and the quality of oocytes and embryos, in women who planned undergoing ART (222-224). Taking this into a count, it can be concluded that adding NAC to letrozole or CC has positive effects, on women with PCOS (225).

CoQ10 is a lipid-soluble vitamin-like agent that plays an important role in the oxidative phosphorylation and reduces oxidative stress damage in the body. CoQ10 also has anti-inflammatory and anti-apoptotic effects (226). Previous research demonstrated that CoQ10 is a regulator of insulin and adiponectin receptors, suggesting that its antioxidant capability can enhance insulin sensitivity (219, 227). Clinical studies showed that CoQ10 supplementation, in women with PCOS, resulted in improved hormonal and metabolic parameters (9, 228, 229).

Vitamin E is not produced by the human body thus it must be consumed from diet. It is an essential lipid-soluble vitamin that acts mainly as an antioxidant. Besides the antioxidant role, vitamin E has other functions, such as anticancer, anti-proliferative, anti-angiogenic, and anti-inflammatory properties. A review suggested the use of vitamin E as one of the natural-based treatment options for PCOS (230).

Carnitine is reported to be lower in women with PCOS and linked to HA, hyperinsulinemia, and reduced oocyte quality (9). Evidence showed that oral carnitine supplementation led to positive effects in glycemic parameters, follicles and size of ovarian cells, weight changes, and oxidative stress. Beyond its effects on weight loss, carnitine is also an antioxidant, anti-inflammatory, and cardioprotective agent (9, 231, 232).

Afshar et al. found that the combined application of magnesium and zinc can improve serum total antioxidant capacity and significantly improve oxidative stress levels of PCOS patients (28, 233).

PUFAs, like omega-3 and omega-6, influence our general health. High dietary intake of PUFA has shown significant endocrine and metabolic effects, in PCOS women. Clinical trials reveal decreased levels of testosterone and insulin, and increased levels of adiponectin, which could favorably affect HA and IR, maintaining metabolic homeostasis. Both omega-3 and omega-6 have been proposed to lower inflammation (234-236). PUFAs were shown to decrease LH levels, which would help bring LH/FSH ratio back to normal and, consequently, regulate ovulation and improve fertility rates. The dietary intake of nuts might have been proven to be beneficial, as intake of almonds have shown to reduce inflammatory markers (234).

Omega-3 fatty acids also have anti-atherosclerotic, anti-inflammatory, and anti-diabetic effects, which might improve insulin sensitivity. As stated before, women with PCOS have diminished insulin sensitivity and, with that in mind, omega-3 fatty acids intake may be beneficial (219).

Curcumin is an active compound in turmeric that acts as an antioxidant and anti-inflammatory agent. It has induction ovulation properties, enhancing the biochemical profile of patients with PCOS (237). A meta-analysis found an improvement in glycemic control, during curcumin intake (237, 238). Although there are benefits, there is also a need for further studies to evaluate the safety of this therapy (9).

Vitamin D is a fat-soluble steroid hormone that regulates calcium, magnesium, and phosphate homeostasis and plays a pivotal role as antiproliferative and immunomodulatory mediator (147). The endorsement of vitamin D supplementation in women with PCOS is based on its role in glucose metabolism. It is believed that vitamin D plays a significant role in the development and onset of most clinical features of PCOS, such as IR (237, 239, 240). Vitamin D appears to improve reproductive and metabolic impairment in PCOS, through its impacts on IR. It also regulates follicular development, once it influences AMH levels, FSH sensitivity and progesterone production (147, 237). Randomized controlled trials have suggested that regular low dose supplementation of vitamin D (< 4000 IU/d), in PCOS patients, is beneficial (237).

However, studies on vitamin D supplementation, in obese patients with PCOS, have yielded mixed results (3). This indicates that doses and timing have a significant weight on the effectiveness of the supplementation, justifying the heterogeneous results found among the studies reviewed (241).

Flaxseed is considered as a functional food containing abundant amounts of α-linoleic acid, phytoestrogenic lignans, and dietary fibers (242). A meta-analysis showed that flaxseed oil supplementation could reduce PCOS' clinical complications (242, 243). Another study showed the reduction in androgen levels, along with an improvement in hirsutism (242, 244). Even though these results are promising, there are only a few studies on this matter.

Berberine (BBB) is a type of isoquinoline extracted from Chinese medicinal herbs. Previous research shows beneficial metabolic effects, including improved IR, visceral adiposity, atherogenic dyslipidemia and lipid profile. It also has an anti-hyperglycemic effect (245-247). Treatment with BBB prior to IVF led to a significant improvement in the pregnancy outcomes, such as clinical pregnancies, live birth, and biochemical pregnancies. (245, 248)

BBB seems to have positive effects in PCOS, but its side effects on the female reproductive system have yet to be discovered to further assess its safety.

Quercetin (QUR) is a flavonoid present in fruits and green leafy vegetables, as well as seeds and nuts (221). When consumed in tolerable doses, QUR may have beneficial biological effects, like antioxidant, anticancer, and anti-inflammatory effects (221, 249). Ding et al., showed that, after 3 months of treatment with QUR, patients with PCOS showed an improvement in LH, LH/FSH ratio and insulin levels. There was also a reduction in inflammatory markers (221). However, there are no relevant studies on the dose and duration of QUR treatment (221, 250).

A meta-analysis has demonstrated the beneficial effect of Chromium on BMI and fasting insulin, and free testosterone levels, in women with PCOS (9, 251). Zczuko et al. concluded that, in women with PCOS, it would be recommended a higher intake of folic acid, vitamin D, vitamin C, and cobalamin. They also suggested that some patients would benefit from supplementation of potassium, magnesium, and zinc (9, 252).

8.6. Microbiome

Shaping the intestinal microflora, through diet and/or supplementation, is important for PCOS women.

Probiotics are live microbes that benefit the host, if ingested in sufficient amounts. They can replenish a seriously disintegrated gut microbiome, reduce cholesterol, TG, and LDL cholesterol levels, elevate HDL cholesterol levels, and improve inflammatory profiles, in women with PCOS (253).

There is evidence that probiotic supplementation (with *L. acidophilus, L. casei, and B. bifidum*) can lead to a significant reduction in weight and BMI, with positive effects on glycemia, TG, and very low-density cholesterol levels (7, 254).

Prebiotics are non-digestible oligosaccharides and fermented food ingredients capable of modifying the gut microflora that show beneficial effects on the host. Prebiotics are able to increase the fermentation of microbes, suppress hunger, and reduce plasma glucose consumption. They also show a noticeable impact on metabolic biomarkers of PCOS patients (253). A study by Fernandes et al. stated that prebiotic intake reduced hyperglycemia and HOMA-IR levels (253, 255).

The regular consumption of resistant dextrin, a prebiotic, helps in the regulation of metabolic parameters and can reduce hyperandrogenism, as well as menstrual cycle abnormalities, in PCOS women (7, 256).

Fiber is the best source of "microbiota accessible carbohydrates". Due to this, fibers are capable of modifying the gut microenvironment and are used as prebiotics. A high fiber-diet is highly effective against PCOS as the intestinal microbes decay the dietary fiber to yield three chief short-chain fatty acids, like acetate, propionate, and butyrate, which maintain the intestinal barrier (253).

Studies propose that protein intake increases the microbial intestinal diversity. For instance, whey and pea protein intake increases the gut commensal microbes, reshaping it and, thereby, helping with PCOS symptoms (253, 257, 258).

Physical activity also flourishes beneficial gut microflora, which responds quickly to the homeostatic and physiological alterations due to exercise (253).

Fecal microbiota transplantation (FMT) refers to the transplantation of fecal microbes from a healthy donor into the gut of an unhealthy patient to alter the microflora and, therefore, treat a disease (253). This therapy is used in Crohn's disease and can be a potential future therapy for PCOS.

8.7. Chinese Medicine

Traditional Chinese Medicine (TCM) is based on the concept of holism, using multi-system regulation and multi-target action to treat PCOS. TCM can effectively improve patients' signs and symptoms, the ovarian environment, the sympathetic nervous system, the endocrine system, and disordered glucose and lipid metabolisms (259).

Acupuncture can control the function of the autonomic nervous system, which, in turn, has been proven to have a certain curative effect on PCOS (259). Acupuncture can also improve vascular endothelial function, regulate dyslipidemia, correct IR, and improve endocrine disorders. In PCOS patients, it can improve menstrual cycle regulation, increase endometrial thickness, promote oocyte growth and follicle development, reduce LH levels, improve ovarian function, and increase ovulation rate (259-261).

When compared to metformin, acupuncture was superior in improving glucose metabolism and had a lower incidence of gastrointestinal side effects (259, 262). On the basis of Western

medicine treatment of PCOS, adding acupuncture treatment can improve the curative effect and shorten the course of the disease (259).

The use of acupuncture in conjunction with Western medicine can also effectively improve the ovulation rate, and reduce LH/FSH ratio, HOMA-IR, and BMI. When compared with no intervention at all, acupuncture had a better effect in promoting the recovery of menstrual cycle and reducing BMI (263).

Although the mechanism of acupuncture for PCOS has been found in modern medicine, most of the trials have small sample sizes and lack consistency in the selection of acupoints (259).

Current evidence suggests that acupuncture is beneficial for PCOS and can improve fertility, endocrine, glycemia and anthropometric outcomes (263).

9. Future Perspectives

Clinically, PCOS can be presented with many different combinations of signs and symptoms, which hinders the earlier diagnosis and comorbidities prevention. In the future, we should bet on the agreement of generalized use of one set of diagnostic criteria and the literacy improvement of health professionals and general society, once it has shown to be an effective way to prevent health complications, later in life.

There are plenty of potential new treatment options for PCOS. Although, before enrolling in these new treatment options, there is a need for further research on genetic causes, molecular mechanisms, and dysbiosis interference. The potential new treatment options include the use of miRNA, IL-22, FMT, GLP-1 and GIP.

The literature regarding complementary therapies is limited in a variety of themes, including the use of TCM, physical activity, specific diet recommendations, among others. Stating this, it would be beneficial to start additional research on these themes as well as elaborating a guideline that helps health professionals in PCOS treatment.

10. Conclusion

PCOS is a heterogeneous disease with different signs and symptoms. The treatment plan for these women is not stablished yet and there is a need to inform health professionals about

the variety of complementary medicines which can help manage PCOS' signs and symptoms.

Pharmacological therapy should not be used as a first-line therapy for these women. Rather, they should be advised to enroll in LSM, with a precise diet and exercise plan. The benefits of non-pharmacological treatments are confirmed by a variety of studies and should not be discarded. Rather, they should be taken into a count and explained to these patients, so they can make an informed decision on their treatment plan.

The reviewed studies led us to believe that the most important premise is a holistic and individualized approach of each woman, according to each PCOS phenotype. In this approach, neither pharmacological nor non-pharmacological treatments should be discarded, rather they can be complemented by one another.

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