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Polycystic ovary syndrome

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Abstract

Polycystic Ovary Syndrome (PCOS) is a heterogeneous disorder and a frequent cause of consultation in adolescents. The etiology is multifactorial, involving genetic and environmental factors (intrauterine and extrauterine).[1] The clinical manifestations are hirsutism, menstrual irregularities, and acne. In addition, metabolic alterations such as hyperinsulinemia, insulin resistance, dyslipidemia and obesity are also associated.[2] The objectives of the treatment are to achieve ovulation, normalize menstrual cycles, reduce and if possible, eliminate hirsutism and acne, obtain an acceptable weight loss, and treat dyslipidemia and hyperglycemia to reduce the risk of cardiovascular disease.[3]

Keywords: Hirsutism; Hyperandrogenism; Anovulation; Polycystic Ovary; Insulin Resistance

1. Introduction

Polycystic Ovary Syndrome (PCOS) is highly prevalent and the most common endocrine metabolic disorder in women of reproductive age.2 It is the most common cause of hyperandrogenism with an incidence of 3% in both adolescent and adult women. It is estimated that it is present in 75% of hirsute women and in premenopausal women from 18 to 45 years old it is from 4% to 8%, and from 35% to 40% in infertile women, constituting one of the most important and common endocrinological abnormalities in women.4 In recent years, it has been established that this disorder is not only limited to the reproductive woman but can manifest itself from the prepubertal period and perhaps even earlier. Currently, four PCOS phenotypes are recognized: 1) hyperandrogenism + oligo-ovulation + polycystic ovarian morphology; 2) hyperandrogenism + oligo-ovulation; 3) hyperandrogenism + polycystic ovarian morphology; and 4) oligo-ovulation + polycystic ovarian morphology; each one with different metabolic and long-term health implications. Physicians should clearly indicate the patient's phenotype when making the PCOS diagnosis. Polycystic Ovary Syndrome is a complex, multifactorial, polygenic, highly heritable disorder. In PCOS, among other symptoms, pathophysiological anomalies in the secretion or action of gonadotropins, ovarian folliculogenesis, steroidogenesis, secretion or action of insulin and adipose tissue function have been described.2

2. Etiopathogenesis

The etiology is multifactorial and genetic and environmental factors[1] both intrauterine (fetal development programming) and extrauterine (diet, obesity, sedentary lifestyle, toxins, and certain drugs) are implicated. Currently, there is a multiple genetic base, families of women with PCOS have an increased risk of presenting the picture than the rest of the population. Genetic studies have focused on those genes that intervene in the metabolic pathways involved in the pathogenesis of PCOS. Genetic alterations affecting the pancreatic β cell and the insulin receptor have been described. Many other genes have been studied with conflicting results. This is the case of the adiponectin gene, where most authors have not been able to find an association between the alteration of the adiponectin gene and PCOS. Variations in the polymorphism (CAG) of exon 1 of the androgen receptor gene produce alterations in the transcription of the gene and consequently clinical variations of the activity of the androgens. Clinical observational studies suggest

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that PCOS may originate in very early stages of development, possibly in intrauterine life. The excess of glucocorticoids [result of fetal hypoxia and intrauterine growth retardation (IUGR)] or the elevation of maternal androgens during pregnancy can promote changes in gene expression that are related to an increased risk of PCOS.[3]

Children with small age gestational age have a reduced number of adipocytes at birth, and if they make a rapid recovery growth, they are not able to accommodate fats, producing hypertrophy of the few available adipocytes, and there is not a correct reservoir for fat. When caloric intakes exceed the storage capacity, there is a risk of developing insulin resistance and subsequently a compensatory response with hyperinsulinemia and central obesity that can alter body fat distribution, and accelerate the onset of adrenarquia and puberty, with early menarche, final height below target height, dyslipidemia, alteration of adipokine profile and subclinical HA in the first postmenarche months, which evolve to clinical PCOS in a significant percentage of cases in 2-3 years. In childhood, the most common form of functional hyperandrogenism is premature pubarche, which can be self-limited or progress to PCOS (15-20%).

HA is associated with excess weight during puberty. Obesity together with hyperinsulinemia, decreased SHBG (steroid sex transporter protein) and increased free testosterone levels, will produce an increase in the production of androgens in the abdominal adipose tissue, which will favor HA. Also, it can alter the regulation of LH pulses during the maturation of the hypothalamic-pituitary-gonadal axis, conditioning a persistent HA.3

Risk factors for the development of PCOS include:

- Early onset obesity associated with insulin resistance.
- Low birth weight associated with rapid and exaggerated postnatal weight recovery and the development of precocious pubarche (appearance of pubic hair before eight years) and/or precocious puberty and hyperinsulinemia.
- Prolongation of the physiological anovulatory period beyond two years postmenarche.
- Congenital adrenal hyperplasia and other virilizing disorders.[3]

3. Fisiopathology

In the complex pathophysiology of polycystic ovary syndrome, at least three interrelated types of alterations stand out: a neuroendocrine dysfunction (hypersecretion of LH), a metabolic disorder (insulin resistance and hyperinsulinemia) and a dysfunction of steroidogenesis and ovarian folliculogenesis.[4]

3.1. Neuroendocrine dysfunction

It is characterized by an increase in LH secretion and normal or decreased FSH secretion. In these patients, an increase in the amplitude and frequency of LH pulses has been observed, which would reflect an increase in gonadotropin-releasing hormone (GnRH) pulses. No alterations in specific neurotransmitters have been identified to explain this disorder and current evidence suggests that it would probably be a hypothalamic dysfunction secondary to high levels of androgens and insulin.[4]

3.2. Metabolic dysfunction

It is mainly represented by peripheral IR that is expressed by hypersecretion of insulin. This in turn promotes increased secretion of androgens by the ovary and adrenals; stimulates LH secretion and decreases hepatic synthesis of SHBG (sex hormone-binding globulin), which increases the free fraction and biological activity of androgens. According to studies by our group, hypersecretion of insulin is manifested from early puberty and precedes biochemical hyperandrogenism. In addition, it should be noted that metabolic dysfunction is mainly associated with classic phenotypes that are accompanied by hyperandrogenemia.[4]

3.3. Dysfunction of ovarian/adrenal steroidogenesis

It is a fundamental pillar in this syndrome and is characterized by an alteration in the biosynthesis of androgens, which in the ovary and adrenals is determined by the activity of an enzyme called cytochrome P450c17. In patients with polycystic ovary syndrome, the activity of this enzyme is increased, leading to increased production of ovarian and adrenal androgens. The increase in intraovarian androgens alters follicle development and ovulation. Functional adrenal hyperandrogenism is present in around 50% of women with polycystic ovary syndrome and is expressed by a moderate elevation of DHEAS. It has been proposed that the dysfunction of this enzyme (P450c17) would be exclusive of polycystic ovary syndrome, being able to be a primary or secondary event to the excess of LH and/or insulin, which

would potentiate this dysfunction. In addition, it is worth noting that adipose tissue plays a predominant role in the pathophysiology of PCOS as it has an intrinsic steroidogenic function and is a white tissue for androgens.[16]

3.4. Folliculogenesis dysfunction

It has been possible to establish, through ultrasonographic studies and ovarian biopsies, that patients with PCOS have a follicle growth pool 2 to 3 times higher than healthy women. The histology of polycystic ovary syndrome is characterized by an increase in preantral and small antral follicles and a greater follicular recruitment. This situation is also accompanied by a stoppage of the follicular selection process, which explains the absence of ovulation. Therefore, in polycystic ovary syndrome there would be greater recruitment and less selection, which maintains an increase in the pool of androgen-producing growing follicles.[17]

4. Diagnosis

In 1935, Stein and Leventhal described a clinical entity consisting of menstrual disorders, sterility, hirsutism, and obesity. In addition, the ovaries of these patients had certain particular morphological characteristics such as: an increase in size, thickening of the albuginea and multiple peripheal subcortical ovarian cysts. With the advent of ultrasound, it was established that healthy women could present ultrasound images suggestive of polycystic ovaries without the clinical syndrome, and on the other hand patients with the florid clinical syndrome did not have the typical ultrasound images, all of which would indicate that the classic Stein Leventhal syndrome would be an exception. Therefore, in 1990, at a consensus conference of the US National Institutes of Health, it was defined as the "presence of hyperandrogenism associated with chronic anovulation without other specific causes of adrenal or pituitary disease associated with menstrual irregularities or excess androgens". However, this definition did not incorporate the morphological aspect of the ovaries. Later, the European Society of Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) at a consensus conference held in Rotterdam in 2003 proposed a new definition of the syndrome that incorporated the presence of polycystic ovaries on ultrasound as a diagnostic criterion.[4]

It was proposed that, after excluding other forms of hyperandrogenism, PCOS could be diagnosed in patients presenting at least two of the three following characteristics: clinical or biochemical hyperandrogenism, oligo-ovulation and the presence of polycystic ovarian morphology, giving rise to four phenotypes (figure 1):

- Hyperandrogenism + oligoanovulation + polycystic ovarian morphology.
- Hyperandrogenism + oligoanovulation.
- Hyperandrogenism + polycystic ovarian morphology.
- Oligoanovulation + polycystic ovarian morphology; each with different metabolic and long-term health implications.[4]

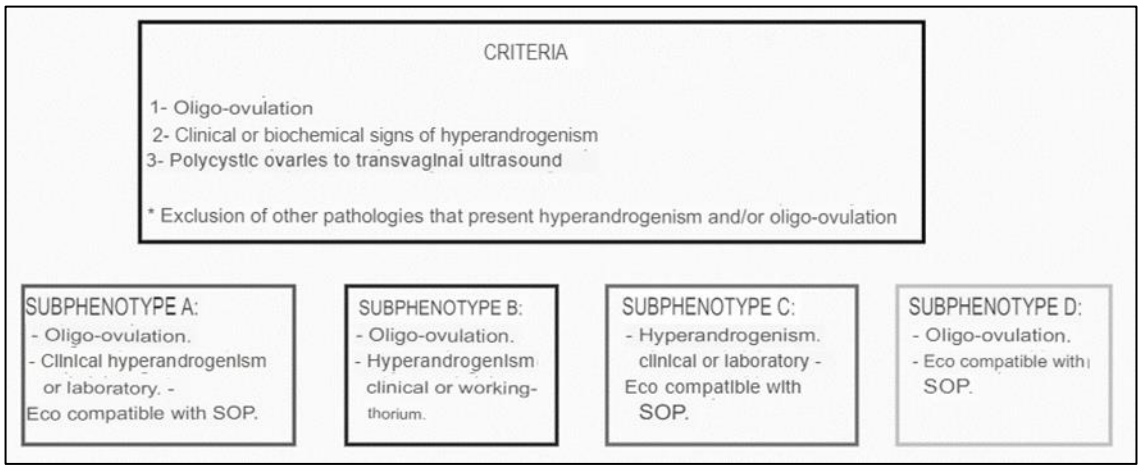

Figure 1 Criteria for polycystic ovary syndrome. Diagnosis and management (adapted from Rotterdam Consensus, 2003)

4.1. Oligo-anovulation or Anovulation

Irregular menstrual cycles and a low rate of ovulation are common in adolescence. One year after menarche, 65% of adolescents have regular cycles (between 21-45 days). After three years, 90% of adolescents have a pattern of 10 or more cycles per year. Therefore, it has been suggested to wait until two years after menarche to assess the regularity of cycles.

Anovulatory cycles are present in 85% of menstrual cycles during the first year after menarche, 59% during the third year and 25% during the sixth year. Anovulatory symptoms can present as primary or secondary amenorrhea, oligomenorrhea (<6 cycles per year) or dysfunctional uterine bleeding associated with elevated androgen and LH levels. Likewise, oligomenorrhea that persisted for more than 2 years postmenarche would be a good predictor of future menstrual irregularities.[3]

4.2. Hyperandrogenism

HA in childhood and adolescence determines alterations in the target tissues, conditioning the appearance of premature pubarche, hirsutism, acne, menstrual disorders or virilization.[3]

The most common clinical sign of hyperandrogenism is hirsutism or the presence of excess terminal hair with a male pattern. Terminal hair refers to hair that grows more than 5 mm long (if not cut), is medullated (with a central core of compact keratinocytes) and often has both shape and pigment. On the other hand, body hair is not medullated, it is softer, usually less than 5 mm long, can be pigmented or not and has a uniform shape. The male pattern refers to the growth of hair in areas where men usually develop terminal hair growth. Clinically, the level of terminal hair growth in male-type areas is evaluated using a visual scale, the modified Ferriman-Gallwey score. This score is obtained by assigning a score of 0 (no visible terminal hair) to 4 (terminal hair growth consistent with that of a normal male individual) in nine body areas (upper lip, chin and neck, upper chest, upper abdomen, lower abdomen or male shield pattern, upper back, lower back, upper arms and thighs) and then summing the values (figure 2).[2]

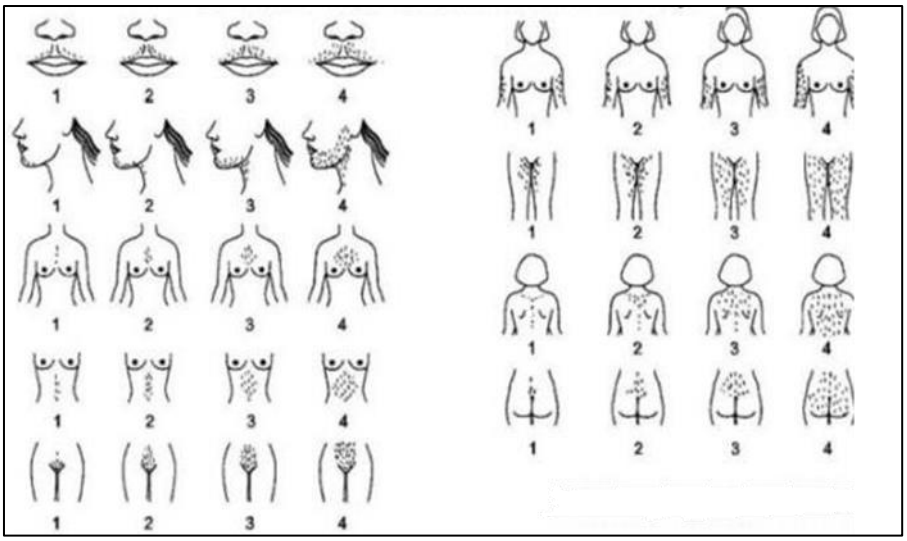

Figure 2 Modified Ferriman-Gallwey (Azziz, R., 2018) [2]

4.3. Polycystic Ovaries

In adult women, SOP diagnostic criteria include: 12 or more follicles of 2-9 mm in at least one ovary or an ovary larger than 10 cc on transvaginal ultrasound. There are two peaks in ovarian volume growth: at 8 years, coinciding with adrenarche, and around 12 years, coinciding with puberty. Between 6-11 years, ovarian volume increases up to 1.19-2.52 cc. During puberty, in response to hormonal stimulus, the ovary becomes more ovoid and has a volume between 1.8-5.7cc with a mean of 4cc developing a multifollicular aspect. The presence of less than six follicles during childhood and in the first years postmenarche is considered a physiological fact. An ultrasound examination between days 2 and 7 of the cycle should be performed with a 7 MHz transvaginal transducer.[3]

In adolescents, the ultrasound diagnosis of polycystic ovaries is difficult, due to the difficulty of performing transvaginal ultrasounds, since abdominal ultrasound is less discriminatory, especially in obese patients. The 8 cc value is currently

accepted as the normal ovarian volume in adolescents. However, ovarian size has little sensitivity as a diagnostic criterion for SOP in adolescents.[18]

Due to the limitations of ultrasound, other markers have been sought, such as anti-Mullerian hormone (AMH), a dimeric glycoprotein of the TGF-β tissue growth factor superfamily, which is a marker of follicular development synthesized by granulosa cells of ovarian follicles. Plasma AMH levels are correlated with the development of preantral and antral follicles, from puberty to the end of the reproductive age. It is elevated in women with SOP and could be a great support data for diagnosis.[18]

5. Research of the laboratory

Patients with Polycystic Ovary Syndrome have discreet or moderate elevation of androgens, such as testosterone, androstenedione, dehydroepiandrosterone sulfate, or all of them. Although the increase of androgens is very frequent, some determinations fall within the normal range, and this does not imply a diagnostic exclusion. The method used to measure the androgens must also be taken into consideration and it must be remembered that after 35 years, the concentrations of androgens decrease by 50% in women.[16]

5.1. Testosterone total

It is the most important circulating androgen in women, and it is also the main androgen responsible for hirsutism in them. However, in PCOS, total testosterone is only discreetly elevated in 50% of cases. In addition, there are numerous tests to measure this hormone, which can be confusing to determine its elevation. According to our experience, testosterone measured by RIA (Diagnostic System Labs, TX, USA) is the one that gives the best correlation with mass spectrometry, which is the most refined method to measure testosterone. For this reason, to establish the presence of hyperandrogenism, the Rotterdam consensus suggests using the free androgen index (FIA), which was initially described by Fox et al and consists of the ratio between total testosterone and its transport protein (SHBG) according to the following formula: Testosterone (nmol)/ SHBG (nmol) x 100 (Normal value <4.5). To transform T into ng/ml to nmol/l it must be multiplied by 3.467.[14]

5.2. Dehydroepiandrosterone sulfate (DHEAS)

This hormone is exclusively originated in the adrenal glands, so it is used as a marker of adrenal hyperandrogenism. Approximately between 25-40% of these patients can present an increase in the serum concentration of DHEAS, which rarely exceeds 600 ng/dl.[14]

5.3. Androstenedione

It is an androgen fundamentally of ovarian origin and it can be the only elevated androgen in a woman with PCOS. Compared to testosterone, this androgen remains elevated until late stages of the menopausal transition. In addition, it has the advantage that its determination is carried out with a single type of assay, which does not generate variability of the results. Although it is not a first-line androgen, it can be determined in case of diagnostic doubt.[14]

5.4. 17 hydroxyprogesterone (17-OHP)

It is the best metabolite to discard deficit of the 21-hydroxylase enzyme; its normal fasting value in the early follicular phase of the menstrual cycle is lower than 2 ng/ml. Values higher than 6 are indicators of enzymatic blockade; Concentrations between 2 and 4 ng/ml make it necessary to perform an ACTH test, which consists of the intravenous administration of 0.25 ug of ACTH (OHP values higher than 10 ng/ml at 60 minutes post ACTH establish the diagnosis). Around 50% of patients with PCOS can present very discreet elevations of this hormone.[18]

5.5. LH/FSH ratio

Patients with polycystic ovary syndrome often (60%) have an increased LH/FSH ratio (greater than 2), which is usually observed in women of normal body weight. Originally it was considered a marker of polycystic ovary syndrome. However, since its normality does not rule out the diagnosis, it is not currently used as part of the PCOS criteria, but it still remains an orienting element. The hormonal study must be completed with the determination of prolactin and thyroid hormones, whose alterations can occur with menstrual irregularities.[14]

Table 1 Pathologies for exclusion before POS diagnosis (Adapted from Winnykamien, I., Dalibón, A., & Knoblovits, P., 2017)

Diagnosis	Proof	Exclude
Congenital adrenal hyperplasia	17 hydroxyprogesterone	Always
Thyroid disfunction	TSH	Always
Hyperprolactinemia	Prolactin	Always
Androgen-secreting tumor	Testosterone and DHEA-S	In the face of suspicion
Pregnancy	Human chorionic gonadotrophin	In the face of suspicion
Acromegaly	GH-IGF 1	In the face of suspicion
Cushing's syndrome	Nocturnal salivary cortisol Nugent test-Urinary free cortisol	In the face of suspicion
Primmary ovarian insufficiency	FSH	In the face of suspicion
Hypothalamic amenorrhea	FSH-LH-Estradiol	In the face of suspicion

6. Related mechanisms to infertility in PCOS

6.1. Genetic bases

Mothers, fathers, brothers/sisters, and children of patients with PCOS have an increased risk of having PCOS or related phenotypic and metabolic alterations. Candidate gene and whole genome association studies have described more than 19 genetic loci, most of them related to neuroendocrine, metabolic, and reproductive functions. They include DENND1A, THADA, FSHR, INS-VNTR and LHR.[19]

6.2. Neuroendocrine dysfunction

It is characterized by an increase in the frequency and amplitude of luteinizing hormone (LH) pulses, increasing its plasma levels and the LH/FSH index. The cause of this dysfunction is not clear, a primary alteration in the Gonadotropin-releasing hormone (GnRh) pulse generator has been postulated, but defects in the kisspeptin circuit have also been described, and more recently, the theory of an alteration of negative estrogen and progesterone feedback caused by hyperandrogenism has gained momentum.[20]

6.3. Hyperandrogenism

The increase in LH secretion stimulates the production of ovarian androgens, but in addition, theca cells (CT) of PCOS patients produce more androgens than controls in response to this stimulus and maintain a persistent hypersecretion in vitro, suggesting an intrinsic defect of them.[20]

6.4. Metabolic alterations

PCOS patients, independently of their BMI, have up to 80% peripheral insulin resistance (IR) and hyperinsulinemia. Hyperinsulinemia induces ovarian and adrenal hyperandrogenism by several mechanisms: it increases the secretion of gonadotropins, amplifies the action of gonadotropins in the ovary, and inhibits the production of Sex Hormone Binding Globulin (SHBG) in the liver, which increases the free fraction and biological activity of androgens. It is believed that the cause would be alterations of postreceptor signaling and dysfunction of the β-pancreatic cell.[21]

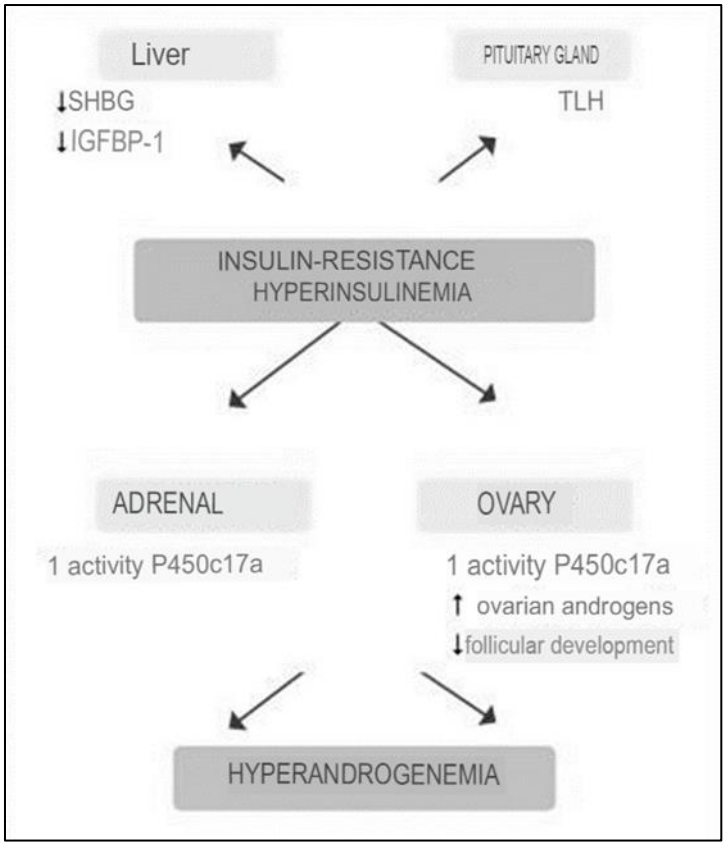

Figure 3 Hyperinsulinemia (Adapted from Silva, V.R., 2010)

7. Treatment

The decision for treatment should be based on the patient's priorities, the effectiveness of treatment, its side effects and the patient's desire to become pregnant.[5]

Lifestyle changes: it is the first-line management of the PCOS associated with cardiometabolic risk. An increase in physical exercise and dietary restriction have shown a reduction in the risk of diabetes in these patients. Exercise 3 times a week for 30 minutes has demonstrated a reduction in body mass index, waist circumference, waist-hip ratio, and insulin resistance, as well as an improvement in oxygen consumption. Weight loss of 10 percent improves menstrual function and fertility, in parallel with the improvement of insulin resistance and metabolic alterations. The rate of insulin resistance in women with PCOS is 50 to 80 percent and a large majority of these women are obese.[5]

Screening for diabetes mellitus: women with a diagnosis of PCOS should undergo screening tests for type 2 diabetes and carbohydrate intolerance with a fasting glucose test and a 75mg glucose tolerance test, due to their 2 to 5 times higher risk of developing it. Women who are categorized with carbohydrate intolerance should be considered within the group of metabolic syndrome and look for associated pathologies. Fasting glucose greater than 126 mg/dl (110-125 mg/dl = intolerance). Postload glucose 75g greater than 200 mg/dl (140-199 mg/dl = intolerance).[6]

Screening for cardiovascular disease: women with PCOS should undergo screening tests for cardiovascular risk by determining BMI, fasting lipids and lipoproteins, and metabolic syndrome risk factors. In addition, they should be periodically reviewed for cardiovascular disease risk factors, as conversion to glucose intolerance approaches 20 percent per year. Regular exercise and weight control are proven methods to reduce morbidity and mortality from cardiovascular disease.[6]

The management of PCOS involves focusing on aspects such as bio-psycho-social support, preventive education, and addressing psychological factors for a better lifestyle, essentially involving significant changes in habits such as diet and prescribed physical activity with its corresponding professional accompaniment to guarantee weight loss. In that sense, the treatment should be integral, including psychological counselling and participation in support groups that allow the construction of effective coping alternatives for the various conditions that affect the quality of life of these patients.[7]

It is interesting to note that despite the psychological distress and deterioration in perceived health quality experienced by patients with PCOS, only 55% of them seek professional help for the resolution of their somatic symptoms, as others consider that the symptoms do not deserve enough attention or identify a poor offer of specialized and efficient health services. Initially, for some patients, increasing the perception of risk can contribute to an increase in protective behavior execution rate. Lifestyle change, together with high self-motivation and self-image, enhances the reduction of metabolic and psychosocial risks, as well as improving their sexual and reproductive health indicators. However, interventions of this kind should be carried out with caution, as if these indicators are high, motivation is reduced; therefore, it is necessary to intervene in the distress to ensure that these patients have access to an appropriate diet and medication management. A useful way to reduce stress and related physiological indicators could be Mindfulness, which, although it reports good results in perceived well-being, needs more studies to confirm the possible generalization of this therapeutic approach to patients with PCOS.[8]

The establishment of dietary programs with and without aerobic exercise accompaniment, contributes to the reduction of weight, to the increase of a functional mood, and to the improvement of perceived quality of life indicators in patients with PCOS. On the other hand, the establishment of psychosocial accompaniment offers allows patients to have spaces for expressing their emotions, strengthening their coping strategies for situations associated with the disease itself, and creating social links, all of which are key alternatives in increasing self-image and self- esteem. Additionally, it is important to include the strengthening of self-control, for example, in the intake of substances not endorsed by the medical community, or in the suggested dosage, and to carry out educational programs, so that patients can deliberately choose between the different therapeutic options available.[9]

7.1. Patients without desire for pregnancy

Oral contraceptives (OCs): there are several options to treat menstrual disorders, but the most commonly used are low-dose combination OCs as a long-term treatment. Moreover, it is considered the first-line treatment for menstrual disorders. These suppress gonadotropin secretion and ovarian androgen production, and the estrogen component increases hepatic production of sex hormone- binding globulin, decreasing the availability of androgens. They confer endometrial protection and reduce terminal hair growth.[10]

Progestins: progesterone OCs or Intrauterine Devices (IUDs) containing progestin are an alternative for endometrial protection but are associated with abnormal bleeding patterns in up to 50-89% of cases.[11]

7.2. Insulin-sensitizing agents

Metformin is a biguanide that acts by decreasing hepatic glucose production, increasing insulin sensitivity by producing greater peripheral uptake. It is used as second- line therapy particularly in women with contraindications to OC use, but it has not demonstrated that it protects the endometrium. Moreover, it is a potential alternative to restore menstrual cyclicity in 50% of women with PCOS. In a meta-analysis (Lord et al., 2003) it was observed that when metformin and clomiphene were compared with clomiphene alone, ovulation occurred in 76% of women who received metformin and clomiphene, compared to 42% of those who received clomiphene alone.[12]

8. Patients with desire for pregnancy

There is no scheme to guide initial and subsequent choices of ovulation induction methods in women with PCOS. The American Society for Reproductive Medicine and the European Society for Reproductive and Embryology (ASRM/ESHRE) recommend emphasizing the importance of lifestyle modifiers, quitting smoking, and reducing alcohol consumption.[13]

8.1. Clomiphene citrate

It was previously considered as the first-line treatment for ovulation induction. The dose is 50mg to 100mg per day for 5 days, starting between day 2 and 5 of the menstrual period, which can be induced with progesterone if necessary. Between 20% and 40% will have a pregnancy within 6 months of treatment initiation.[15]

8.2. Gonadotropins

It is used in women whose clomiphene citrate has failed. Low-dose gonadotropin therapy offers higher rates of ovulation and monofollicular development with significantly lower risk of ovarian hyperstimulation syndrome.[15]

8.3. Ovarian drilling

It is recommended as second-line treatment. Laparoscopic ovarian drilling with diathermy is performed in infertile women with anovulation and indeterminate PCOS. The long-term effects of laparoscopic ovarian drilling on ovarian function are not clear. There is no available evidence suggesting that it improves live birth rates when used alone or in combination with clomiphene citrate.[14]

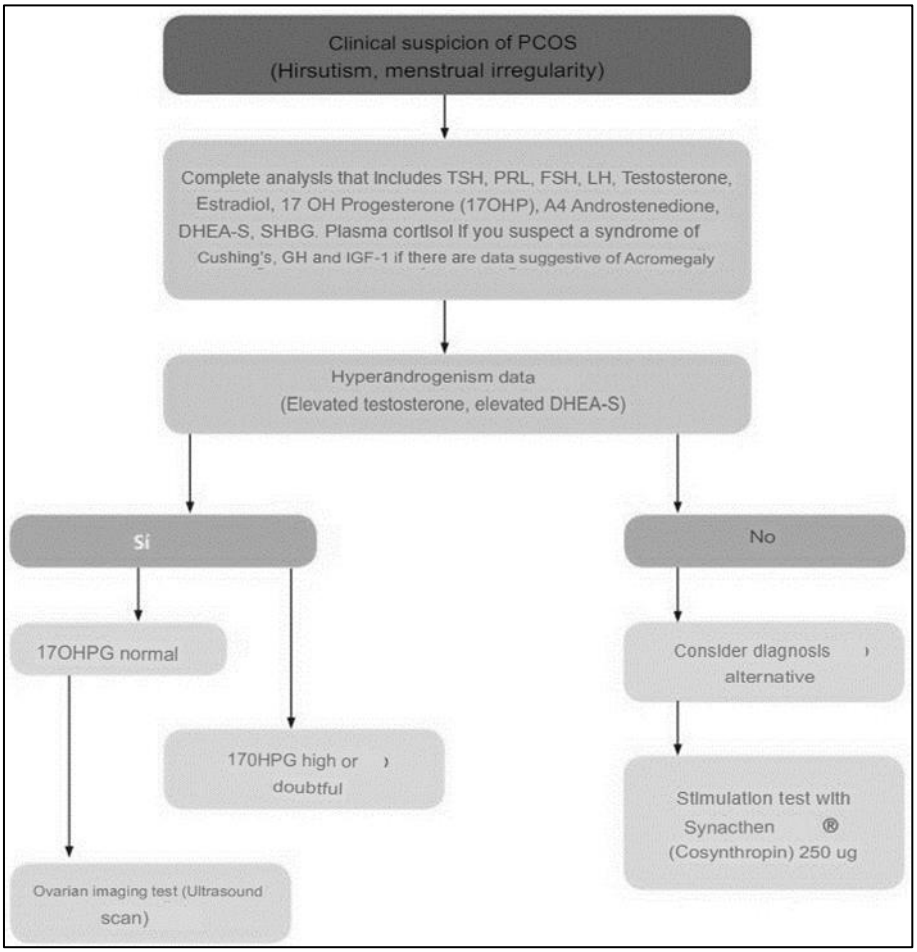

Figure 4 Management algorithm for polycystic ovary síndrome (Adapted from Del Castillo Tirado, F.J., 2014)

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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