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IMPACTS OF HYPERANDROGENISM IN MENACMEN WITH POLYCYSTIC OVARY SYNDROME: A LITERATURE REVIEW

Isabela Rodrigues da Silva
Universidade do Oeste Paulista (UNOESTE)
Jaú - SP
https://orcid.org/0000-0003-0840-722X

Shi Juin Lam
Universidade Anhembi Morumbi (UAM)
Piracicaba - SP
https://orcid.org/0000-0003-3529-5489

Anna Vitória de Matos Carneiro
Medicina Faculdade de Tecnologia e ciência(UNIFTC)
Salvador - BA
https://orcid.org/0000-0002-3335-9613

Polyana Aparecida Bisinoto
Centro Universitário Maurício de Nassau de Cacoal (Uninassau Cacoal)
Cacoal - RO
https://orcid.org/0000-0002-8034-5804

Rubia de Souza Olivo
Universidade Cidade de São Paulo (UNICID)
São Paulo - SP
https://orcid.org/0000-0001-9928-8179

Adriely Portela Souza Lima
Universidade Nilton Lins (UNL)
Manaus - AM
https://orcid.org/0000-0002-0349-2827

Rafael Leituga de Carvalho Cavalcante
Universidade Estácio de Sá (UNESA)
Rio de Janeiro - RJ
https://orcid.org/0000-0001-6436-3968

Marina Farias Lira
Universidade Alto Vale do Rio do Peixe (UNIARP)
Caçador - SC
https://orcid.org/0000-0002-7034-4138

Júlia Rocha Morão
Faculdade de Medicina de Itajubá (FMIT)
Itajubá - MG
https://orcid.org/0000-0002-9210-7694

Yasmim de Paula Deitos
Centro Universitário Alfredo Nasser (UNIFAN)
Aparecida de Goiânia - GO
https://orcid.org/0000-0002-5086-7556

Livia Cararo Nogueira
Faculdade multivix Cachoeiro de Itapemirim (MULTIVIX)
Cachoeiro de Itapemirim - ES
https://orcid.org/0000-0003-0935-748X

Neidejany de Assunção do Sacramento
Universidad Nacional de Rosario (UNR)
Rosario - Argentina
https://orcid.org/0000-0001-7050-6697

Abstract: Goal: Discuss the impacts of the pathophysiological process of hyperandrogenism in menacme diagnosed with polycystic ovary syndrome (PCOS). Method: Narrative Bibliographic Review carried out in October and November 2022 in the Scielo and Pubmed databases. Of the 370 articles found, 11 studies were selected after applying the inclusion and exclusion criteria. Discussion: The clinical manifestations of PCOS such as ovulatory disorders, infertility, hirsutism, acne, and androgenic alopecia are configured as the pathophysiological impacts of androgenism. Hyperinsulinemia is a condition present in women diagnosed with PCOS and which contributes in different ways to androgen-dependent anovulation. It is believed that irregular menstrual cycles are indicative of anovulation, considered favorable for infertility associated with PCOS. Final Considerations: In view of the expressive influence of the patient's physical conditions, therapies aimed at changes in lifestyle constitute the first management of such a situation.

Keywords: Polycystic ovary syndrome; Hyperandrogenism; Infertility; insulin resistance.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine-metabolic disorder in women of childbearing age, affecting 5 to 20% of women in the reproductive period (AZZIZ R., 2018), with an average age of 25.9 years. years to onset of disease presentation. Observed in 60 to 80% of women with the syndrome, it is characterized by increased production of androgenic hormones by the ovaries and its most common clinical manifestation is hyperandrogenism (CHEN J. et al, 2021).

The etiology of PCOS is multifactorial and depends on the interaction between

predisposing genetics and lifestyle habits. Among its risk factors are family history of dyslipidemia, type 2 diabetes mellitus and obesity (TABARES RG et al., 2018). Adipose tissue is an important target of aromatization, increasing estrogen and androgen levels, which lead to inadequate secretion of gonadotropic hormones (TABARES R.G. et al., 2018). About 30 to 60% of women who have PCOS associated with obesity manifest hyperandrogenism (AZZIZ R., 2018).

Insulin resistance (IR) is closely linked to the etiological factors of PCOS, and is characterized by reduced glucose absorption due to a poor response from insulin receptors. Although there are other factors that contribute, such as genetic and epigenetic dysfunctions, its pathophysiology stems from an abnormality in the intracellular signaling of the insulin receptor and one of its main pathognomonic signs is acanthosis nigricans, observed on physical examination by the darkening in areas of skin flexion, mainly armpit and neck (CHEN J. et al., 2021).

Ovulation disorders due to increased androgens impair follicular development, leaving them immature, causing non-ovulation (ORTIZ-FLORES A. et al., 2019), and are the cause of infertility in about 25% of women. PCOS is the main cause of anovulatory infertility, with approximately 70% of all these cases (CUNHA A.; PÓVOA A.M., 2021).

According to the Rotterdam criteria, the diagnosis of PCOS depends on the presence of hyperandrogenism, ovulatory disorders and polycystic ovary morphology on imaging. However, some disease phenotypes do not present all the mentioned characteristics (ORTIZ-FLORES A. et al., 2019). The combinations of manifestations that include hyperandrogenism are generally related to the greater severity of reproductive and metabolic changes in affected patients (TABARES, RG et al., 2018). In this context, the objective of the present study is to discuss and elucidate the impacts of the pathophysiological process involving hyperandrogenism in menacme, diagnosed with PCOS.

METHODOLOGY

This study is a bibliographic review developed between October and November 2022. The PVO strategy was used, an acronym that represents population or research problem, variables and outcome, for the elaboration of the research through its guiding question "What are the impacts of pathophysiological processes involving hyperandrogenism in menacme, diagnosed with polycystic ovary syndrome?". In this sense, according to the parameters mentioned above, the population or problem of this research refers to female patients (population) of childbearing age (menacme), who have polycystic ovary syndrome correlated with hyperandrogenism (variables) for the discussion of the impacts Pathophysiological factors in women's health (outcome).

The searches were carried out through searches in the PubMed Central (PMC) and Scientific Electronic Library Online (SciELO) databases. The descriptors associated with the Boolean term "AND" were used: Polycystic Ovary Syndrome; Hyperandrogenism; Infertility; Insulin Resistance. Inclusion criteria were: in English, Portuguese and Spanish published in the period from 2018 to 2022 and that addressed the themes proposed for this research, studies of the type (bibliographic review, systematic review, cohort, original article, case report), made available in full. Exclusion criteria were: duplicate articles, available in summary form, which did not directly address the studied proposal and which did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 370 articles were found. Of which 367 belonged to the PubMed database and 3 articles to SciELO. After applying the inclusion and exclusion criteria, 9 articles were selected from the PubMed database and 2 articles from the SciELO database, using a total of 11 studies to compose the collection.

DISCUSSION

Hyperandrogenism is the main alteration found in PCOS, affecting around 80% of women diagnosed with the syndrome. This condition is characterized by peripheral or systemic accumulation of androgen (CHEN J. et al, 2021). Androgens are produced in the ovaries from cholesterol, converted into androstenedione, the main precursor of testosterone and estrogen. In the ovaries, but specifically in the theca cells, this androstenedione is converted, by stimulation of luteinizing hormone (LH), to testosterone, which in turn, in granulosa cells is converted into estrogen, by stimulation of follicle-stimulating hormone (FSH). (SANCHEZ-GARRIDO M.A. and TENA-SEMPREM., 2020).

After an increase in androgenic hormones, there is an increase in the frequency of pulses of the gonadotropin-releasing hormone (GnRH) in the hypothalamus, thus increasing the release of (LH) and decreasing that of (FSH), so that the levels of androgens produced increase, however, these are not converted into estrogens as described above. As a result, antral follicles are recruited, but they do not mature properly, accumulating in the ovaries and leading to the formation of immature follicles (SANCHEZ-GARRIDO M.A. and TENA-SEMPERE M., 2020).

The organism in hyperandrogenism presents with several clinical manifestations reflex of virilization, thus causing hirsutism, acne, seborrhea and androgenetic alopecia. All these changes have a great psychological impact on patients, where depression is one of the most common mood disorders in women with PCOS, in addition to a significant reduction in self-esteem (ETHIRAJULU A. et al., 2021).

It is known that exposure to androgens during intrauterine life can permanently alter the pattern of GnRH release in girls, increasing the production of LH and consequently of androgens. In view of this, children born to women with PCOS have an increased risk of developing the pathology throughout their lives (SANCHEZ-GARRIDO M.A., TENA-SEMPERE M., 2020). Furthermore, 40% of women with PCOS also have gestational diabetes, with fetal hyperinsulinemia and subsequent metabolic dysfunction. Exposure to androgens during pregnancy can be identified right at birth, as newborns (NB) affected by this condition have a transient increase in facial sebum, a sensitive marker of exposure to intrauterine testosterone, and an increased anogenital distance, in a ratio of 2:4 (ABBOTT D.H. et al., 2019).

It is known that 65-70% of women, regardless of body mass index (BMI), who have PCOS have IR (SANCHEZ-GARRIDO M.A. and TENA-SEMPERE M., 2020; BELLVER J. et al., 2018). For Sanchez Garrido M A. and Tena-Sempere M. (2020), IR with hyperinsulinemia is a key factor in the pathophysiology of PCOS generation. In most cases, this condition has high-grade obesity (II and III) as its etiology. Thus, obese women are more prone not only to the development of IR with hyperinsulinemia, but also to PCOS and, in the long term, diabetes mellitus 2 (DM2).

Studies suggest that androgen accumulation also affects leptin's ability to stimulate energy expenditure, which promotes the accumulation of visceral fat and consequently significantly increases the risk

of developing metabolic syndromes (MS). Furthermore, non-alcoholic hepatic steatosis is also related to the metabolic characteristics found in PCOS, such as obesity, dyslipidemia and IR. Accordingly, recent studies have described hyperandrogenism as a hepatic inflammatory factor, also showing a significant increase in circulating levels of alanine aminotransferase (ALT).

According to Ding H. et al. (2021) women with PCOS and IR may have etiological genetic factors, especially those related to specific receptors that may contribute to hyperinsulinemia. Research demonstrates a reduction, in women with PCOS, of the inhibitory phosphorylation receptor substrate insulin-172-1. In addition, the existence of a mutation in the melatonin receptor 1 gene (MTNR1B) is capable of delaying insulin production and leading to hyperglycemia.

Even in IR conditions, pancreatic cells in a compensatory attempt increase insulin release, in a way that ends up contributing to hyperinsulinemia. Such compensatory hyperinsulinemia contributes in several ways to androgen-dependent anovulation, as insulin potentiates the stimulating function of the hormone LH. This hormone acts on ovarian theca cells by increasing androgen production, in addition to inhibiting the release of sex hormone-binding globulin (SHBG) from the liver, a protein responsible for testosterone transport. Such potentiation results in an increased bioavailability of free testosterone. Added to this, extra-ovarian factors, such as IR, hyperinsulinemia, metabolic syndromes; together with the mentioned intra-ovarian factors, they promote a chronic pro-inflammatory state and hypersecretion of androgens that potentiate the clinical picture of the patient (BELLVER J. et al., 2018).

According to Velaz L. M et al. (2021), the association of high levels of insulin and androgens may affect follicular maturation. As a consequence, the triggering of menstrual irregularity, anovulatory subfertility and accumulation of immature follicles and subsequent ovarian polycystosis. Irregular menstrual cycles are indicative of anovulation, which is a determining factor for PCOS-associated infertility. The literature also points out that eumenorrheic women with polycystic ovary morphology may have higher androgen levels than eumenorrheic women without the polycystic characteristic, which suggests that the first group may have a higher risk of anovulatory cycles at some point in life (LOUWERS, Y LAVEN J.S.E., 2020).

Faced with the conditions of metabolic dysregulation associated with the pathogenesis of PCOS, lifestyle changes strategies are presented as the main therapeutic measure (SANCHEZ-GARRIDO M.A. and TENA-SEMPERE M., 2020). One must firstly focus on changes in diet and practice of physical exercises, since the reduction of 5 to 10% of weight can considerably reduce the amount of circulating androgen hormones. And evidence suggests that such interventions are more effective than possible drug treatments (BELLVER J. et al., 2018).

FINAL CONSIDERATIONS

The impacts of the pathophysiological process of hyperandrogenism in menacme associated with PCOS result from the metabolic dysfunction generated by this condition, mainly involving the mechanisms of insulin resistance, hyperinsulinemia and ovulatory disorders that lead to anovulatory infertility, hirsutism, acne and psychological imbalance. In view of the expressive influence of the patient's physical conditions, therapies aimed at changes in lifestyle constitute the first management of such a condition. However, it is still necessary to deepen the knowledge about the various pathophysiological aspects and alterations generated by the

hyperandrogenism associated with PCOS, in order to mitigate or prevent the worsening of the clinical manifestations generated in the affected patients, since such manifestations can lead to the emergence of psychic illnesses and severe metabolic disorders when not controlled.

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