

Polycystic ovary syndrome therapeutic methods: A systematic review

Métodos terapêuticos para síndrome dos ovários policísticos: revisão sistemática

DOI:10.34119/bjhrv6n1-304

Recebimento dos originais: 17/01/2023

Aceitação para publicação: 17/02/2023

Vitória Ribeiro Farinha

Graduated in medicine by Centro Universitário de Mineiros

Institution: Centro Universitário de Mineiros (UNIFIMES)

Address: R. 22 esq. c/ Av. 21, Setor, Aeroporto, Mineiros - GO, CEP: 75833-130

E-mail: vitoriafarinha@outlook.com

Beatriz Ribeiro Farinha

Resident in Nephrology by Pontifícia Universidade Católica de São Paulo (PUC - SP)

Institution: Pontifícia Universidade Católica de São Paulo (PUC - SP)

Address: R. Joubert Wey, 290, Vila Boa Vista, Sorocaba - SP, CEP: 18030-070

E-mail: beatrizribeirofarinha@gmail.com

Tamires Lopes Silva

Doctor in Immunology and Parasitology by Universidade Federal de Uberlândia

Institution: Instituto do Coração do Hospital das Clínicas da FMUSP (InCor)

Address: Av. Dr. Enéas Carvalho de Aguiar, 44, Cerqueira César, São Paulo - SP,
CEP: 05403-900

E-mail: tlopes_s@yahoo.com.br

Danila Malheiros Souza

Doctor in Health Sciences by Universidade Federal do Triângulo Mineiro

Institution: Centro Universitário de Mineiros (UNIFIMES)

Address: R. 22 esq. c/ Av. 21, Setor, Aeroporto, Mineiros - GO, CEP: 75833-130

E-mail: danila@unifimes.edu.br

Mariana de Souza Castro

Graduated in medicine by Centro Universitário de Mineiros

Institution: Centro Universitário de Mineiros (UNIFIMES)

Address: R. 22 esq. c/ Av. 21, Setor, Aeroporto, Mineiros - GO, CEP: 75833-130

E-mail: marianasouza2917@hotmail.com

Nadiny Paim Solano

Graduated in medicine by Centro Universitário de Mineiros

Institution: Centro Universitário de Mineiros (UNIFIMES)

Address: R. 22 esq. c/ Av. 21, Setor, Aeroporto, Mineiros - GO, CEP: 75833-130

E-mail: nadinypaim@hotmail.com

Vanessa Resende Souza Silva

Doctor in Immunology and Parasitology by Universidade Federal de Uberlândia
Institution: Centro Universitário de Mineiros (UNIFIMES)
Address: R. 22 esq. c/ Av. 21, Setor, Aeroporto, Mineiros - GO, CEP: 75833-130
E-mail: vanessa.resende@unifimes.edu.br

ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine disorder, whose prevalence in women varies from 6 to 10% in the reproductive period. It can lead to health complications, such as menstrual dysfunction, infertility, hirsutism, acne and metabolic syndrome. The biggest difficulties with this syndrome is to recognize its etiopathogenesis and select the best therapy. This study is a systematic review, which carried out an electronic search in the following databases SCIELO, LILACS, PUBMED, selected 34 articles. The purpose of the review is: to understand the therapeutic methods available for treatment, although there is no cure for the syndrome, the aim of the approach is to minimize the clinical signs and improve the quality of life of these women. The first therapy to be used is the change in lifestyle and changes in the diet, in the background medications are applied. Treatment must be individualized according to the complaints of each patient.

Keywords: polycystic ovary syndrome, vitamin D/PCOS, metformin/PCOS, physical exercise/PCOS, treatments/PCOS.

RESUMO

A síndrome dos ovários policísticos (SOP) é um distúrbio endócrino complexo e heterogêneo, cuja prevalência em mulheres varia de 6 a 10% no período reprodutivo. Pode acarretar complicações de saúde, como disfunção menstrual, infertilidade, hirsutismo, acne e síndrome metabólica. Uma das maiores dificuldades sobre essa síndrome é reconhecer sua etiopatogênese e selecionar a melhor terapia. Este estudo trata-se de uma revisão sistemática, a qual realizou-se busca eletrônica nas seguintes bases de dados SCIELO, LILACS, PUBMED, selecionados 34 artigos. O propósito do trabalho é: compreender os métodos terapêuticos disponíveis para tratamento, ainda que não exista cura para a síndrome o intuito da abordagem é minimizar os sinais clínicos e melhorar a qualidade de vida dessas mulheres. A primeira terapia a ser empregada trata-se da mudança no estilo de vida e modificações na dieta, em segundo plano aplica-se medicamentos. O tratamento deve ser individualizado de acordo com as queixas de cada paciente.

Palavras-chave: síndrome dos ovários policísticos, vitamina D/SOP, metformina/SOP, exercício físico/SOP, tratamentos/SOP.

1 INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrinopathy that causes problems in public health and currently affects around 6 to 10% of women worldwide during the reproductive age, depending on the diagnostic criteria used.¹ In the 1960s, the term “polycystic ovary syndrome” emerged as a functional ovarian hyperandrogenism, to characterize the circulating androgens

typical cutaneous signs.² In the current context, the definition is due to ovulatory dysfunction and hyperandrogenism.^{3,4}

The 2003 Rotterdam consensus considers the presence of at least two of the three criteria to determine the presence of PCOS: clinical and/or biochemical hyperandrogenism, anovulation or polycystic ovarian appearance which is detected by ultrasound (US), excluding other causes of menstrual irregularity and hyperandrogenism, such as hyperprolactinemia, hypothyroidism, hyperthyroidism, Cushing's syndrome, non-classical forms of congenital adrenal hyperplasia and androgen-secreting neoplasms.^{3,5}

In fact, the exact etiology of PCOS is unknown, and the clinic is heterogeneous, including the occurrence of metabolic disorders and cardiovascular risk factors relevant, such as insulin resistance (IR), dyslipidemia, diabetes mellitus (DM), systemic arterial hypertension (SAH), endothelial dysfunction, central obesity and changes in chronic pro-inflammatory markers.^{6,7} During pregnancy, these women are at an increased risk to develop gestational diabetes, pre-eclampsia, also the baby is affected resulting in fetal macrosomia, fetus delayed development and perinatal mortality.^{5,8}

Importantly, women that is affected by PCOS possess an increased tendency to develop premature unfavorable clinical factors, such as metabolic syndrome, as well psychological morbidity with the occurrence of depression, loss of self-esteem, high levels of stress and anxiety.⁷

Currently, therapy for PCOS is not restricted to reproductive parameters, it is also considered the prevention and promotion of cardiovascular health and other complications arising from the disease.⁶

2 METHODOLOGY

In order to develop the systematic review, we performed an electronic search in the databases: LILACS (Latin American and Caribbean Literature in Health Sciences), SCIELO (Scientific Electronic Library Online) and MEDLINE/Pubmed (Medical Literature Analysis and Retrieval System Online). The polycystic ovary syndrome (PCOS) was used as primary keyword that was crossed with the descriptors: vitamin D, metformin, physical exercise, and treatments. The following inclusion criteria were adopted: articles published in English, Spanish and Portuguese, studies with samples in the population, randomized studies, observational studies, books, literature reviews that were published between 2011 and 2020, except for one study of 2008 that was extremely relevant. Also, for exclusion criteria, we determined that

studies without information regarding the analysis performed, studies using animals, as well as theses and dissertations should be eliminated.

To determine the relevance of the information for our study, first, the title of the journals found was analyzed, and then the abstract, afterward we systematically read and analyzed the full text, comparing the literature data with the objectives of this study.

3 RESULTS

Considering the research through all the databases, 15712 articles were found, and after selection 34 met the selection criteria. In consideration of the local of studies, we found out that studies were developed in Brazil, Poland, Chile, Australia, United Kingdom, China, India, England, United States and Greece.

According to data analysis and considering the relevance of the theme, it is important to seek for new therapeutic methods approach, regarding that there is no curative treatment for the syndrome. The results confront the best therapeutic methodology indicating that individual parameters of each patient should be considered.

Importantly, the pathogenesis of the disease is not totally understood, hence, several controversies exist regarding the treatment of this disease, and there is no single therapy. Notwithstanding, it is extremely important to recognize the complaints of each patient to minimize them. Considering the performed analysis, we verified that it is necessary a randomized clinical study to compare all existing methodologies.

4 DISCUSSION

To understand the therapeutic approach, it is necessary to understand the findings regarding the pathology.

In the study performed by Facio-Lince Garcia et al.⁹ (2015), it was described the relationship of the syndrome pathogenesis and adipose tissue, and it was pointed out that adipocytes have high lipolytic activity, resulting in an increased free fatty acids amount, contributing to insulin resistance. Else more, it was presented that family history and age are parameters that predispose women with PCOS to develop metabolic disorders. Thus, this analysis is important to understand the resistance to treatments and therapeutic procedures that will be performed.⁹

Several studies have reported that over 50% of women with PCOS are overweight or obese, meanwhile, around 70% of those women have at least one alteration in the lipid profile, in spite of BMI, such as increased levels of low-density lipoprotein (LDL-cholesterol) and

triglycerides, and decreased high density (HDL-cholesterol).^{9,10} Those changes favor the risk of the cardiovascular disease development turning the therapeutic management complex and although, those data are not part of the diagnostic criteria, they are extremely prevalent.

The majority of articles pointed out that non-drug treatment are the most effective treatment for PCOS, however, some women are not adept this kind of treatment and seek for drug therapies to reduce the anxiety and because of the believe in a rapid improvement by drug therapy.^{6,7,11-13}

Taking into account the hyperandrogenism, Bednarska and Siejka¹⁰ (2017) explained the mechanism responsible for clinical symptoms, such as alopecia, hirsutism, and acne, which are related to the excess of testosterone production due to stimulation of ovarian theca cells by insulin. Additionally, these signs frequently induce women to search for medical support.

Several reports solely addressed the biological parameters of the disease, which are of great relevance for understanding the necessary treatments. Nevertheless, those studies did not mention the psychological problems occurred as a consequence of the syndrome which also helps to turn the woman with PCOS sick. These symptoms bring light to the nomination of the syndrome as “the thief of womanhood” due to depreciation of woman aesthetic resulted from hyperandrogenism and obesity that contributes to impaired self-esteem.¹⁴

In this systematic review, we addressed an updated in several resources concerning the PCOS, aiming a better quality of life for women with the syndrome.

During the last decades, it has been noticeable that the world population changed their eating habits and behavioral. In fact, urbanization and industrial development induced a nutritional change faced by society due to excessive consumption of processed foods, mainly in the metropolises, where there is a predominance of fast-food companies. In addition, the enhancement of advertising technology, influences the consumption of industrialized products, which favors the novel harmful eating habits created by the population.

The evaluation of population habits demonstrated that exist a relationship between women with PCOS and overweight and / or obesity, being necessary to seek cultural changes in primary health care, in order to discuss individual non-pharmacological drugs strategies to improve the disorders resulted from the syndrome. Considering this, it should be evaluated the objectives, routine and economic factor of each woman for an appropriated indication of physical exercise and new nutritional habits, increasing the adherence to this therapy, turning it into a new lifestyle.^{2,6,7}

According to Azevedo et al.⁶ (2008), regular physical exercise is considered the primary strategy for the treatment of women with PCOS, however, there is a lack of evidence concerning

the prescription of specific exercise type and duration of activity.^{6,13} Studies have shown an improvement in adiposity patterns whether activities of moderate intensity are performed for at least 150 minutes / week or with vigorous intensity 75 minutes / week, maintained for at least 12 weeks. Additionally, if the training period was stopped early, the achieved benefits were nulled. Into the beneficial activities are include aerobic exercise, resistance training, flexibility training, yoga, tai chi chuan and pilates. In contrast, an analysis performed by Kite and contributors did not find any amelioration of clinical effects by diet combined exercise or just diet.^{6,7,11,12}

Importantly, it was possible to observe that after twelve weeks of aerobic physical activity of moderate intensity, a decreasing of jejum insulin of PCOS patients, amelioration of lipidic profile, indicating an reduction of LDL cholesterol amount and increasing in the HDL cholesterol level, meanwhile the ovulatory profile were reestablished, in other words, the fertility were enhanced. These exigences are important for adults ranging from 18 to 64 years, however, there is a divergence in the duration and intensity of physical activity according to age.^{6,11}

Stepito et al.¹¹ (2019), evaluated that apart from to the clinical parameters benefits, it is estimated that non drug therapy reduces long-term costs of public health system by approximated AUD\$ 1,900/person/year, due to the prevention of chronic metabolic diseases that is extremely important once in Brazil the primary care services is overburden by this healthy problem.

Emphasizing, studies prove the effectiveness of non-drug therapy for women with PCOS focusing not only on the benefits for metabolic health, but also in fertility, mental health and health public system spends. Oppositely, the study performed by Scott et al.¹⁵ (2017) and Hiam et al.¹ (2019) demonstrated that a small percentage of women with PCOS did not achieve any improvements in reducing total body fat and insulin sensitivity and it is related to heredity. Even though it was reached the expected responsiveness, patients significantly reduced relative central adiposity and improved aerobic capacity during exercise.

Non-drug therapy is the most suitable for patients independent of clinical symptoms for prevention of symptoms and improvement of life quality, however, PCOS can also be treated with medications depending on the clinical manifestation such as: infertility, menstrual disorders, obesity and symptoms of hyperandrogenism such as acne, hirsutism and alopecia; especially, when exist a resistance to non-pharmacological intervention.¹⁰

In Brazil, only three drugs are accepted by ANVISA for the treatment of obesity, which are Orlistate, Liraglutide and Sibutramine. In addition, bariatric surgery can be indicates

depending on established parameters, and brings several benefits, such as improvement in comorbidities associated with PCOS. On the other hand, it can lead to malabsorption of nutrients and psychological disorders, including eating disorders.¹⁶

Regarding the hyperinsulinemia, Iwata et al.¹⁷ (2015) addresses the usage of insulin sensitizing agents, pointing out that metformin (dimethylbiguanide), a biguanide, that increases the insulin sensitivity in peripheral tissues, decreasing hepatic glucose production and increasing the translocation of glucose transporters (GLUT-1 and GLUT-4) (IWATA et al, 2015) is commonly used for treating obesity. Although, these medicaments are not effective in the treatment of acne, hirsutism or anovulatory infertility when used solely, it improves irregular menstrual cycle.^{18,19}

Thiazolidinediones, rosiglitazone and pioglitazone are other insulin-sensitizing agents but they are not used frequently due to side effects, such as risk of bone fractures and bladder cancer.¹⁸

Hyperinsulinemia increases the levels of free testosterone and reduces levels of sex hormone-binding globulin (SHBG), leading to menstrual disorders, ovarian cysts, hirsutism and anovulatory infertility (hyperandrogenism).^{13,18} Jiang, Gao and Zhang²⁰ (2019), correlated insulin sensitivity and fertility in women with PCOS, demonstrating that in patients with PCOS, dimethylguanide regulates the abnormal secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH), which in the pathophysiology of disease have reduced and increased production, respectively. In addition, there was a beneficial response regarding the dynamics of the ovarian follicle. Combined treatment with oral contraceptives and clomiphene citrate appears to improve the results when comparing the usage of any of these drugs alone; however, few studies validate this assertion.^{17,20}

Acupuncture has gained attention for treating insulin sensitivity, since this therapy certainly mediates the activation of sensory nerve fibers which regulates the sympathetic activity in the ovaries and in the central nervous system¹⁸. According to Balen et al.²¹ (2016) this therapy suppresses the secretion of cortisol in the adrenals, and modulates the secretion of beta-endorphin, influencing the release of GnRH, presupposing that acupuncture can acts in the anovulation resulted from PCOS.

The study carried by Li et al.¹⁸ (2017) suggested an improvement in signaling pathways related to insulin resistance, through electrical stimulation, meanwhile manual stimulation has a prevalent effect on glucose tolerance, raising the hypothesis of superiority of acupuncture usage in comparison to metformin to improve insulin sensitivity, however there is a lack of high quality studies to confirm this hypothesis.

Another suitable alternative for treating hyperinsulinemia conditions is the use of inositol, because of a defect observed in the second messenger inositol phosphoglycan (IPG) production, promoting an impairment in the insulin pathway, considering that IPG participates in the control of oxidative metabolism and glucose uptake by GLUT4 in the extracellular environment.^{22,23}

The chemical structure of inositol belongs to the vitamin complex. This complex is similar to the glucose molecule, and can be produced in the human body, from glucose-6-phosphate. Inositol can be found in foods and plants, such as beans and fruits. Genazzani²² (2016) and Unfer et al.²³ (2016) reported the use, of two stereoisomers: myo-inositol (MYO) and D-chiro-inositol (DCI). In the ovary, the myo-inositol (MYO) mediates the glucose uptake and FSH signaling; while the D-chiro-inositol (DCI) synthesizes insulin-mediated androgens, obtaining a collect of favorable oocytes.

Genazzani²² (2016) indicates that MYO is converted into DCI, an important factor for the prescription of inositol. It appears that both isomers are efficient by different actions. Meanwhile, the administration of DCI was relevant to increase the chances of ovulation, and to reduce the concentrations of insulin and androgens; MYO improved the majority of hormonal parameters, recovering fertility and menstrual function, as well as promoting weight loss, restoring the lipid profile.

Importantly, considering infertility treatment options, the infertile couple should be investigated, and the change in lifestyle should be encouraged, since ovulation induction is less effective when the body mass index (BMI) is higher than 28 kg/m², therefore, weight loss contributes to the restoration of ovulation.^{10,24}

Costello et al.¹⁶ (2019), Mascarenhas and Balen²⁵ (2020) demonstrated the current evidence and recommendations for the use of Letrozole, an aromatase inhibitor, as the first-line drug for ovulatory induction. Despite the previous usage of clomiphene citrate alone, Letrozol presented improved results in terms of: ovulation, pregnancy per patient and live births per patient, but the rates of multiple pregnancy and abortion were not different. The mechanism that induces ovulation induction by this drug it is still unknown, however it is known that this drug class avoids the aromatase-induced conversion of androgens to estrogens, and increases the secretion of FSH leading to the development and maturation of the ovarian follicle. The Letrozole increases the formation of gonadotropin to induce ovulation through an feedback to the hypothalamic-pituitary axis (HHP). This mechanism appears to have less multifollicular development in relation to clomiphene since it maintains HHP feedback.²⁵

Clomiphene citrate is an estrogen receptor modulator that directly affects the hypothalamic-pituitary axis, acting as a competitive estrogen antagonist, thereby leading to compensation through HHP, increasing GnRH pulse secretion, releasing gonadotropins that will act on ovulation.²⁵ For a long time, this drug was considered first-rate because it is a rapid and effective medication that increases conceived pregnancy rates by 75% in the first three months of treatment, but increases the chance of multiparity by 10%.^{10,24,25} Around 15% of patients are considered resistant to this drug and do not respond to treatment.¹³

In cases of therapeutic failure, it is possible to use gonadotropins, preferably recombinant FSH, laparoscopic surgeries such as laparoscopic ovarian perforation (LOD), or in vitro fertilization (IVF).^{10,24} Before initiate any of these treatments, patients should be advised of high costs, risks of twin pregnancy and ultrasound monitoring.¹⁶ Furthermore, Tannus, Burke and Kol (2015) state that adding human chorionic gonadotropin (hCG) for triggering ovulation does not improve the reproductive effect and does not decrease the abortion rate.¹³

The archives of Eftekhari et al.⁸ (2020) and Voulgaris et al.²⁶ (2017) point out the relationship between vitamin D (cholecalciferol) and reproductive activities, since vitamin D receptors were found in several tissues of reproductive system. In addition, it was proven the relationship of vitamin D deficiency and calcium dysregulation.²⁷ Women with PCOS and high BMI tend to present hypovitaminosis D, considering that adipose tissue capture the vitamin D bioavailability, thus, assuming that exist a relationship of vitamin D deficiency or insufficiency with the phenotype of women with PCOS.^{28,29}

Indubitable, the majority women with PCOS are infertile, and have high levels of vitamin D deficiency, for thirreazon supplementation of cholecalciferol can be associated as an adjunct to the therapies mentioned above, since it is a simple complement and with low risk of effects adverse effects.³⁰ Vitamin D may also be associated with other metabolic disorders, therefore, there is cooperation in the pathogenesis of PCOS.^{8,26,27}

The use of oral contraceptives (OCA), especially for women whom do not want a previous pregnancy, is commonly used in the treatment of PCOS. The combined therapy of estrogen and progesterone is the fundamental one, admitting that the combination of cyproterone acetate (ACP) with ethinylestradiol is the widely used.^{10,31} Additionally, progestogens that composes the pills are originate from testosterone and have androgenic activity, for example drospirenone and ACP existing as androgen receptor antagonists.³¹

These drugs decrease the levels of circulating androgens, improve menstrual patterns, hirsutism, and reduce endometrial thickness, having a protective effect against endometrial

cancer, therefore, despite the contraceptive effect, they improve the clinical signs of the syndrome. However, there is no improvement in insulin resistance, depending on the type of progestin used, it can even worsen it.^{19,32}

A study carried out in India pointed out the risks and benefits regarding the use of oral contraceptives (OCA), in women with PCOS, showing two main concerns with long-term use: the decrease in bone density and the risk of venous thromboembolism. In addition, a worsening of the lipid profile, increased risk of hypertension, liver and breast cancer also glaucoma can be identified. Furthermore, the use of metformin and OCA were compared, and it was shown that metformin is more effective than oral contraceptives in reducing fasting insulin, and less effective in improving menstrual patterns, hirsutism or reducing testosterone.¹⁹

Recent studies support the metformin and OCA should be used together, combining the benefits of both and presenting better clinical responses.³³

Other drugs that can be used to treat hyperandrogenism, but they are not commonly used, include long-acting GnRH analogs, ketoconazole, glucocorticoids, flutamide, finasteride, spironolactone and isotretinoin.^{10,31}

Finasteride is a 5-alpha reductase inhibitor, used for treating for alopecia, mainly in combination with mixodil presented satisfactory results, as well as the association of cyproterone acetate with finasteride. However, it does not seem to be effective for treating acne.^{10,31}

According to Bernarska and Siejka¹⁰ (2017) isotretinoin was introduced to treat acne in patients with PCOS, being only less effective than ACO.

Spironolactone is an aldosterone antagonist, and it was cited by Moura et al to treat hirsutism, acne and alopecia, because depending on the dose it can block the binding of 5-alpha-dihydrotestosterone to androgen receptors in the skin, consequently, elevates the SHBG, reduces the action of 5 alpha reductase and diminish the generation of androgens.³¹

The GnRH analogues have an antigonadotrophic action, stimulate the pulsatile secretion of GnRH in the hypothalamus, inhibiting HHP. They have low adherence and are hardly used, due to the side effects, especially hypogonadism, leading to estrogen deficiency and increasing risk of osteoporosis. Also, these drugs decrease quality of life and present high cost.³⁴

Both, ketoconazole and glucocorticoids have an action on the adrenal gland, reducing the androgenic effect. Glucocorticoids also have anti-inflammatory action, which is relevant, due to the fact that obese and non-obese PCOS patients have systemic inflammation, and this effect acts as a protector of the oocyte and surrounding cells against the damage generated by oxidative stress, blocking atresia follicular.¹⁰

Finally, flutamide, is a potent blocker of androgen activity, despite acting against acne, hirsutism and alopecia, has a high cost and is highly hepatotoxic, and can be fatal. Therefore, other therapies mentioned are preferable.³¹

On the other hand, Chinese medicine has a range of herbs and mixtures that are used to relieve the symptoms of PCOS, however there is insufficient evidence to recommend the use of herbal medicines in the treatment of PCOS, considering that the majority trials have not been performed on women with the disease. Balen et al.²¹ (2016) demonstrated that *Vitex agnus-castus* reestablished menstrual cycles and increased pregnancy rates. Also, the use of herbs containing *Glycyrrhiza glabra* and *Paeonia lactiflora* called *Shakuyaku-Kanzo-To* (TJ-68) for 24 weeks reduced serum androgens by 35%, and had no adverse effects, as well as a mixture of Chinese herbs, *Sairei-to*, appears to decrease androgens and induce ovulation. The teas made from *Mentha spicata Labiatae* (mint) in women with hirsutism could decrease the concentrations of free testosterone and LH.

Due to the uncertain pathophysiology of the disease, there are several treatment alternatives for PCOS, the best therapy depends on the complaints of each patient, considering that none of these therapies control the patients' metabolic impairment.

5 CONCLUSION

Controlling the clinical signs of PCOS is a major challenge, since there is no curative therapy. Treatments do not address the cause, but minimize the effects and complications of the disease.

Overall, the main interventions are changes in lifestyle and drug therapy, with behavioral management, diet and exercise being the first form of treatment, however there is little evidence in high quality studies regarding recommendations for physical exercise based on indicators for women with PCOS.

It is also observed that metformin is being used in combination with other medications and favorable results were obtained, which enriches the treatment for these women.

It should be remembered that the treatment needs to be individualized, based on the patient's complaints, promoting the quality of life.

REFERENCES

1. Hiam D, Patten R, Gibson-Helm M, Moreno-Asso A, Mcilvenna L, Levinger I. et al. The effectiveness of high intensity intermittent training on metabolic, reproductive and mental health in women with polycystic ovary syndrome: study protocol for the iHIT- randomised controlled trial. *Trials. Australian.*, Apr. 2019;20(221). doi: 10.1186/s13063-019-3313-8
2. Avila MAP, Bruno RV, Barbosa FC, Andrade FC, Silva ACO, Nardi AE. Polycystic ovary syndrome: implications of metabolic dysfunction. *Rev. Col. Bras. Cir. Rio de Janeiro*, Apr 2014;41(2):106-110. doi:10.1590/S0100-69912014000200006
3. Spritzer PM., Oppermann K. Ginecologia endócrina: Hiperandrogenismo. In: Passos EP, Ramos JGL, Martins-Costa SH, Magalhães JA, Menke CH, Freitas F, organizators. *Rotinas em Ginecologia*. 7 ed. Porto Alegre: Artmed; 2017. p. 741-759.
4. Spritzer PM., Cruz PD, Machry RV. Reprodução: Síndrome dos ovários policísticos. In: Silveiro SP, Satler F. *Rotinas em Endocrinologia*. 1 ed. Porto Alegre:Artemed; 2015. p. 395-401.
5. Sousa RML, Chein MBC, Silva DSM, Dutra MB, Navarro PAAS, Figueiredo Neto JA et al. Perfil metabólico em mulheres de diferentes índices de massa corporal com síndrome dos ovários policísticos. *Rev. Bras. Ginecol. Obstet. Rio de Janeiro*, Sep 2013; 35(9):413-420. doi:10.1590/S0100-72032013000900006
6. Azevedo GD, Costa EC, Micussi MTABC, Sá JCF. Modificações do estilo de vida na síndrome dos ovários policísticos: papel do exercício físico e importância da abordagem multidisciplinar. *Rev. Bras. Ginecol. Obstet. Rio de Janeiro*, May 2008; 30(5):261-267. doi:10.1590/S0100-72032008000500009
7. Kite C, Lahart IM, Afzal I, Broom DR, Randeva H, Kyrou I et al. Exercise, or exercise and diet for the management of polycystic ovary syndrome: a systematic review and meta-analysis. *Syst Ver. United Kingdom*, Feb 2019; 8(51). doi:10.1186/s13643-019-0962-3
8. Eftekhari M, Mirhashemi ES, Molaei B, Pourmasumi S. Is there any association between vitamin D levels and polycystic ovary syndrome (PCOS) phenotypes? *Arch. Endocrinol. Metab. São Paulo*, Feb 2020; 64(1):11-16. doi:10.20945/2359-3997000000177
9. Facio-Lince Garcia A, Pérez-Palacio MI, Molina-Valencia JL, Martínez-Sánchez LM. Síndrome de ovario poliquístico y complicaciones metabólicas: más allá del exceso de andrógenos. *Rev. chil. obstet. ginecol. Santiago*, Dec 2015; 80(6):515-519. doi:10.4067/S0717-75262015000600013
10. Bednarska S, Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: What's new? *Adv Clin Exp Med. Poland*, Mar-Apr 2017; 26(2):359-367, Mar-Apr 2017. doi: 10.17219/acem/59380
11. Stepto NK, Patten RK, Tassone EC, Misso ML, Brennan L, Boyle J et al. Exercise Recommendations for Women with Polycystic Ovary Syndrome: is the evidence enough?. *Sports Medicine*, Jun 2019; 49(8):1143-1157. Springer Science and Business Media LLC. doi:10.1007/s40279-019-01133-6

12. Lin AW, Kazemi M, Jarrett BY, Brink HV, Hoeger KM, Spandorfer SD et al. Dietary and Physical Activity Behaviors in Women with Polycystic Ovary Syndrome per the New International Evidence-Based Guideline. *Nutrients*, Nov 2019; 11(2711). doi:10.3390/nu11112711
13. Tannus S, Burke YZ, Kol S. Treatment strategies for the infertile polycystic ovary syndrome patient. *Womens Health: London*, Nov 2015; 11(6):901-912. doi:10.2217/whe.15.40
14. Avila MAP, Borges LP, Paes MS, Bruno RV, Nardi AE, Pessoa ACM et al. Acanthosis nigricante: inter-relações metabólicas inerentes à síndrome dos ovários policísticos. *Rev. Bras. Ginecol. Obstet. Rio de Janeiro*, Sep 2014; 36(9):410-415. doi:10.1590/SO100-720320140005078
15. Scott D, Harrison CL, Hutchison S, Courten B, Strepto NK. Exploring factors related to changes in body composition, insulin sensitivity and aerobic capacity in response to a 12-week exercise intervention in overweight and obese women with and without polycystic ovary syndrome. *Plos One*, Aug 2017; 12(8). doi:10.1371/journal.pone.0182412
16. Costello MF, Misso ML, Balen A, Boyle J, Devoto L, Garad RM et al. Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility. *Human reproduction open*, Jan 2019; 2019:1-24. Oxford University Press (OUP). doi:10.1093/hropen/hoy021
17. Iwata MC, Porquere L, Sorpreso ICE, Baracat EDD, Soares Junior JM. Association of oral contraceptive and metformin did not improve insulin resistance in women with polycystic ovary syndrome. *Rev. Assoc. Med. Bras. São Paulo*, Jun 2015; 61(3):215-219. doi:10.1590/1806-9282.61.03.215
18. Li J, Ng EHY, Stener-Victorin E, Hu Z, Shao X, Wang H et al. Acupuncture treatment for insulin sensitivity of women with polycystic ovary syndrome and insulin resistance: a study protocol for a randomized controlled trial. *Trials. China*, 2017; 18(115). doi:10.1186/s13063-017-1854-2
19. PCOS Society (India). Consensus Statement on the Use of Oral Contraceptive Pills in Polycystic Ovarian Syndrome Women in India. *Journal of human reproductive sciences*, Apr-Jun 2018; 11(2):96-118. doi:10.4103/jhrs.JHRS_72_18
20. Jiang J, Gao S, Zhang Y. Therapeutic effects of dimethyldiguanide combined with clomifene citrate in the treatment of polycystic ovary syndrome. *Rev. Assoc. Med. Bras. São Paulo*, Sep 2019; 65(9):1144-1150. doi:10.1590/1806-9282.65.9.1144
21. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. *Hum Reprod Update*. Nov 2016; 22(6):687-708. doi:10.1093/humupd/dmw025
22. Genazzani AD. Inositol as putative integrative treatment for PCOS. *Reprod Biomed Online*. Dec 2016; 33(6):770-780. Elsevier BV. doi:10.1016/j.rbmo.2016.08.024
23. Unfer V, Nestler JE, Kamenow ZA, Prapas N, Facchinetti F. Effects of Inositol(s) in Women with PCOS: a systematic review of randomized controlled trials. *International Journal Of Endocrinology*, 2016: 2016:1-12. Hindawi Limited. doi:10.1155/2016/1849162

24. Motta ELA, Domingues TS, Soares Junior JM. O uso de sensibilizadores de insulina no tratamento de infertilidade em pacientes com síndrome dos ovários policísticos (SOP). *Rev. Bras. Ginecol. Obstet.* Rio de Janeiro, Mar 2012; 34(3):99-101. doi:[10.1590/S0100-72032012000300001](https://doi.org/10.1590/S0100-72032012000300001)
25. Mascarenhas M, Balen AH. Treatment update for anovulation and subfertility in polycystic ovary syndrome. *Current Opinion In Endocrine And Metabolic Research.* Jun 2020; 12:53-58. Elsevier BV. doi:[10.1016/j.coemr.2020.03.003](https://doi.org/10.1016/j.coemr.2020.03.003)
26. Voulgaris N, Papanastasiou L, Piaditis G, Angelousi A, Kaltsas G, Mastorakos G et al. Vitamin D and aspects of female fertility. *Hormones.* Greece, 2017; 16(1):5-21. doi:[10.14310/horm.2002.1715](https://doi.org/10.14310/horm.2002.1715)
27. Krul-Poel YHM, Koenders PP, Steegers-Theunissen RP, Boekel E, Wee MM, Louwers Y et al. Vitamin D and metabolic disturbances in polycystic ovary syndrome (PCOS): A cross-sectional study. *PloS one.* Dec 2018; 13(12) e0204748. doi: [10.1371/journal.pone.0204748](https://doi.org/10.1371/journal.pone.0204748)
28. Davis EM, Peck JD, Hansen KR, Neas BR, Craig LB. Associations between vitamin D levels and polycystic ovary syndrome phenotypes. *Minerva endocrinológica.* Jun 2019; 44(2):176-184. doi:[10.23736/S0391-1977.18.02824-9](https://doi.org/10.23736/S0391-1977.18.02824-9)
29. Lumme J, Sebert S, Pesonen P, Piltonen T, Jarvelin MR, Herzig KH et al. Vitamin D Levels in Women with Polycystic Ovary Syndrome: A Population-Based Study. *Nutrients.* Nov 2019; 11(2831). doi:[10.3390/nu11112831](https://doi.org/10.3390/nu11112831)
30. Trummer C, Schwetz V, Kollmann M, Wolfler M, Munzker J, Pieber TR et al. Effects of vitamin D supplementation on metabolic and endocrine parameters in PCOS: a randomized-controlled trial. *European journal of nutrition,* 2019; 58(5):2019-2028. doi:[10.1007/s00394-018-1760-8](https://doi.org/10.1007/s00394-018-1760-8)
31. Moura HHG, Costa DLM, Bagatin E, Sodr e CT, Manela-Azulay M. S ndrome do ov rio polic stico: abordagem dermatol gica. *An. Bras. Dermatol.* Rio de Janeiro, Feb 2011; 86(1):111-119. doi:[10.1590/S0365-05962011000100015](https://doi.org/10.1590/S0365-05962011000100015)
32. Soares Junior JM, Baracat MCP, Maciel GAR, Baracat EC. Polycystic ovary syndrome: controversies and challenges. *Rev. Assoc. Med. Bras. S o Paulo,* Dec 2015; 61(6):485-487. doi:[10.1590/1806-9282.61.06.485](https://doi.org/10.1590/1806-9282.61.06.485)
33. Barthelme s EK, Naz RK. Polycystic ovary syndrome: current status and future perspective. *Frontiers in bioscience (Elite edition).* Morgantown(WV), Jan 2014; 6:104-19. doi:[10.2741/e695](https://doi.org/10.2741/e695)
34. Brasil. Minist rio da Sa de. Protocolo Cl nico e Diretrizes Terap uticas Portaria SAS/MS n  1.321, de 25 de novembro de 2013. S ndrome de ov rios polic sticos e hirsutismo/acne. Bras lia. 2013.