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Insulin resistance, a metabolic disorder in women with polycystic ovary syndrome and its implications for clinical management

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ABSTRACT
Polycystic ovary syndrome (PCOS) is a multifactorial endocrine-metabolic disorder that contains several theories about its etiology, including insulin resistance (IR) as a possible triggering factor for PCOS. Given this thesis, the implication of insulin resistance in the clinical management of PCOS is questioned. This research aimed to review the characteristics and pathophysiology of polycystic ovary syndrome, having as main focus women with PCOS who have insulin resistance and what this would imply in the etiology and its clinical management. An integrative bibliographic review of scientific studies, published between 2012-2022, was carried out on the relationship between PCOS and metabolic disorders linked to IR that interferes with clinical management. The analysis of the articles revealed that IR interferes with the pathophysiology of PCOS and may be related to its origin. It was also found that the use of oral contraceptives can affect the IR in individuals with PCOS and that the first choice in clinical management is to change the lifestyle of this population. It is concluded that the first-line treatment in this population is a lifestyle change, however, studies on the correlation of PCOS and IR regarding its etiology and the use of oral contraceptives in patients with PCOS associated with IR are still lacking.

Keywords: Diet, Etiology, Insulin resistance, Oral contraceptives, Polycystic ovary syndrome, Treatment.

1 INTRODUCTION

For a long time, polycystic ovary syndrome (PCOS) was neglected, possibly because it presents an etiology, still unknown, having several theories around its genesis. However, it is currently known that PCOS is a very common endocrine-metabolic disorder in women of reproductive age and has several factors involving genetic components, related to pre-and postnatal metabolic processes, hereditary endocrine disorders, and environmental factors such as diet and physical activity (ROSA-E-SILVA, 2019).

"Its prevalence ranges from 6% to 10% in women in menacme" (ROSA-E-SILVA, 2019, p. 518), and "its relationship with the deviations of lipid and glycide metabolism has been the target of many studies, because today PCOS is seen as a metabolic disease, with all its implications" (ROSA-E-SILVA, 2019, p. 518). Concerning these aspects presents a higher risk of developing infertility, hyperandrogenic characteristics such as hirsutism and acne in addition to obesity, and along with it comes accompanied by an exponential increase in developing metabolic syndrome, insulin resistance, type 2 diabetes mellitus, and cardiovascular diseases (SILVA, et. al. 2021).

It is estimated that 75% of women of reproductive age who have such a syndrome have impaired insulin action; although its relationship with PCOS is consistently shown in several studies, the mechanisms underlying its primary origin remain unclear (MOGHETTI; TOSI, 2020).

It is known that insulin resistance and its association with hyperinsulinemia can induce both endocrine and reproductive characteristics of the syndrome, however, hyperandrogenemia, in turn, impairs the action of insulin, directly and/or through several changes that occur in different tissues, especially in muscle and adipose tissue, developing a series of reactions (MOGHETTI; TOSI, 2020).

His diagnosis, according to Febrasgo's Femina magazine, published in 2019, is made through:

> A consensus proposed by Teede et al., published in August 2018, in which the presence of at least two of the three diagnostic criteria – oligomenorrhoea, clinical and/or laboratory hyperandrogenism, and ultrasound morphology of ovarian polycystic – determines the diagnosis, provided that other diseases that also course with hyperandrogenism are excluded (ROSA-E-SILVA, 2019, p. 519).

From these criteria, it is possible to observe that typically PCOS is characterized by increased androgens and evidence of ovarian dysfunction, however, it is left to be desired when they exclude other abnormalities that are often seen in women with polycystic ovary syndrome (MOGHETTI; TOSI, 2020).

This whole process evidences a vicious cycle, in which there are relationships between androgen excess and insulin resistance, associated with the contribution of several other factors, making it extremely difficult to understand where everything originates from (MOGHETTI; TOSI, 2020).

Faced with this problem, the analysis of the implication of insulin resistance in the clinical management of polycystic ovary syndrome is questioned, establishing doubts about the clinical management of PCOS considering that the first-line treatment is oral contraceptives (OCTs), which focus on the concomitant control of menstrual irregularity, acne, and hirsutism, bringing to light the debate on risks versus benefits of the use of such drugs in this population. (DOKRAS, 2016)

This debate has been based on some studies that focused on the cardiovascular and metabolic adverse effects that COs caused in women with PCOS, which suggests a worsening of insulin resistance and glucose tolerance, as well as potential adverse effects on lipid patterns, raising concerns about such treatment (AMIRI; et. al., 2017, p. 3).

Thus, the current clinical management in patients with PCOS, who have associated IR, is focused on physical exercise and dietary adjustments, as an improvement in the metabolic, hormonal, and reproductive indices of women with PCOS was observed, resulting in weight reduction and recovery of the clinical characteristics of the syndrome in a significant proportion of affected women; this management is done together with insulin-sensitive drugs, such as metformin, pioglitazone, and Inositol isoforms; that target metabolic and reproductive abnormalities of those with polycystic ovary syndrome (MACUT, et. al. 2017).

The study in question aimed to review the characteristics and pathophysiology of this syndrome, focusing mainly on women with PCOS who have insulin resistance and what this would imply in the etiology and its clinical management.

2 MATERIAL AND METHODS

An integrative literature review was performed based on studies on the relationship of polycystic ovary syndrome and metabolic disorders linked to insulin resistance, which implies the clinical management of the syndrome, where the articles were searched and obtained from the databases Pubmed, SciELO, Diabetes Research and Clinical Practice, Febrasgo, Journal of Clinical Endocrinology and Metabolism, Santa Catarina Archives of Medicine and Elsevier.

Restrictions were applied from the date of publication, from 2012 to 2022, and thirty-two scientific papers were selected, and one article was published in 1991 and used as a historical citation in this review. These were selected by independent evaluations, following the topics covered, which are: insulin resistance in polycystic ovary syndrome, metabolic disorders in polycystic ovary syndrome, contraceptive use and its relationship with insulin resistance, polycystic ovary syndrome, and physiology of polycystic ovary syndrome.

Studies that did not correspond to the chosen metabolic disorder, that had information outside the proposed, and that did not have an objective conclusion about the relationship between polycystic ovary syndrome and insulin resistance were excluded. The survey was closed on June 30, 2022, in the municipality of Mafra.

3 RESULTS AND DISCUSSIONS

Polycystic ovary syndrome is a multifactorial disorder that contains several theories about its etiology and presents as clinical characteristics of anovulation and hyperandrogenic aspects having as main aspects hirsutism and acne, in addition, it has a combination of biochemical factors such as excess

androgenic, as already mentioned, and high concentrations of luteinizing hormone (LH), in addition to ovarian morphological characteristics (CALCATERRA; et. al., 2021). Along with such particularities, polycystic ovary syndrome presents an increased risk of developing metabolic syndrome, insulin resistance, type 2 diabetes mellitus, and cardiovascular diseases (SILVA, et. al. 2021).

As stated earlier, this multigenic disorder is complex in terms of etiology, where many doubts remain and there may be contributions of predisposing and protective genetic variants that interact with environmental factors resulting in different phenotypes of polycystic ovary syndrome (ESCOBAR-MORREALE, 2018).

Such phenotypes are obtained based on the Rotterdam diagnostic criteria, and four types are identified: type A: hyperandrogenism (AH), ovulatory dysfunction and polycystic ovaries present in ultrasound; type B: hyperandrogenism and ovulatory dysfunction; type C: hyperandrogenism and presence of polycystic ovaries on ultrasound and finally type D: ovulatory dysfunction and presence of polycystic ovaries on ultrasound (MACUT; et. al., 2017).

This syndrome is a common endocrine-metabolic disorder, which affects 12-18% of women (JEANES; REEVES, 2017) and its incidence is believed to be increasing as a result of lifestyle-related changes, where an unbalanced diet, reduced physical activity, increased contact with endocrine disruptors, increased radiation exposure, sleep disturbances, elevated stress levels, and other environmental factors fit in (PARKER; et. al., 2022).

Currently, it is questioned whether the central etiology and the primary endocrine characteristics of PCOS are hyperandrogenemia (AH) and insulin resistance (IR), which can interact with each other in the occurrence and development of PCOS, because their relationships, between androgen excess and insulin resistance, associated with the contribution of several other factors brings to light the debate about the vicious cycle that polycystic ovary syndrome has before its origin, for little is known about who comes first, the syndrome or insulin resistance (WANG, et. al. 2019).

Insulin is synthesized and secreted by pancreatic beta cells in response to increased blood glucose, which then stimulates cellular glucose uptake (SITRUK-WARE; NATH, 2013). This uptake occurs by insulin-responsive target tissues (adipocytes, skeletal and cardiac muscles), as well as by suppressing hepatic glucose production. It also suppresses lipolysis, leading to a decrease in the levels of circulating free fatty acids, in addition, insulin also has other metabolic functions such as mitogenic and reproductive actions (DIAMANTI-KANDARAKIS; DUNAIF, 2012).

When the body enters a state of inability to perform glucose uptake through a certain amount of this hormone, it is defined as insulin resistance, that is, it is when the peripheral tissues have a lower sensitivity to the action of insulin, requiring a higher concentration of this hormone resulting in a state of compensatory hyperinsulinemia (CALCATERRA; et. al., 2021).

This increase in insulin, caused by IR, is linked to hyperandrogenemia in several ways, firstly, it is necessary to remember that insulin receptors are distributed in ovarian and stromal cells and that the

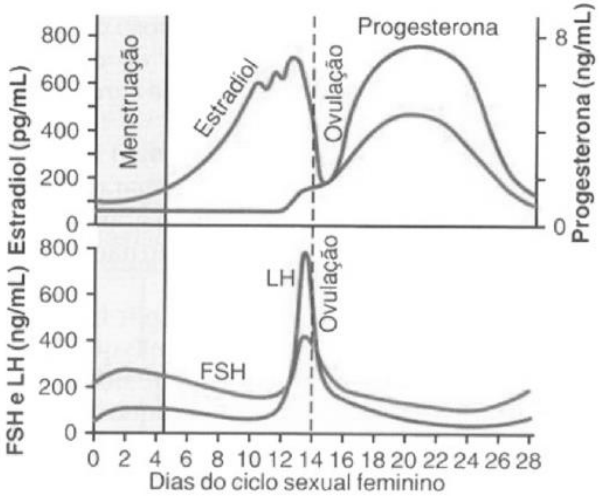
production of androgens is carried out, predominantly, in teak cells. However, it seems that in women with PCOS, these cells become hyper-responsive to insulin stimuli, increasing the response of theca cells to circulating LH and promoting the increase of androgens (CALCATERRA; et. al., 2021).

In addition, insulin is also involved in reducing the production of sex hormone-binding globulin (SHBG) by the liver; these two effects added together increase the concentration of free testosterone, that is, the active fraction of the hormone, responsible for the clinical signs of hirsutism, acne, and alopecia, all this together with insulin-like growth factor type 1 (IGF-1) (ROSA-E-SILVA, 2019).

To understand more about polycystic ovary syndrome it is important to understand a little about the physiology of the female sexual cycle. This cycle is characterized by monthly rhythmic changes in hormone secretion and has an average duration of 28 days, and may vary according to each woman. The cycle is divided into phases called the follicular phase, ovulation, luteal phase, and menstrual cycle which vary according to the female hormonal system.

This sexual cycle consists of three hormonal hierarchies: the hypothalamic-releasing hormone called gonadotropin-releasing hormone (GnRH), the anterior pituitary sex hormones corresponding to follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and finally, the group of ovarian hormones, estrogen, and progesterone (GUYTON *et. al.*, 2017). Such hormones are released according to the phase of the corresponding female sexual cycle being demonstrated in the figure below:

Figure 1- Variations in hormone concentrations during the female sexual cycle.



Source: Guyton *et. al.* (2017)

Ovarian changes during the female cycle depend entirely on GnRH, FSH, and LH. The gonadotropin-releasing hormone (GnRH) is released by the hypothalamus through short pulses, it acts on the anterior pituitary gland stimulating the release of FSH and LH, these hormones, in turn, induce their target cells to bind, to the specific FSH and LH receptors, present in the membrane of the ovarian target cells. This process results in the activation of protein synthesis kinases and multiple phosphorylations of enzymes that induce the synthesis of sex hormones (GUYTON *et. al.*, 2017).

During hormone synthesis, the production of progesterone and androgens, all based on blood-derived cholesterol, occurs first in the teak cells. Only in the follicular phase will almost the entire amount of androgen and much of the progesterone be converted into estrogen by aromatase in the granulosa cells. Once this is done, both estrogen and progesterone are transported by the blood through their weak binding with plasma albumin and sex hormone-binding globulins (SHGB) (GUYTON *et. al.*, 2017).

Table 1 – Function of hormones of the female sexual cycle.

HORMONE	FUNCTION
Gonadotropin-releasing hormone (GnRH)	Stimulates the anterior pituitary gland to release FSH and LH
Follicle-stimulating hormone (FSH)	It acts in the follicular phase of the cycle, and induces the accelerated growth of 6-12 primary follicles, through the rapid proliferation of granulosa cells. In addition to stimulating aromatase in the synthesis of estrogen.
Luteinizing hormone (LH)	It acts in the luteal phase and performs the transformation of granulosa and internal thecal cells into luteal cells. In addition to secreting estrogen and high amounts of progesterone.
Estrogen	It promotes the proliferation and growth of the cells of the body responsible for the development of secondary female sexual characteristics.
Progesterone	It prepares the uterus for pregnancy by enlarging the endometrium, and the breasts for lactation.

Source: Research data (2022)

Given such information, it is possible to understand the feedback system that controls the rhythm of the female sexual cycle, which begins with the corpus luteum, formed in the luteal phase by the increase in LH, which is responsible for secreting large amounts of progesterone and estrogen, as well as inhibin, in the period between ovulation and the beginning of the menstrual cycle. This hormonal release is responsible for the negative feedback under the anterior pituitary and hypothalamus, which causes suppression of FSH and LH secretion, 3 to 4 days before the onset of menstruation (GUYTON *et. al.*, 2017).

In this period the follicular growth phase begins with the remission of the corpus luteum, so at the time menstruation begins the pituitary secretion of FSH begins to increase again, and after several days of menstruation increases the level of LH. These hormones stimulate the growth of new ovarian follicles and the increase in estrogen and progesterone levels, such a process results in the effect of negative feedback on FSH and LH pausing their release (GUYTON *et. al.*, 2017).

After the decline of FSH and LH begins the preovulatory peak, whose sudden increase in LH and, to a lesser extent of FSH, is produced by the positive feedback of the estrogen peak in the anterior pituitary. The large excess of LH induces ovulation and the development of the corpus luteum initiating a new cycle (GUYTON *et. al.*, 2017).

However, in women with polycystic ovary syndrome, this physiological process is altered, with the blocking of several phases of the cycle. During the early stages of folliculogenesis, there is an increase in

anti-Müllerian hormones, which are released by the granulosa and produce a considerable inhibitory effect on FSH levels, impairing the onset of primordial follicles (DING; et. al., 2021).

It also participates in the dysregulation of the hypothalamic-pituitary-ovarian (HHO) axis with increased stimulation and release of GnRH and luteinizing hormone (LH) which leads to increased androgen synthesis in the ovarian teak cell. This hyperandrogenemia results in decreased sensitivity to estradiol and progesterone, reinforcing the hypersecretion of GnRH and LH making it a cycle (DING; et. al., 2021).

Women with IR associated with polycystic ovary syndrome have one more aggravating factor in the hypersecretion of GnRH and LH, insulin. As seen, this hormone increases circulating androgen levels, which in turn produce negative progesterone feedback under GnRH, however, insulin also sends stimuli to the central nervous system (CNS) interfering with GnRH signaling by increasing its pulse concomitantly with the increase in LH. This imbalance between gonadotrophins at the hypothalamic and pituitary levels leads to ovarian dysfunction (CALCATERRA; et. al., 2021).

In summary, serum LH concentrations are elevated in women with PCOS, while FSH levels are normal or slightly suppressed, which leads them to not reach the threshold levels needed to stimulate follicular maturation during the menstrual cycle (DIAMANTI-KANDARAKIS; DUNAIF, 2012).

Based on this situation, we enter into the problem of clinical management of patients with PCOS linked to insulin resistance, which is the therapy of first choice, hormonal contraceptives, focusing on the concomitant treatment of menstrual irregularity, acne, and hirsutism, bringing to light the debate about risks versus benefits of hormonal contraceptives in this population. (DOKRAS, 2016)

In clinical matters the oral contraceptive (OC) brings benefits through androgenic decrease, however, there are disadvantages to its use, because as previously stated, carriers of this syndrome have an increased risk of developing various metabolic disorders, such as insulin resistance, hyperglycemia, type 2 diabetes mellitus (DMII) and decreased glucose tolerance (IGT), in addition to increased LDL and decreased rates of HDL cholesterol, increased risk of developing problems cardiovascular diseases that are associated with the use of COs (NAZ, 2014). However, what is more, emphasized is the relationship between the use of oral contraceptives in women with polycystic ovary syndrome diagnosed with insulin resistance.

This clash is not of now, there are studies since 1991 that sought to demonstrate the effects that oral contraceptives bring to users with insulin resistance. The article published in the Journal of Clinical Endocrinology and Metabolism, Godsland (1991) advocated that insulin resistance is intertwined with metabolic changes such as changes in glucose, insulin, lipids, and lipoproteins, as well as increased blood pressure and disorders of the hemostatic system; which indicates a link with oral contraceptives as these can cause such disorders including glucose tolerance and hyperinsulinemia. These latter changes suggest that oral contraceptives cause insulin resistance, and have been proven by oral glucose tolerance tests.

It is currently known that there are oral contraceptives that cause greater changes under glycemic homeostasis being estrogens, progestins, or the molar concentration ratio of the estrogen-progesterone compound. This occurs because there is a reaction between sex steroids and insulin which interact in the target tissues for the hormones already mentioned. In short, high concentrations of sex steroids in women appear to contribute to the development of insulin resistance, in the same way, that low plasma levels of such steroids or hyperandrogenism seem to increase the risk of developing type 2 diabetes (CORTÉS; ALFARO, 2014).

With this, it is concluded that the estrogenic component of contraceptives plays a relevant role in changing insulin sensitivity because, in the presence of glucose, estradiol increases insulin secretion. After all, this hormone ends up decreasing the sensitivity of peripheral tissues to insulin. While progestins alter the dynamics of insulin, prolonging its half-life and increasing the insulin response to glucose when associated with ethinylestradiol (EE) (PILTONEN; et. al., 2012).

In this line, the second (GONZÁLEZ et al.) cited by (CORTÉS; ALFARO, 2014) where investigated the influence of estradiol on the insulin receptor of rats treated with different hormonal doses. Research has shown that high doses of estradiol cause changes in the carbohydrate mechanism that decrease insulin sensitivity, evidencing the relevance of estrogen dose and concentration to the glycosidic metabolism of women using oral or hormone replacement hormonal contraceptives.

Another study done with healthy women on treatment with oral contraceptives, showed as a result of greater responsiveness of growth hormone to hypoglycemia, as well as hyperglycemic conditions and, higher serum concentrations of growth hormone than women without oral contraceptives (FRIEDRICH; et. al., 2012).

Among the various contraceptives, it has been shown that combined contraceptives (CCs) have greater adverse effects when it comes to glucose metabolism, as their use can lead to chronic inflammation, regardless of their route of administration. However, the long-term consequences of these metabolic changes remain unclear and should be investigated in long-term follow-up studies, especially in women at increased risk of developing T2DM or cardiovascular disease (CVD) (PILTONEN; et. al., 2012).

Given this, the importance of monitoring glucose metabolism during the use of contraceptives especially combined contraceptives, and the possibility of considering alternative contraceptive methods in women with known risk factors (PILTONEN; et. al., 2012) is highlighted.

However, among the articles studied, many still defend the use of oral contraceptives as the main choice for treatment in patients with the syndrome (ESCOBAR-MORREALE, 2018; OGUZ; YILDIZ, 2021; DING; Et. al., 2021; YELA, 2019; ROSE-AND-SMITH, 2019). to regulate menstruation and improve hyperandrogenic characteristics (OGUZ; YILDIZ, 2021).

Another form of treatment, which is based on the assumption that hyperinsulinemia is a pathogenic factor for the development of hyperandrogenism and polycystic ovary syndrome, presented in the literature was the role of intervention with insulin-sensitizing drugs, such as metformin or thiazolidinediones (TZDs),

which reduce insulin levels and circulating androgens, increase levels of SHGB and improve ovarian function in women with the syndrome (SANCHEZ-GARRIDO; TENA-SEMPERE, 2020).

Some studies indicate the use associated, or not, of oral contraceptives with metformin (YELA, 2019; ESCOBAR-MORREALE, 2018) however it was seen that this association does not improve insulin resistance as occurs in the use of metformin alone (IWATA; et. al., 2015).

Metformin is a biguanide, that is, an insulin-sensitizing agent, being widely used and associated with a significant benefit when it comes to glucose metabolism and metabolic syndrome. It acts on the liver by reducing liver glucose synthesis, going against the action of glucagon and activating protein kinase (AMPK) which also increases insulin sensitivity by modulating lipid metabolism (ABDALLA; et.al., 2021).

In addition, it is related, in a significant percentage, satiety is often associated with weight loss (DING; et. al., 2021). It also helped regulate hyperinsulinemia, reduce androgen levels, and control the menstrual cycle in women with PCOS (NAZ, 2014).

There is also another line of treatment that produces an effect similar to insulin and is even considered a new sensitizing agent of this hormone in women with PCOS, inositol. Recently it has been realized that the use of myoinositol, alone or in association with D-chiro-inositol, produces restorative effects under ovulation and improves fertility (MACUT; et. al., 2017).

Despite several possibilities of pharmacological interventions, it is known that the first line of clinical management of PCOS includes lifestyle changes, dietary interventions, and weight loss associated with high-intensity physical exercise over a short period, known as HIIT (CALCATERRA; et. al., 2021). This is because physical exercise and dietary adjustments can improve the metabolic, hormonal, and reproductive rates of women with PCOS, as they result in weight reduction and recovery of the clinical characteristics of the syndrome in a significant proportion of affected women (MACUT, et. al. 2017).

Given the prevalence of overweight, obesity, and insulin resistance in women with PCOS, a low-energy diet, that is, rich in complex carbohydrates, especially unrefined foods and fiber, are being associated with higher insulin sensitivity, being seen as a 5-15% reduction in the weight of such individuals (CALCATERRA; et. al., 2021).

The time-restricted diet during meals is a form of intermittent fasting, which is beneficial for weight loss and cardiometabolic health. It may also be beneficial for anovulatory PCOS aimed at weight loss primarily in reducing body fat. It also shows an improvement in the menstrual cycle, hyperandrogenemia, insulin resistance, and chronic inflammation, and can be introduced in women with the syndrome who have hyperinsulinemia (LI; et.al., 2021).

Finally, a study showed that diet was significantly related to improvements in IR and body composition, with calorie-restricted diets being the ideal choice in the PCOS population. In addition, the effects were associated with the course of treatment, that is, the longer the duration, the greater the improvement (SHANG; et.al., 2020).

In addition to diet, many studies have investigated the relationship between gut microbiota changes and PCOS, suggesting that the microbiota is intrinsically linked to the development of insulin resistance and menstrual disorders in individuals with PCOS. It was also seen that the use of probiotics and symbiotics in this population improved the rates of FSH and SHGB (CALCATERRA; et. al., 2021). Another recent study exposed that the gut microbiota and its metabolites regulate PCOS-related ovarian dysfunction and insulin resistance (HE; LI, 2020).

Lifestyle change involving exercise is the first step in

treatment of PCOS. In addition to these aspects, dietary changes can rapidly alter the relative abundance of species of intestinal flora. A low-carb diet will help increase the production of short-chain fatty acids that reduces the incidence of chronic inflammation (HE; LI, 2020).

A little-remembered factor in the clinical management of polycystic ovary syndrome is the role of micronutrients, their inadequate intake, especially of zinc magnesium, and selenium is involved in decreasing the secretion and activity of insulin in the body of individuals with PCOS. Both selenium and zinc regulate the enzymes linked to the production and neutralization of reactive oxygen species (ROS), that is, they act as antioxidants decreasing the oxidative stress involved in the syndrome. Another important micronutrient is chromium(III), its supplementation has been shown to effectively improve glucose tolerance by increasing the sensitivity of peripheral tissues to insulin (CALCATERRA; et. al., 2021).

Other supplementations can be made as needed by the patient, such as D-vitamin, which when at good levels improves pancreatic beta cell function and increases insulin sensitivity. B vitamins, especially B12, and folate, decrease the amount of homocysteine that is often seen in women with PCOS. Berberine is an isoquinoline alkaloid, it acts by reducing serum glucose and regulates lipids among other functions in the cardiovascular system. Curcumin has been identified in animal studies that it acts as an insulin sensitizer being effective in metabolic syndrome (CALCATERRA; et. al., 2021).

Given the various options for the clinical management of polycystic ovary syndrome in patients with insulin resistance, it should be remembered that there is no universal treatment for this syndrome, it is always individualized and adapted to the real needs of the patient. Emphasizing that the clinical management of PCOS is long-term, dynamic, and moldable to the circumstances of each individual (ESCOBAR-MORREALE, 2018).

4 CONCLUSION

Polycystic ovary syndrome is a metabolic disorder with multigenic factors, which is associated with several clinical features mainly related to hyperandrogenism. Its association with insulin resistance is well documented, but there are still uncertainties about its etiology and who came first: the syndrome or hyperinsulinemia. Several studies have demonstrated its link, but none have been able to consolidate its origin.

Although the etiology of PCOS is not known for sure, it is known that when associated with insulin resistance, its clinical management becomes a little more complex because many articles have associated the use of oral contraceptives with the clinical worsening of the syndrome, while others support its use by instituting it as first-line. Although there is more of this clash within the research of this syndrome it is known that the first choice of PCOS treatment includes lifestyle changes, dietary interventions, and weight loss associated with physical exercise.

Such changes are focused on a calorie-restricted diet and high-intensity exercise at short intervals of time, in addition to being associated with vitamin and micronutrient supplements, the use of probiotics and symbiotics, and insulin sensitizers such as metformin.

Faced with so many conflicts, more studies are still needed on the etiology of insulin resistance and the use or not of oral contraceptives and their implications when individuals with PCOS have insulin resistance.

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