

Polycystic Ovary Syndrome and Insulin Resistance

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Abstract

Polycystic ovary syndrome is a complex and heterogeneous disease that involves menstrual dysfunction and reproductive difficulty as well as metabolic problems. Therefore, it was proposed that insulin resistance is the pathophysiological basis for this syndrome. Insulin resistance, as a metabolic disorder linked to anovulation, should be studied in patients who meet with a gynecologist. For this purpose, simple methods to quantify insulin sensitivity are available, and we propose reasonable treatment with dietary or pharmaceutical measures to improve not only the metabolic changes but also clinical hyperandrogenism and fertility.

Keywords: Metabolic syndrome; Polycystic ovary syndrome; Insulin resistance

Introduction

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disease that involves menstrual dysfunction and reproductive difficulty as well as metabolic problems. The expert conference by the European Society for Human Reproduction and Embryology and the American Society for Reproduction Medicine recommended that PCOS be defined when at least two of the following three features were present [1]:

- oligo- and/or anovulation
- hyperandrogenism
- polycystic ovaries

These criteria also recognize that other causes of androgen excess and related disorders should be excluded before confirming the diagnosis of PCOS. This definition is more generic and will probably increase its already high prevalence: it is the most common endocrinopathy in women and affects 7-14% of women of childbearing age worldwide [2]. It was proposed that insulin resistance (IR) is the pathophysiological basis for this syndrome. The primary interest in diagnosing these patients is not to assist in conception but to prevent possible future medical complications, including diabetes mellitus and cardiovascular disease [3].

IR refers to a decrease in the capacity of insulin to exert its biological action in its primary target tissues. This concept is so important that it is currently considered to be a common characteristic of multiple diseases, such as diabetes, dyslipidemia, and hypertension, which together form the basis of metabolic syndrome [4].

A considerable proportion of women with PCOS display IR. The mechanisms responsible for this insensitivity are currently unknown, although it has been postulated that IR results from altered adipose and muscular cell glucose uptake, which is caused by a genetic defect that is independent of obesity. Although IR does not occur exclusively in obese women with PCOS, the incidence is more frequent among these patients because PCOS may be an additional cause of insulin resistance [5]. In addition, the potential for genetic predisposition indicates that the patient's direct family members may also be affected by this condition, and they must be warned of this risk [6].

Similarly, a frequent association between IR and hyperandrogenism has been observed, although the cause and effect relationship is not well understood. A chronic androgen effect on the physiology of

the adipocyte and the homeostasis of glucose has not been detected, although tests have indicated that hyperinsulinism tends to be a cause rather than a result of excess androgens [7,8].

In practice, it is important to recognize the occurrence of IR among women with PCOS. Furthermore, various studies have attempted to demonstrate that anovulatory patients with some extent of IR display greater difficulty in follicle development with exogenous follicle stimulating hormone (FSH) than women with normal ovulation or who do not have IR. The short-term benefit of an insulin decrease during anovulation has been repeatedly demonstrated, both in women with an appropriate diet and in women who were treated with pharmaceutical agents. Thus, some clinics prefer to delay fertility treatment until the patients have reached an appropriate weight or have leveled out their insulin numbers [9].

A number of publications have expressed the possibility that a woman with PCOS may display a greater risk of suffering cardiovascular disease or diabetes at later age. In this context, it would be helpful to investigate these effects in future studies. However, even with this knowledge gap, there is existing evidence of the relationship between these effects: type 2 evidence for adult diabetes and early arterial disease, and type 3 evidence for hypertension or dyslipidemia [10-12].

Clearly, IR and hyperinsulinism are important factors related to PCOS due to the etiological implications and because different therapeutic strategies should be used with these markers. We should keep in mind that for certain patients who seek an anovulation consult, their families should be warned, and kept under long-term monitoring due to the special risk of suffering from diabetes or arteriosclerosis.

Diagnosis of IR in Patients with PCOS

The diagnostic of IR can be suspected by any of the data showed in Table 1

The hyperinsulinemic euglycemic clamp technique is considered

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• anovulation and hyperandrogenism
• prior gestational diabetes
• relatives with diabetes mellitus
• obesity
• Upper waist more than 88 cm
• Hyperglycemia
• Hyperlipidemia
• Hypertension
• Adolescent with persistent anovulation

Table 1: Signs that suspect IR

to be the gold standard for quantifying sensitivity to insulin. However, the difficulty of performing this technique in clinical practice has led to the development of other, simpler techniques (Table 2) [13,14]. For example, *Homeostatic Model Assessment* (HOMA) is a method based on a mathematical model that provides a semi-quantitative measure of the sensitivity to insulin. The normal range of HOMA values is between 2 and 3, although there is no consensus to establish a limit to begin treatment. On average, we have used a threshold value of 3.2.

IR, PCOS and Pregnancy

On the other hand, pregnancy is characterized as a temporary condition of insulin resistance that occasionally leads to gestational diabetes or complicates pre-existing diabetes. Some authors have found an association between PCOS and glucose intolerance during pregnancy. In the absence of insulin measurements, a risk marker for diabetes mellitus among patients with PCOS may be the appearance of certain disorders related to carbohydrate metabolism during pregnancy. In fact, it is known that the appearance of glucose intolerance during pregnancy increases the risk of suffering from adult diabetes by 50%. As a result, a positive result in routine examinations in clinical obstetrics to identify patients with glucose intolerance not only achieves an improvement of the perinatal outcome, but can also be considered to be a cardiovascular and metabolic risk marker. A history of PCOS can be considered to be a risk marker of gestational diabetes based on the available evidence without implying other pregnancy complications, such as fetal macrosomia, when good metabolic control is performed by the pregnant woman and she does not excessively increase her weight [15].

Treatment of IR

The first steps after diagnosing a patient with PCOS and IR should be to recommend a change in diet together with the investigation and treatment of other cardiovascular risk factors (dyslipidemia, hypertension, diabetes) However, the persistence of HOMA values greater than 3.2 after 6 months on a diet and with exercise is an indication for drug treatment [8].

Currently, a therapeutic arsenal is available for drug treatment with proven effectiveness in improving sensitivity to insulin. Metformin in particular has shown the greatest success. There are other preparations available within the glitazone, inositol, and alpha-glucosidase inhibitor families. In general, we refer to metformin when discussing IR treatment, and even when there is no concrete indication of IR in the patient's records, there are reasons to use this agent as part of a therapeutic treatment, not only among patients with metabolic syndrome but also those with obesity, sterility, oligomenorrhea or hirsutism [16].

The mechanism of metformin action is fundamentally centered on stopping hepatic gluconeogenesis; however, its hypoglycemic effect is limited to patients with hyperglycemia. An improvement in

insulin sensitivity has also been observed, along with a decrease in the intestinal absorption of glucose, an increase in its peripheral uptake and utilization, and also a decrease in serum cholesterol, triglycerides, plasminogen activator inhibitor-1 (PAI-1) and arterial pressure. In contrast to other oral anti-diabetic agents, metformin does not alter pancreatic insulin secretion. There is also no known stimulating effect on germ cells or the ovarian stroma, resulting in an interesting connection with ovulation-inducing medicines [17].

In most studies of patients who have PCOS, between 1500 and 2000 mg of metformin has been given daily, although no optimal dosage has been established. We recommend starting with this dosage, split into two doses (during mealtimes), to avoid the frequent gastrointestinal effects which occur with metformin. This dosage may be maintained for 14 days for patients with a poor tolerance of this pharmaceutical agent, although it may be convenient to increase the dosage to 1700 mg/day for a duration that is judged necessary for treatment [18-22].

The use of metformin among women with PCOS has been accompanied by an improvement in IR, ovarian functions or both, which leads to a number of interesting perspectives (Table 3). However, neither clinical trials, reviews, nor even therapeutic guides have made it sufficiently clear who benefits most from the use of this agent. In some articles, more benefit over the combined hormonal contraceptives has not been observed [23,24].

This is perhaps because the design of these metformin clinical trials has not discriminated between excess weight, fat distribution, and IR itself (it is curious that most patients do not even have a diagnosis of IR). For this reason, it seems logical that women with IR who have not improved their diet or started exercising are the individuals who will benefit the most from taking this agent [25].

Another controversial aspect in the use of metformin has been the decision to continue its use during pregnancy (which can occur without the help of another treatment). The FDA has designated this agent as category B, which indicates that the safety for pregnant women has not been definitively established, although there is no experimental evidence of teratogenicity. To adequately understand what is really involved in a correction of hyperinsulinism, some studies have observed that the continuation of treatment during the first months of pregnancy protects against miscarriages, perhaps because metformin can rectify the state of hypercoagulability (an increase in PAI-I), which is displayed as an excess insulin level [26,27].

• Basal Glucose/Insulin < 4,5
• Basal Insuline > 16 mU/l
• Abnormal oral glucose test
• HOMA= basal insuline (mcU/ml) x basal glucose (mg) / 405
• Insuline sensibility= basal insuline / 91 x 0,05551 (normal ≥1)
• HOMA β cell= 360x basal insulin / basal glucose (mg) – 63 (normal=100%)

Table 2: Methods to diagnose IR

• Improvement of the insulin sensitivity
• Decrease of total and free testosterone
• Decrease of luteinizing hormone (LH)
• Increase of steroid hormone binding globulin (SHBG)
• Regularity of menstrual cycles
• Ovulation in clomiphene-citrate resistant PCOS
• Decrease of ovarian hyperstimulation syndrome
• Decrease of pregnancy loss rate

Table 3: Summary of metformine benefits

In summary, IR, as a metabolic disorder linked to PCOS, should be studied in patients who meet with a gynecologist. For this purpose, this short revision shows the simple methods to quantify insulin sensitivity and proposes reasonable treatment with dietary or pharmaceutical measures to improve not only the metabolic changes but also clinical hyperandrogenism and fertility.

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