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# Clinical Features of PCOS

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## Abstract

Polycystic ovary syndrome (PCOS) is a widespread pathology that affects multiple aspects of the general health of women, with long-term effects that go well beyond the reproductive age. The considerable variability of the clinical presentation, together with the lack of universally accepted diagnostic criteria, has so far contributed to making it difficult to identify a clear etiology of the disease. The exact etiology of PCOS is still not perfectly clear to date. It is therefore a multifactorial etiology, sharing of genetic and environmental factors. The contribution of genetics to the pathogenesis of PCOS is not due to a single gene but inheritance of gene clusters. The term “polycystic ovary syndrome” does not completely reflect the complexity of this syndrome which manifests a wide spectrum of clinical manifestations and comorbidity and important metabolic implications. PCOS patients showed an increase risk of developing type 2 diabetes mellitus, dyslipidaemia, endometrial cancer and cardiovascular diseases. The clinical aspects of PCOS are hyperandrogenism, oligomenorrhoea and ultrasound morphology of the ovary. The identification of the different manifestations of PCOS in the various phases of life, can, of course, help to organize individual therapeutic strategies and likely to prevent long-term metabolic consequences. The therapeutic choices will be based on the type and extent of the disorders and if there is a desire for pregnancy.

**Keywords:** polycystic ovary syndrome, hyperandrogenism, ultrasound, insulin, insulin resistance, metformin, hyperinsulinaemia, inositol, infertility, menstrual irregularities, anovulation, obesity

## 1. Introduction

Polycystic ovary syndrome (PCOS) was first observed by Stein and Leventhal who in 1935 described seven women with amenorrhoea, hirsutism and increased volume of the ovaries characterized by the presence of numerous cysts [1]. The exact etiology of PCOS is still not perfectly clear to date. It is therefore a multifactorial etiology, sharing of genetic and environmental factors [2]. The contribution of genetics to the pathogenesis of PCOS is not due to a single gene but inheritance of gene clusters [3]. The metabolic dysfunction in PCOS patients mainly reflects molecular dysfunction of insulin signaling pathway, mainly at the level of the skeletal muscle and of the adipose tissue. These defects seem to be partly intrinsic and partly acquired because of hormonal and metabolic situation. Androgens, bioactive mediators (adipokines) and other pro-inflammatory molecules contribute to the altered action of insulin on peripheral tissues.

Insulin acts as a regulator of glucose balance by stimulating the uptake of glucose from insulin-sensitive tissues, such as adipose tissue and skeletal and cardiac

muscle, and suppressing hepatic glucose production. Insulin is also able to suppress lipolysis leading to a decrease in free fatty acid levels (FFAs), which can mediate the action of insulin on the hepatic production of glucose. Insulin resistance is defined as a decreased ability of insulin to carry out these metabolic actions inherent in the uptake of glucose, the production of glucose and lipolysis, which then leads to the need for more circulating insulin to maintain the same effects. Thus insulin resistance is characterized by increased circulating levels of insulin, both basal and after loading glucose, if pancreatic function is normal [4].

## **2. Clinical aspects of PCOS**

A biochemical and clinical hyperandrogenism of ovarian origin and to a lesser extent adrenal is evident in about 60–80% of PCOS patients, resulting in one of the main features of the syndrome [5]. Ovarian hyperandrogenism is mainly due to a defect in the intrinsic steroid synthesis in ovarian thecal cells. Extra-ovarian factors, such as high levels of LH and insulin and low levels of FSH, and intraovarian factors, such as anti-Müllerian hormone (AMH) and inhibin, may enhance the hyperandrogenism state. Also high levels of androgens are recognized as one of the possible causes of PCOS insulin resistance. An excess of androgens during intrauterine life and in the immediate post-natal period may lead to accentuate visceral adiposity and insulin resistance. Medications with anti-androgenic activity may improve insulin resistance. Androgens by acting directly on the insulin signaling system may contribute to the peripheral insulin resistance in patients with PCOS. Insulin resistance and compensatory hyperinsulinaemia are involved in all three main clinical aspects of the syndrome: hyperandrogenaemia, ovarian dysfunction and metabolic alterations [6].

The increased pulsatility of the LH leads to increased circulating LH levels that stimulate the ovarian cortex synthesis of androgens. Increased levels of LH are partly due to an altered negative feedback exerted by androgens on the hypothalamic–pituitary axis [8]. Insulin, in synergy with LH, will enhance the stimulation of androgen production by theca cells of the ovary and to a lesser extent the adrenal cortex. Insulin is also involved in the ovarian dysfunction by increasing the expression of LH receptors on the granulosa cells [9]. The first therapeutic approach in obese patients with PCOS is to achieve weight loss. In addition to an improvement of metabolic comorbidities associated with obesity, weight loss reduces hyperinsulinaemia with a consequent increase of insulin sensitivity, decreased LH and androgen levels and improvement of both menstrual cycle and fertility [10].

Patients with PCOS have an altered metabolism of inositol, and there is a connection between insulin resistance and inositol deficiency [11]. In women with PCOS, at the level of muscle tissue, the conversion of myo-Inositol into D-chiro-inositol is reduced due to a reduction in epimerase activity. Furthermore, these patients show reduced serum D-chiro-inositol levels and an increase in urinary excretion of inositol phosphoglycan, which is inversely related to insulin sensitivity, supporting the hypothesis according to which women with PCOS present a serious alteration of the metabolism of inositols, characterized by an excess of myo-inositol and a deficiency of D-chiro-inositol and a decrease in epimerase activity. This hypothesis has led to focus the attention on the importance of myo-inositol and D-chiro-inositol supplementation to restore normal ovarian function [12].

### 3. PCOS and metabolic syndrome

The identification of the different manifestations of PCOS in the various phases of the life, can, of course, help to organize individual therapeutic strategies and likely to prevent long-term metabolic consequences. Women with PCOS may have different degrees of insulin resistance (IR) that contribute to the increased risk of metabolic syndrome. The latter, defined in the past as “syndrome X” or “insulin resistance syndrome” or “plurimetabolic syndrome”, is described by the association of various metabolic disorders, each of which is a known cardiovascular risk factor.

The definition of metabolic syndrome according to the National Cholesterol Education Expert Panel (NCEP) on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III—ATPIII) provides for the presence of three or more disorders between:

1. Central obesity (waist circumference  $\geq 88$  cm).
2. Impaired glucose levels (fasting blood sugar  $\geq 110$  or  $\geq 140$  mg/dl after 2 hours after oral glucose test (OGTT)).
3. Arterial hypertension (PA  $\geq 130/85$ ).
4. Hypertriglyceridaemia ( $\geq 150$  mg/dl).
5. Reduced HDL cholesterol ( $< 50$  mg/dl).

These criteria are most frequently used in scientific research [13].

The presence of obesity in women with PCOS results in the worsening of the clinical presentation, both from a metabolic and reproductive point of view [14]. Obese women with PCOS present:

1. Increased prevalence of impaired fasting glucose (IFG) and type 2 diabetes mellitus.
2. Higher prevalence of hirsutism (73% of obese vs. 56% of non-obese) [15].
3. Worst lipid profile.
4. Increased risk of metabolic syndrome and, therefore, cardiovascular diseases [16].
5. Higher prevalence of oligomenorrhoea, amenorrhoea and infertility [17].
6. Lower rate of ovulation and conception in response to clomiphene citrate. and to exogenous gonadotrophins, with need for higher doses.
7. Lower percentage of pregnancies in assisted reproduction techniques (IVF, ICSI) and increased frequency of spontaneous abortions [18].

It should be noted that a greater predisposition to the metabolic syndrome has been described throughout the body mass index (BMI) range, indicating that PCOS, independently of obesity, can confer an increased risk of developing this complication, due to the intrinsic insulin resistance that characterizes it. Women with PCOS and a combination of metabolic syndrome would exhibit greater insulin

resistance, higher levels of free testosterone, lower levels of SHBG and, phenotypically, greater frequency of acanthosis nigricans [16]. The prevalence of metabolic syndrome, however, would be higher in patients with high BMI than in those with normal BMI.

#### **4. Pathophysiology**

The considerable variability of the clinical presentation, together with the lack of universally accepted diagnostic criteria, has so far contributed to making it difficult to identify a clear etiology of the disease.

The three main endocrine changes of PCOS are:

1. Hyperandrogenism.
2. LH hypersecretion.
3. Hyperinsulinism.

The mechanisms by which these factors interact with each other in PCOS are extremely complex and not yet completely clarified [17].

The rapid onset of hyperandrogenism may be caused by steroid-secreting ovarian or adrenal tumors that must be ruled out in the differential diagnosis. On the contrary, the slow and progressive appearance of hyperandrogenism is often associated with medical history for a gradual increase in weight over time [19].

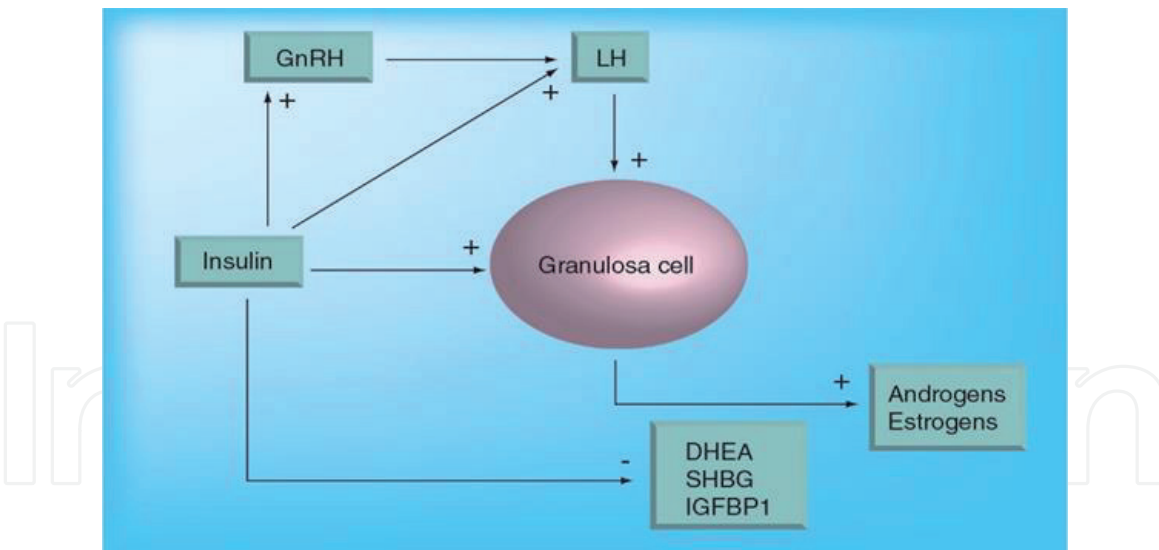
Several mechanisms that could determine Insulin resistance (IR) are:

- Excessive serine phosphorylation of the insulin receptor subunit.
- Mutations of the insulin receptor gene or IRS-1 (substrate of the insulin receptor, phosphorylated by its tyrosine kinase activity, Tyr-K).
- Depletion of intracellular adenosine.
- Post-receptor defect of glucose transport.
- Impaired insulin clearance in peripheral tissues.

Obesity amplifies insulin resistance and hyperinsulin state in PCOS patients, and that, therefore, obese patients are more insulin-resistant and more hyperinsulinaemic of the normal-weight counterpart. Despite the peripheral insulin resistance, ovarian tissue remains sensitive to action of insulin, probably because at this level, the transduction system involves a different second messenger, inositol phosphoglycan.

So, insulin can act directly on the cells of the ovary, activating cytochrome P450c17 and enhancing the synthesis of androgen induced by LH. The increased proactive androgenic action of insulin also manifests itself indirectly, by suppressing the hepatic synthesis of sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding protein 1 (IGFBP-1), with consequent increase in the bioavailability of free testosterone of IGF-I. The latter would act by stimulating the secretion of progesterone and oestradiol and increasing the aromatase activity and production of androgens, respectively, in granulosa and thecal cells (**Figure 1**).





**Figure 1.**  
 Insulin actions and androgen production [7].

Insulin acts by modifying the pulsatile secretion of GnRh increasing the sensitivity of gonadotropic cells to GnRh.

An important role to the genesis of insulin resistance has been attributed to free fatty acids (FFA) [20]. The visceral adipocytes of women with PCOS have increased the lipolytic activity of abdominal fat with subsequent marked lipolytic activity that enhances the massive release of FFA in the portal blood. FFAs once they reach the liver trigger an inflammatory parenchymal state, induce a reduction in androgen clearance and inhibition of SHBG synthesis, but above all inhibit the hepatic extraction of circulating insulin. In this way FFA contribute to peripheral hyperinsulinaemia. FFA also compete with glucose as the energy substrate of skeletal muscles [21], and with this modality, they would contribute to the genesis of insulin resistance.

A contribution to hyperinsulinaemia also comes from a secretory pancreatic defect, found in some patients with PCOS even in the absence of glucose intolerance or a frank type 2 diabetes [22]. In particular, an exaggerated pancreatic secretion was demonstrated in the first phase of the response to a hypoglycaemic stimulus administered in order to test pancreatic secretory capacity. This anomaly is present in lean PCOS as well as in obese PCOS resulting in a defect independent of other confounding factors such as BMI, adipose tissue distribution, peripheral sensitivity to insulin or a family history of noninsulin-dependent diabetes mellitus (NIDDM).

From the neuroendocrine point of view, PCOS represents distinctive feature of the inappropriate secretion of gonadotrophins. There are numerous studies that demonstrate the existence of an alteration of the hypothalamic–pituitary–ovary axis which is expressed on the hormonal level in:

- An increase in the secretion of LH: in particular, an increase in the amplitude and frequency of the LH observed in basal conditions [23].
- The relative suppression of FSH suggests that partial pituitary desensitization is secondary to the increased frequency of GnRH secretion [23].

An alteration of the circadian rhythm of LH is also observed with persistence of nocturnal hyperactivity typical of adolescence. This suggests the existence of a

marked hypersensitivity of the LH-secreting pituitary cells to the action of GnRH [24]. Another hypothesis suggests the presence of a partial loss of feedback control mechanisms on the hypothalamus that lead to a greater autonomy of the GnRH pulsatility generating centre [25]. All this will contribute to irregularity in the hormonal pattern of LH. LH is in turn responsible for the hyperplasia of the theca cells of the ovary which represents the anatomopathological substrate that supports hyperandrogenism.

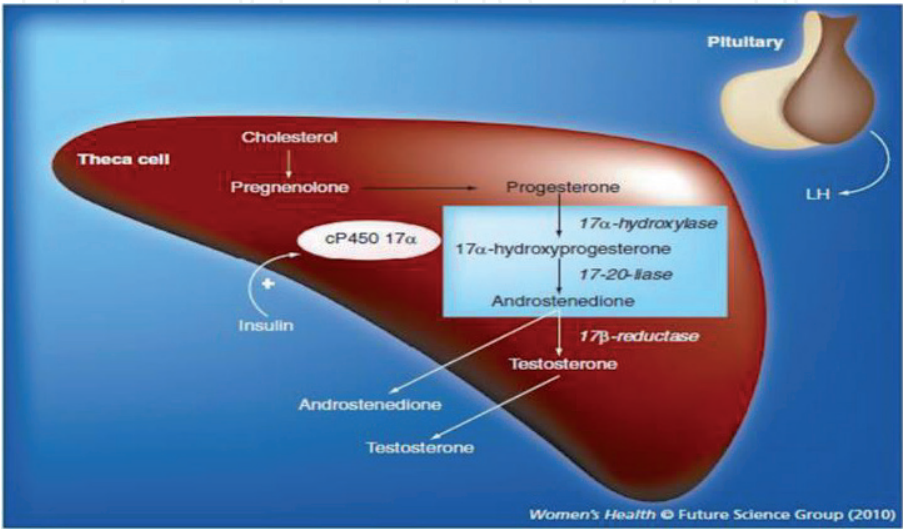
Parallel to the hyperactivity of the LH-theca ovarian axis, there is a hypo-functionality of the FSH-ovarian granulosa axis: in fact here is a constantly uniform FSH concentration, settled at values approximately 30% lower than the reference values [26]. The relative decrease of FSH levels may enhance a defective folliculogenesis that lead to maturation of follicles at the antral phase. Another factor influencing anovulation is the hyperandrogenic state and in particular the high concentration of androgens in the follicular microenvironment (**Figure 2**).

Two other important mechanisms of action of insulin are responsible for hyperandrogenaemia:

1. The inhibition of the hepatic synthesis of SHBG (sex hormone-binding globulin), which determines a greater bioavailability of free oestrogens and androgens [27].
2. The inhibition of hepatic production of IGFBP-1 (insulin-like growth factor-binding protein-1) which increases the circulating levels of IGF-1 and its activity [28, 29]. Among the various actions, IGF-1 also appears to stimulate the activity of the enzyme 5 $\alpha$ -reductase, responsible for converting testosterone into dihydrotestosterone, its active metabolite.

The concentration of insulin-like growth factor-binding protein-1 (IGFBP-1) is directly correlated to the degree of obesity, in fact overweight reduces its concentrations even in non-PCOS women. As a result, obesity also plays an essential role in the pathogenesis of hyperandrogenism in PCOS, as BMI is the main determinant of IGFBP-1 Levels [29].

There is evidence that a vitamin D deficiency could be involved in the genesis of insulin resistance and metabolic syndrome in PCOS and would also play a role in determining the hormonal status of PCOS patients [30, 31].



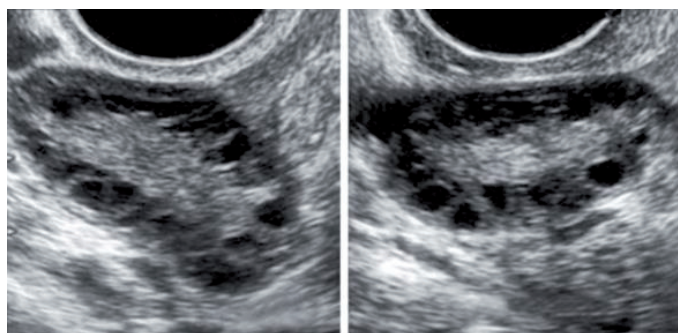
**Figure 2.**  
*Insulin action on the theca cell steroidogenesis [7].*

## 5. Clinical evaluation: Diagnostic criteria for PCOS in adult women

The prevalence of PCOS varies according to the diagnostic criteria used which usually include extension of hirsutism, level of circulating androgens, degree of irregularity of the menstruation and ultrasound morphology of the ovary.

Patients suffering from PCOS most frequently complain of:

1. Menstrual irregularities: usually associated with anovulation which is the cause of oligomenorrhoea (less than nine menstrual cycles per year; cycles of average duration exceeding 36–40 days). Anovulation in 30% of cases is accompanied by secondary amenorrhoea (no menstrual periods for three or more consecutive months) which occurs after a period of variable oligomenorrhoea.
2. Hyperandrogenism. The most characteristic clinical presentations are hirsutism and acne. Total testosterone is the best to reflect the androgenic status as the free testosterone level may not be very accurate. Total testosterone can be measured on any day of the menstrual cycle [32]. Other laboratory investigations that can be made are:
  - Free androgen index (FAI) is the ratio between total testosterone and SHBG.
  - Androstenedione is the direct precursor of testosterone, produced by the ovaries, adrenals and peripheral tissues. In women with PCOS, androstenedione levels can be increased even when the total testosterone is normal [33].
  - DHEA-S is almost exclusively of adrenal origin and is increased in about 20–30% of PCOS patients. Hyperandrogenaemia, therefore, is predominantly of ovarian origin and supported by the increased activity of the P450c17 enzyme complex in thecal cells, which has two activities, 17 $\alpha$ -hydroxylase, which converts progesterone to 17-OH-P, and 17–20 lyase, which transforms the latter into androstenedione (**Figure 2**). Androstenedione will then be converted into testosterone by 17 $\beta$ -hydroxysteroid dehydrogenase. In particular, the activity of 17 $\alpha$ -hydroxylase is increased. Furthermore, it appears to be an adrenal contribution to hyperandrogenaemia, again due to the excessive activation of the same microsomal enzyme P450c17, predominantly in the activity of 17–20 lyase, although a hyper-responsiveness to ACTH is not to be excluded. Insulin is able to directly stimulate the enzymatic activity of P450c17, both at the adrenal and ovarian level [34]. A recent study has shown that androstenedione and total testosterone level helps to better assess the risk of developing metabolic syndrome in women with PCOS [33].



**Figure 3.**  
*Ultrasound imaging of polycystic ovaries [35].*



3. Polycystic ovary morphology: according to the Rotterdam criteria, the ovaries are defined as “polycystic” at least 1 ovary showing 12 or more follicles with average diameter 2–9 mm, regardless of their disposition, and/or a total ovarian volume  $>10 \text{ ml}^3$ , examined with a transvaginal probe, and the evaluation must be carried out both in longitudinal and transverse scanning plane. It is sufficient that only one ovary has these characters, if evaluated in the follicular phase and in the absence of any hormonal treatment. Peripheral distribution of the follicles and hypertrophy of the ovarian stroma may be present but are not necessary for diagnosis (**Figure 3**).

## 6. Therapeutic approach

Therapeutic choices will be based on the type and extent of the disorders and if there is a desire for pregnancy.

The goals of the therapeutic action are:

- Improvement in menstrual cycles
- Reduce circulating androgens and signs of hyperandrogenism
- Reduce insulin resistance and prevent metabolic complications and decrease cardiovascular risk
- Try to achieve the ideal weight
- Treatment of infertility and improving the response to ovulation induction therapies
- Endometrial protection to prevent endometrial carcinoma

The therapeutic options available for PCOS are represented by lifestyle changes and the use of oral contraceptives, androgen receptor antagonists and insulin-sensitizing drugs such as metformin and inositol-based supplements.

The first therapeutic approach in women with PCOS must be represented by lifestyle changes, by nutrition and in the presence of obesity or overweight by weight loss. In addition to an improvement in the metabolic comorbidities associated with obesity, weight loss reduces hyperinsulinaemia and increases insulin sensitivity, leading also to a decrease in LH and androgen levels.

Palomba et al. demonstrated in two cohorts of patients followed for 24 weeks, one of which was subjected to a regular exercise programme while the other to hypocaloric hyperproteic diet, in both cases there was a decrease in insulin resistance and improvement in menstrual cycles, fertility, SHBG and androgen levels [36].

Improvements of ovulation were found after weight loss in the PCOS obese patient as weight reduction could play the most significant role in restoring ovulation [37].

### 6.1 The use of combined oral contraceptive (COC) pill

This treatment produces regular menstrual cycles, decreases the risk of endometrial hyperplasia and improves acne and hirsutism. The treatment with COC pill represents therefore the therapy of first choice for the treatment of hyperandrogenism.

COC treatment increases the hepatic synthesis of SHBG, reducing the proportion of free and therefore metabolically active testosterone. Among the progestogens that can be used in various associations, those with anti-androgenic activity are preferred, such as cyproterone acetate (which acts by preventing the binding of androgens to their cellular receptors) and drospirenone (which is a progestin with an anti-androgenic and anti-mineralocorticoid action).

## 6.2 Insulin-sensitizing treatment

The rationale of the use of insulin sensitizers in PCOS derives from the fact that 45–65% of PCOS patients have insulin resistance and compensatory hyperinsulinaemia [38] which alter the steroidogenesis of the ovary and follicular maturation [39].

The classic insulin-sensitizing treatment is metformin, a biguanide traditionally used in the treatment of people with type 2 diabetes. Metformin acts by increasing the uptake and utilization of glucose at the level of skeletal muscle and adipose tissue by reducing the insulin resistance and decreasing hepatic gluconeogenesis; it is also able to reduce intestinal glucose absorption and lipolysis, causing the reduction of substrates for gluconeogenesis.

Metformin has a significant effect on the reduction in circulating androgen levels, weight loss and regularization of menstrual cycles and ovulatory cycles [40].

Metformin action on androgens and the mechanisms by which metformin acts on hyperandrogenaemia are:

- Reduced production of androgens in the ovaries [41] and adrenals [42].
- Reduced pituitary secretion of LH [43].
- Increased SHBG liver production [44].

## 6.3 Inositol

It exerts an important control over glucose homeostasis, and when incorporated into phosphoglycans, it functions as an intracellular mediator of the action of insulin.

Inositol improves insulin sensitivity and ovulation rate, decreasing the testosterone concentration, blood pressure and plasma triglyceride concentrations [45].

The insulin-sensitizing action of inositol is the myo-inositol and the D-chiro-inositol. The conversion of myo-inositol into D-chiro-inositol by the epimerase is dependent on insulin, so the liver and muscle (the insulin-sensitive tissues) are those in which the greatest conversion occurs. They are both chemical mediators of insulin. The activation of phospholipids containing myo-inositol by insulin causes an increase in the permeability of the cell membrane to glucose with consequent increase in its internalization and availability for use. D-chiro-inositol, on the other hand, may allow the intracellular accumulation of glucose in the form of glycogen. The result of the action of both is however the increase in insulin sensitivity with consequent reduction in the circulating levels of insulin [46].

## 7. Conclusion

PCOS is a widespread pathology that affects multiple aspects of the general health of women, with long-term effects that go well beyond the reproductive age.

The term “polycystic ovary syndrome” does not completely reflect the complexity of this syndrome which manifests a wide spectrum of clinical manifestations and comorbidity and important metabolic implications. PCOS patients showed an increase risk of developing type 2 diabetes mellitus, dyslipidaemia, endometrial cancer and cardiovascular diseases.

The main features of PCOS are hyperandrogenism, oligomenorrhoea and ultrasound morphology of the ovary.

PCOS is also associated with reduced fibrinolytic activity due to increased levels of inhibitor of the plasminogen activator (PAI-I), independently of body mass index, as it is also found in thin women suffering from this syndrome and appears to correlate with the risk of abortion [47].

Atypical endometrial hyperplasia, whose incidence is increased, seems to be due both to chronic exposure to high levels of oestrogens, not balanced by an adequate amount of progesterone (due to chronic anovulation).

Patients with PCOS also have reproductive alterations, evidence of insulin resistance, anxiety and depression. If pregnant, these women have a significant increase in the risk of developing gestational complications like miscarriage, gestational diabetes, pre-eclampsia and preterm birth [48].

The mechanisms that could determine insulin resistance (IR) are excessive serine phosphorylation of the insulin receptor subunit, mutations of the insulin receptor gene, depletion of intracellular adenosine, post-receptor defect of glucose transport and impaired insulin clearance in the peripheral tissues.

The PCOS Consensus Workshop Group in Rotterdam in which the diagnostic criteria were reviewed, allowing a broader spectrum of PCOS phenotypes to be included in the diagnosis defining PCOS as the presence of at least two of the following criteria after excluding other causes of hyperandrogenism [49], is as follows:

- Oligo-anovulation
- Hyperandrogenism with clinical or biochemical signs
- Polycystic ovary appearance on ultrasound examination

The therapeutic choices will be based on the type and extent of the disorders and if there is a desire for pregnancy.

The goals of the therapeutic action are to reduce circulating androgens and signs of hyperandrogenism, reduce insulin resistance and prevent metabolic complications and decrease cardiovascular risk.

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## References

- [1] Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clinical Epidemiology*. 2013;**6**:1-13
- [2] Jahanfar S, Seppala M, Eden JA, Nguyen TV, Warren P. A twin study of polycystic-ovary-syndrome. *Fertility and Sterility*. 1995;**63**(3):478-486
- [3] Legro RS, Driscoll D, Strauss JF, Fox J, Dunaif A. Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. *Proceedings of the National Academy of Sciences of the United States of America*. 1998;**95**(25):14956-14960
- [4] Kahn CR. The molecular mechanism of insulin action. *Annual Review of Medicine*. 1985;**36**:429-451
- [5] Franks S. Diagnosis of polycystic ovarian syndrome: In defense of the Rotterdam criteria. *The Journal of Clinical Endocrinology and Metabolism*. 1 March 2006;**91**(3):786-789
- [6] Diamanti-Kandarakis E. Polycystic ovarian syndrome: Pathophysiology, molecular aspects and clinical implications. *Expert Reviews in Molecular Medicine*. 2008;**10**:E3
- [7] Genazzani AD, Ricchieri F, Lanzoni C. Use of metformin in the treatment of polycystic ovary syndrome. *Women's Health (London, England)*. 2010;**6**(4):577-593
- [8] Jonard S, Dewailly D. The follicular excess in polycystic ovaries, due to intra-ovarian hyperandrogenism, may be the main culprit for the follicular arrest. *Human Reproduction Update*. 2004;**10**(2):107-117
- [9] Diamanti-Kandarakis E, Argyrakopoulou G, Economou F, Kandarakis E, Koutsilieris M. Defects in insulin signaling pathways in ovarian steroidogenesis and other tissues in polycystic ovary syndrome (PCOS). *The Journal of Steroid Biochemistry and Molecular Biology*. 2008;**109**(3-5):242-246
- [10] Jensterle MJA, Mlinar B, Marc J, Prezelj J, Pfeifer M. Impact of metformin and rosiglitazone treatment on glucose transporter 4 mRNA expression in women with polycystic ovary syndrome. *European Journal of Endocrinology*. 2008;**158**:793-801
- [11] Baillargeon JP, Iuorno MJ, Apridonidze T, Nestler JE. Uncoupling between insulin and release of a d-chiro-inositol-containing inositolphosphoglycan mediator of insulin action in obese women with polycystic ovary syndrome. *Metabolic Syndrome and Related Disorders*. 2010;**8**(2):127-136
- [12] Vittorio Unfer JEN, Kamenov 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**:1849162
- [13] Essah PA et al. Metabolic syndrome in women with polycystic ovary syndrome. *Fertility and Sterility*. 2006;**86**(Suppl 1):S18-S19
- [14] Salehi M et al. Pathogenesis of polycystic ovary syndrome: what is the role of obesity? *Metabolism*. 2004;**53**(3):358-376
- [15] Kiddy DS et al. Differences in clinical and endocrine features between obese and non-obese subjects with polycystic ovary syndrome: An analysis of 263 consecutive cases. *Clinical Endocrinology*. 1990;**32**(2):213-220
- [16] Apronidaze T et al. Prevalence and characteristics of the metabolic



- syndrome in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 2005;**90**(4):1929-1935
- [17] Gambineri A et al. Obesity and the polycystic ovary syndrome. *International Journal of Obesity and Related Metabolic Disorders*. 2002;**26**(7):883-896
- [18] Pasquali R et al. Obesity and the reproductive disorders in women. *Human Reproduction Update*. 2003;**9**(4):359-372
- [19] Snyder BS. Polycystic ovary syndrome (PCOS) in the adolescent patient: Recommendations for practice. *Pediatric Nursing*. 2005;**31**(5):416-421
- [20] Martin ML, Jensen MD. Effects of body fat distribution on regional lipolysis in obesity. *The Journal of Clinical Investigation*. 1991;**88**:609
- [21] Randle PJ, Hales CN, Garland PB, Newsborne EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet*. 1963;**1**:785
- [22] Dunaif A, Finegood D.  $\beta$ -Cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 1996;**81**:942
- [23] Waldstreicher J, Santoro NF, Hall JE, Filicori M, Crowley WF. Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: Indirect evidence for partial gonadotroph desensitization. *The Journal of Clinical Endocrinology and Metabolism*. 1 January 1988;**66**(1):165-172
- [24] Rebar R, Judd HL, Yen SSC, Rakoff J, Venderberg G, Naftolin F. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. *The Journal of Clinical Investigation*. 1976;**57**:1320-1329
- [25] Christman GM, Randolph JF, Kelch RP, Marshall JC. Reduction of gonadotropin-releasing hormone pulse frequency is associated with subsequent selective follicle stimulating hormone secretion in women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism*. 1991;**72**:1278-1285
- [26] Yen SSC, Vela P, Rankin J. Inappropriate secretion of follicle-stimulating hormone and luteinizing hormone in polycystic ovarian disease. *The Journal of Clinical Endocrinology and Metabolism*. 1970;**30**:435
- [27] Bach LA. The insulin-like growth factor system: Basic and clinical aspects. *Australian and New Zealand Journal of Medicine*. 1999;**29**:355-361
- [28] Le Roith D, McGuinness M, Shemer J, Stannard B, Lanau F, Faria TN, et al. Insulin-like, growth factors. *Biological Signals*. 1992;**1**(4):173-181
- [29] Kelly CJ, Stenton SR, Lashen H. Insulin-like growth factor binding protein-1 in PCOS: a systematic review and meta-analysis. *Human Reproduction Update*. 2011;**17**(1):4-16
- [30] Alvarez JA, Ashraf A. Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. *International Journal of Endocrinology*. 2010;**2010**:351-385
- [31] Ngo DT, Chan WP, Rajendran S, et al. Determinants of insulin responsiveness in young women: Impact of polycystic ovarian syndrome, nitric oxide, and vitamin D. *Nitric Oxide*. 2011;**25**(3):326-330
- [32] Trikudanathan S. Polycystic ovarian syndrome. *The Medical Clinics of North America*. 2015;**99**(1):221-235

- [33] O'Reilly MW, Taylor AE, Crabtree NJ, et al. Hyperandrogenemia predicts metabolic phenotype in polycystic ovary syndrome: The utility of serum androstenedione. *Journal of Clinical Endocrinology & Metabolism*. 2014;**99**(3):1027-1036
- [34] Qin KN, Rosenfield RL. Role of cytochrome P450c17 in polycystic ovary syndrome. *Molecular and Cellular Endocrinology*. 1998;**145**(1-2):111-121
- [35] Balen AH, Laven JSE, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: International consensus definition. *Human Reproduction Update*. 2003;**9**:505-514
- [36] Palomba SGF, Falbo A, et al. Structured exercise training programme versus hypocaloric hyperproteic diet in obese polycystic ovary syndrome patients with anovulatory infertility: A 24-week pilot study. *Human Reproduction*. 2008;**23**(3):642-650
- [37] Hoeger KM, Kochman L, Wixom N, Craig K, Miller RK, Guzick DS. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: A pilot study. *Fertility and Sterility*. 2004;**82**(2):421-429
- [38] Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: A comprehensive review. *Endocrine Reviews*. 2009;**30**(1):1-50
- [39] Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A, Licholai T. Evidence for distinctive and intrinsic defects in insulin action in polycystic-ovary-syndrome. *Diabetes*. 1992;**41**(10):1257-1266
- [40] Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ. Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. *Metabolism: Clinical and Experimental*. 1994;**43**(5):647-654
- [41] Nestler JEJD. Decreases in ovarian cytochrome P450c17 alpha activity and serum free testosterone after reduction of insulin secretion in polycystic ovary syndrome. *The New England Journal of Medicine*. 1996;**335**(9):617-623
- [42] La Marca AMG, Paglia T, Ciotta L, Cianci A, De Leo V. Effects of metformin on adrenal steroidogenesis in women with polycystic ovary syndrome. *Fertility and Sterility*. 1999;**72**:985-989
- [43] Coyral-Castel S, Tosca L, Ferreira G, Jeanpierre E, Rame C, Lomet D, et al. The effect of AMP-activated kinase activation on gonadotrophin-releasing hormone secretion in GT1-7 Cells and its Potential Role in Hypothalamic Regulation of the Oestrous Cyclicity in Rats. *Journal of Neuroendocrinology*. 2008;**20**:335-346
- [44] Bailey CJ, Turner RC. Metformin. *The New England Journal of Medicine*. 1996;**334**:574-579
- [45] Nestler JE, Jakubowicz DJ, Reamer P, et al. Ovulatory and metabolic effects of D-chiroinositol in the polycystic ovary syndrome. *England Journal of Medicine*. 1999;**340**:1314-1320
- [46] Huang LC, Fonteles MC, Houston DB, Zhang C, Larner J. Chiroinositol deficiency and insulin resistance. III. Acute glycogenic and hypoglycemic effects of two inositol phosphoglycan insulin mediators in normal and streptozotocin-diabetic rats in vivo. *Endocrinology*. 1993;**132**(2):652-657
- [47] Glueck CJ, Wang P, Fountaine RN. Plasminogen activator inhibitor activity:

An independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. *Metabolism*. 1999;**48**:1589-1595

[48] Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with poly-cystic ovary syndrome. *Human Reproduction Update*. 2006;**12**:673-683

[49] Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertility and Sterility*. 2004;**81**:19-24