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Recent achievements in understanding the etiopathogenesis of insulin resistance and its connection with polycystic ovarian syndrome

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Abstract. *Polycystic ovary syndrome (PCOS) is a widespread reproductive disorder that affects ovarian dysfunction and affects various metabolic processes in the body. PCOS manifests itself as hyperandrogenism, polycystic ovary disease and anovulation and is currently one of the leading causes of menstrual complications and infertility in women. But, in addition to reproductive disorders, PCOS is often accompanied by hyperinsulinemia, dyslipidemia, overweight or obesity, which is a risk factor for diabetes and cardiovascular disease. Despite the prevalence of this disease and the long history of its study, the problems of etiology, pathogenesis and treatment of this syndrome have not been fully resolved. Currently, there is no single treatment regimen for PCOS, and it depends to a large extent on the prevailing symptoms. Moreover, the mechanism by which insulin resistance can lead to reproductive dysfunction requires further investigation.*

Purpose: *present a modern point of view on etiopathogenesis, clinical and biochemical relationships, as well as the main diagnostic markers of insulin resistance in PCOS and summarize the results of research in this area over the past few years.*

Relevance of the topic. *It is known that the frequency of detecting disorders of carbohydrate-lipid metabolism in PCOS is significantly higher than in a healthy population of women of reproductive age [37] [38]. Nevertheless, insulin resistance often goes unnoticed and the percentage of cases of late diagnosis of insulin metabolism disorders in PCOS and the subsequent development of complications remains at a high level. Therefore, the main objective of this review is to provide concepts of the relationship between insulin resistance and PCOS, which is important for a correct understanding of clinical objectives and the development of individual treatment regimens.*

Materials and methods. *The analysis and generalization of modern medical literature in the electronic library systems PubMed, Elibrary.ru, Cochrane, Medline, HINARY, etc., including data on the etiopathogenetic factors of the development of PCOS, as well as on the links of PCOS with metabolic abnormalities and, in particular, with resistance to insulin.*

A total of 296 publications (2011 - 2021) were found that met the search criteria.

Keywords: *polycystic ovary syndrome, insulin resistance, infertility, polycystic ovary disease, reproductive disorder.*

Incomplex approach and delayed diagnosis of metabolic disorders in PCOS sometimes leads to irreversible reproductive (infertility, miscarriage) and endocrine (diabetes mellitus, hormonal changes, obesity) disorders. Also, serious concomitant manifestations in PCOS are psychoemotional disorders, increased cardiovascular risks and risks of venous thrombosis [24]. Insulin resistance plays an important role in the development of all these complications.

The pathophysiological mechanisms of PCOS development are not fully understood, but it is known that they include a complex of interactions between gonadotropins, ovaries, androgens, and insulin. Insulin resistance (IR) leads to compensatory hyperinsulinemia (HI), which stimulates androgen production by the ovaries in women genetically predisposed to PCOS [43].

According to some authors, the secretion of insulin by the beta cells of the pancreas is increased in order to compensate for insulin resistance. This HI mechanism in polycystic ovary syndrome (PCOS) may be adaptive [29].

HIs play an important role in androgen hypersecretion and the development of PCOS. This follows from the observation of a decrease in fasting insulin levels during therapy with insulin sensitizers, which is accompanied by a decrease in the level of androgens and an improvement in ovarian function [8]. Increased androgen production is one of the consequences of HI.

One of the main theories regarding the relationship between insulin resistance and PCOS is that IR underlies the pathogenesis of both metabolic syndrome and PCOS [46].

It is assumed that IR can result from disturbances at one of three levels: pre-receptor, receptor, and post-receptor [48].

IR at the prereceptor level can develop due to mutations in the coding gene for insulin, the presence of autoantibodies to insulin, or due to the synthesis of proinsulin instead of insulin by the pancreas. However, it is still unclear whether pancreatic dysfunction in PCOS is primary or secondary to IR.

At the receptor level, IR can be the result of a disturbance in signal transmission from the insulin receptor, which uncouples the action of insulin and the corresponding insulin receptor, the IRS protein.

IR in PCOS can also develop in visceral adipose tissue at the post-receptor level, which is characterized by a decrease in the amount of the carrier protein.

The close relationship of PCOS with insulin resistance explains the alertness of doctors about the possible adverse metabolic consequences of taking hormonal contraceptives, since they are aimed more at relieving the symptoms of PCOS.

Quite a lot of studies have been carried out on this topic, but it is problematic to fully generalize their results: the data are contradictory, probably due to the different types of drugs used, different sample parameters (age, anthropometric and genetic differences), the assessment methods used and the duration of observation.

Pathogenetically grounded treatment of patients in these groups involves not only the appointment of hormonal drugs in order to regulate the menstrual cycle, but also the correction of the pathophysiological processes accompanying insulin resistance leading to ovarian dysfunction. Otherwise, metabolic disorders can cause more serious consequences and affect not only the reproductive system, but also cause diseases of the cardiovascular, nervous, endocrine and other systems [50].

Observations show that the combination therapy of combined oral contraceptives with metformin (a drug that increases the sensitivity of peripheral receptors to insulin and the utilization of glucose by cells) in women with PCOS without clinical manifestations and glucose tolerance increases insulin sensitivity, which in turn leads to an improvement in temporary and quantitative indicators of insulin secretion and a decrease in the integral production of insulin upon stimulation with glucose [49]. The consequence of changes in carbohydrate metabolism is a decrease in the degree of compensatory HI, which was present against the background of insulin resistance characteristic of PCOS.

At the biochemical level, insulin stimulates the hormonal activity of all parts of the ovary: granulosis, flow, stroma, which leads to an increase in the synthesis of all sex steroids. However, the most significant effect of insulin on increasing the activity of 17α-hydroxylase and 17α-lyase, key enzymes in the biosynthesis of androgens in the ovaries. Activation of steroidogenesis also occurs due to an increase in the number of luteinizing hormone (LH) receptors in granulosis, caused by hyperinsulinism. The growth effects of insulin on the ovary are manifested in the stimulation of theca cells, which, in addition to hyperandrogenism, leads to the formation of a polycystic structure and an increase in its volume. An excess of androgens inhibits folliculogenesis, causing premature atresia of the follicles.

The central mechanisms of insulin action are sensitization of pituitary cells to the action of gonadotropin-releasing hormone (GnRH). LH secretion is more sensitive to its effects, in addition, the half-life of LH is longer than that of follicle stimulating hormone (FSH).

The consequence of this is an imbalance of gonadotropins due to a predominant increase in the synthesis of LH. This condition is aggravated by the influence of monotonic levels of

ovarian estrogens, which inhibit FSH more strongly. A high basal LH level, in addition to overstimulation of theca, inhibits follicular development, causing chronic anovulation.

Summarizing the data, we can say that ovarian steroidogenesis in insulin resistance is characterized by excessive formation of androgens, and the effect of hyperinsulinism on the gonadotropic activity of the pituitary gland is to increase the level of LH secretion, which leads to an increase in the vicious circle leading to anovulation, oligomenorrhea, hyperandrogenism, polycystic morbidity.

The above-mentioned features of the functioning of the reproductive system in IR form a typical symptom complex of PCOS: chronic anovulation, hyperandrogenism, polycystic morphology of the ovaries.

Metabolic syndrome is characterized by the presence of tissue insulin resistance, hyperinsulinemia, impaired glucose tolerance, arterial hypertension, dyslipidemia, as well as abdominal obesity and hyperuricemia. Accordingly, when confirming the diagnosis of polycystic ovary syndrome, patients should be examined for the above associated diseases. It is important to note that the central role of insulin resistance is traced in the pathogenesis of all of the above diseases. The prevalence of polycystic ovary syndrome among women of reproductive age ranges from 4% to 12%, and metabolic syndrome - from 3% to 23% [44]. This is a fairly high degree of prevalence, which determines the importance of studying and timely diagnosis of associated diseases.

Currently, there are opinions regarding one of the important metabolic disorders in patients with PCOS, which also indirectly affects the development of insulin resistance. The central role of this disorder is occupied by the so-called "mitochondrial dysfunction", which is closely related to oxidative stress (OS). Mitochondria play the most important role in the metabolic activity of cells, and disruption of their functioning leads to profound changes in cellular activity. The universal process of catabolism of carbohydrates and fats occurs in mitochondria resulting in aerobic processes of the Krebs cycle in the matrix and oxidative phosphorylation in the membrane complex of high-energy molecules (adenosine triphostaphate, ATP), which provides energy to all cells. When any of these processes are disturbed, reactive oxygen species (ROS) can accumulate, causing an increase in oxidative stress (OS). This stimulates the inflammatory response of cells, triggering apoptosis, and, conversely, in OS conditions, the generation of ROS by mitochondria is autocatalytically enhanced, and the processes of OS and apoptosis are further aggravated in the future [13] [15] [18] [33].

A wide range of publications presented in the literature demonstrates the important role of mitochondrial dysfunction imbalance in the formation of a number of disorders associated with PCOS. OS and decreased antioxidant activity in women with PCOS contribute to IR. In this

regard, OS markers are advisable to use in the complex diagnosis of PCOS and the prediction of associated complications. The issue of using antioxidants in the complex correction and prevention of disorders accompanying PCOS deserves special attention.

From all of the above, it can be argued that until now there is no consensus about whether metabolic syndrome is a simple combination of risk factors or there is some one reason that serves as a triggering factor for the galaxy of pathological conditions that make up this syndrome - genetic anomaly, abdominal obesity, dysfunction endothelium, oxidative stress, or inflammation.

Without denying the importance of insulin resistance in the development of PCOS, it should be emphasized that, nevertheless, the main marker of this syndrome is hyperandrogenism, and not IR, since IR is not the only mechanism for the formation of hyperandrogenism.

Methods for detecting metabolic syndrome

1. Glucose tolerance test with determination of insulin levels.

2. Lipid metabolism disorders (total CS, TG, CS HDL, CS LDL, CS VLDL).

3. Purine metabolism disorders (uric acid).

4. Oxidative stress (7 indicators): malonic dialdehyde, total coenzyme Q10 (ubiquinone, oxidized form), vitamin E (alpha-tocopherol), vitamin C (ascorbic acid), vitamin A (retinol), beta-carotene (trans-form), glutathione free

Assessment of hormonal status

Determination of hormones on the 3rd - 5th day of the spontaneous cycle: total testosterone, SHBG (with the calculation of the index of free androgens), prolactin, LH, FSH, daily urinary excretion of free cortisol.

Morphofunctional research methods

Also, to detect metabolic syndrome, it is important to conduct an ultrasound scan of the liver, adrenal glands, pelvic organs, mammary glands and calipermetry (measuring the thickness of subcutaneous fat in the region of the anterior abdominal wall and triceps muscle of the shoulder).

Identifying insulin resistance

1. Study of the concentration of glycosylated hemoglobin;
2. Standard glucose tolerance test - blood sugar is determined on an empty stomach and 2 hours after oral ingestion of 75 g of glucose;
3. Study of lipid profile (cholesterol, triglycerides, HDL, LDL).

For a unified assessment of insulin resistance, the HOMA-IR indicator was developed, measured in arbitrary units (formula 1)

$$HOMA - IR = \frac{\text{fasting glucose (mmol/l)} \times \text{fasting insulin (μU/l)}}{22.5}$$

Formula 1 – Calculation of the index of insulin resistance

If the HOMA-IR index is more than 2.7, then we can talk about insulin resistance.

A literature review of the relationship between insulin resistance and PCOS has shown that insulin is a reproductive as well as a metabolic hormone that acts as a co-gonadotropin through its cognate receptor to modulate ovarian steroidogenesis. This effect may persist despite resistance to the metabolic effects of insulin in the periphery, as well as on the ovaries, which is an example of selective insulin resistance. Insulin signaling to the CNS is also critical for ovulation. Human studies have confirmed that hyperinsulinemia increases androgen production in PCOS. Intrinsic abnormalities in steroidogenesis appear to be necessary for this action of insulin to manifest, because a decrease in insulin levels does not affect circulating androgen levels in normal women.

Since insulin has a direct effect on androgen production in the ovaries in vitro, insulin resistance may play a decisive role in the pathophysiology of PCOS [43].

PCOS requires changes in terminology, diagnosis and treatment. Particular attention should be paid to metabolic disorders, venous and arterial risks. The drugs used for PCOS, especially COCs, should be relatively metabolically neutral.

Also, it must be remembered that, like any complex endocrine pathology, polycystic ovary syndrome is a serious diagnosis that requires examination for a number of associated diseases and an understanding of the entire complex of pathogenetic mechanisms in order to normalize both the hormonal and metabolic status of patients in general.

Thus, insulin resistance can directly and indirectly affect the development of PCOS, and, in some cases, be one of the main causes of this syndrome. However, there are no confirmed clinical studies on this issue in the medical community, since the mechanisms of IR development are not fully understood. However, this does not negate the fact that it is necessary to take into account the possibility of inheritance and early development of IR and the prospects of its influence on the development of PCOS, since IR, acting as a compensatory reaction aimed at protecting the body, can acquire a pathological orientation, contributing to various metabolic disorders directly or indirectly. Perhaps, in the future, testing for insulin resistance in children and adolescents before menarche will be a mandatory routine examination.

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