TREATMENT OF METABOLIC ALTERATIONS IN POLYCYSTIC OVARY SYNDROME

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TREATMENT OF METABOLIC ALTERATIONS IN POLYCYSTIC OVARY SYNDROME (Abstract). Polycystic ovary syndrome is a common endocrinopathy characterized by oligo ovulation or anovulation, signs of androgen excess and multiple small ovarian cysts. It includes various metabolic abnormalities: insulin resistance, hyperinsulinemia, impaired glucose tolerance, visceral obesity, inflammation and endothelial dysfunction, hypertension and dyslipidemia. All these metabolic abnormalities have long-term implications. Treatment should be individualized and must not address a single sign or symptom. Studies are still needed to determine the benefits and the associated risks of the medication now available to practitioners. Keywords: POLYCYSTIC OVARY SYNDROME, METABOLIC SYNDROME, COMBINED ORAL CONTRACEPTIVES.

Polycystic ovary syndrome (PCOS), a frequent endocrine dysfunction among women of reproductive age, has important short- and long-term metabolic consequences thus affecting the quality of life. According to the Rotterdam consensus, PCOS is defined by two of the following three criteria: irregular or absent ovulation, androgen excess (clinical or laboratory findings, following the exclusion of other pathologies, such as androgen-secreting tumors, Cushing's syndrome etc) and enlarged ovaries with at least 12 antral follicles each (1). This syndrome is characterized by various metabolic abnormalities: insulin resistance (IR), hyperinsulinemia, impaired glucose tolerance (IGT), visceral obesity, inflammation and endothelial dysfunction, hypertension and dyslipidemia. The management of these imbalances and their impact on health is still a challenge.

Etiology. The etiology remains unclear, but it involves interactions between endocrine (hypothalamic, ovarian, adrenal), genetic, environmental and behavioral factors (2). The sequence of the phenomena is unclear: it has not been established whether hyperandrogenism results from hyperinsulinemia secondary to insulin resistance (IR) or vice versa, but increasingly more studies show that hyperinsulinemia plays an important role in the pathogenesis of this syndrome.

Physiopathogenesis. Women with PCOS have certain metabolic and cardiovascular abnormalities. Obesity is common...
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among them and is associated with increased IR, IGT and dyslipidemia. IR is present in 60-80% of women with PCOS, and is more prevalent among the obese ones. Obesity seems to be the main factor for the development of IR, but defects in post-receptor intracellular signaling also seem to play a role. IR and the resulting hyperinsulinemia are found in both normal weight and overweight or obese women and significantly increase the prevalence of IGT and diabetes mellitus type 2 (DM2) in women with PCOS. Up to 35-40% of women with PCOS have IGT and 10% will develop DM2 in the third and fourth decade of life. IGT and DM2 are common among women with PCOS, and significant percentage of teenage women (mainly obese) are at risk of developing these diseases.

Dyslipidemia is another metabolic abnormality in women with PCOS and includes: increased levels of total cholesterol, LDL-C and triglycerides (TG) and low levels of HDL-C. Genetic and ethnic factors, hyperandrogenemia and obesity are linked to dyslipidemia in women with PCOS.

In women with PCOS, especially in the presence of obesity, elevated levels of the markers of cardiovascular disease have been reported (C-reactive protein (CRP), endothelin-1, adiponectin, homocysteine, plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor and markers of oxidative stress.

There is a substantial overlap between PCOS and the metabolic syndrome (MS), a group of metabolic disorders related to increased cardiovascular risk (3). The International Diabetes Federation consensus (2006) definition of MS is central obesity (waist circumference) and 2 of the following criteria: raised triglycerides: over 150 mg/dL (1.7 mmol/L), low HDL-C: below 40 mg/dL (1.03 mmol/L) in men and below 50 mg/dL (1.29 mmol/L) in women, raised systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg, raised fasting blood glucose or DM2. The prevalence of MS in PCOS varies between 1.6% and 43% depending on the population studied (4, 5). In PCOS, the most common features are decreased HDL-C, obesity and high blood pressure (4). In the general population, MS leads to a 2-fold increase in cardiovascular risk. In women with PCOS there is limited evidence of cardiovascular events of increased heart disease mortality.

Given the multifactorial pathogenesis of PCOS, a multidirectional therapeutic strategy should be established. Currently there are many drugs that can be used, but which, although may be beneficial for certain metabolic aberrations, can aggravate other abnormalities. Some treatment options include: oral contraceptives and antiandrogens, oral antidiabetic agents (metformin, thiazolidinedione), statins, acupuncture, various dietary supplements (vitamin D, vitamin B1, folic acid) or hygienic-dietary regimes.

TREATMENT

1. CONTRACEPTIVES. Oral contraceptives have been the treatment of choice of PCOS for many years, especially combined oral contraceptives (COCs), but progestin only minipills have also been used. COCs contain an estrogen component (ethynyl-estradiol or estradiol) and a progestosterone, which varies according to the type of pill. In most PCOS women, oral contraceptives resulted in amelioration of clinical manifestations, such as normalization of menstrual cycles, hirsutism and acne relief, and sometimes to regression of
male pattern alopecia. The effects are assigned to the decreased LH secretion, inhibition of ovarian and adrenal androgen production, and reduced free testosterone levels due to increased liver production of SHBG.

Contraceptives are not used specifically for the treatment of metabolic alterations, even though they inflict various influences on the metabolism. On the contrary, some studies suggest that oral contraception may have a negative effect on metabolic abnormalities in PCOS women.

There is an association between their use and development of IR, which suggested a potential adverse effect on the metabolism, but the results of the studies are yet inconclusive. Their influence on carbohydrate metabolism varies from DM to its improvement. Studies show that low-dose estrogen COCs (<50mcg) are associated with decreased risk for DM2, but investigations are still needed in order to determine the progestogen with the lowest impact on carbohydrate metabolism. Studies on the impact of COCs on lipid metabolism have limitations due to their heterogeneity, leading to inconsistent results. In general, it has been shown that treatment with oral contraceptives leads to an increase in LDL-C, total cholesterol, HDL-C and TG (6). Minipill administration seems not to interfere with lipid parameters (7). Increased TG seems to be the most common side effect of contraceptive treatment (6,7). The potential effect of this type of treatment appears to be the result of the action of estrogen on liver, by lowering TG clearance, so COCs with lower estrogen doses may lead to a lower increase of TG levels and transdermal systems might not affect the lipid profile (8). In addition, various COCs lead to increased HDL-C levels, the effect being attributable to the action of estrogen component on the apolipoprotein AI gene expression in liver cells. A Cochrane review (9) analyzed the results of four randomized trials comparing oral contraceptives with metformin and showed no differences between the 2 types of treatment in clinical metabolic effects (development of DM2 and cardiovascular diseases) and biological effects (insulin, glucose, total cholesterol), the only difference being the increase of TG in contraceptive therapy as compared to the metformin therapy.

Regarding hypertension, COCs can induce high blood pressure and are therefore contraindicated in hypertensive women with PCOS and should be stopped if hypertension develops during treatment.

The effect of oral contraceptives on weight is still controversial: some studies found an increase in body weight while others showed no differences in weight (10).

In conclusion, oral contraception may have a negative effect on metabolic abnormalities in PCOS women and the long term benefits are unclear, especially in patients with IGT, DM2 and dyslipidemia. The decision to administer this treatment must take into account the patient's phenotype and history.

2. **ANTIANDROGENS.** In women with PCOS, hyperandrogenemia was suggested as an initiating factor of metabolic abnormalities. Androgens exert their effects through the androgen receptor, which is expressed in the visceral adipose tissue, acting through competitive inhibition and by decreasing androgen production. In addition, the direct effect on insulin signaling pathway appears to contribute directly to IR in PCOS. Antiandrogens, such as cyproterone acetate, spironolactone and
flutamide, have been used in women with PCOS mainly for the treatment of hirsutism. They are generally used in combination with oral contraceptives, having synergistic effect, but also because a contraceptive method during the treatment with antiandogens is required because of the potential feminization of male fetuses.

Cyproterone acetate is a progestational antiandrogen which competitively inhibits the binding of testosterone and its more potent conversion product 5α-dihydrotestosterone to the androgen receptor.

Spironolactone is an aldosterone antagonist and a competitive inhibitor of the androgen receptors. Its use leads to the inhibition of androgen production and of the action of 5α reductase. In normal weight women it increases HDL-C and lowers TG (11).

Flutamide is a selective androgen receptor with progesterone-like activity. It reduces the conversion of testosterone to its more active metabolite, dihydrotestosterone, in the target tissues. In patients with PCOS it improves the androgenic manifestations. The effect on carbohydrate metabolism is insignificant, but it lowers total cholesterol, LDL-C and TG, independent of body mass. Used in conjunction with COC and metformin it causes a sharp decrease in LDL-C and increase in HDL-C, but does not prevent TG increase associated to COCs (12).

3. ORAL ANTIDIABETICS. The strong association between IR and PCOS led to the use of drugs that increase the sensitivity to insulin ("insulin sensitizers") in the treatment of this syndrome.

Metformin, a biguanide, acts mainly by suppression of hepatic gluconeogenesis, but also increases peripheral insulin action in skeletal muscle and decreases glucose uptake from the digestive tract, without having a direct effect on pancreatic insulin production. It improves the lipid profile through various mechanisms and directly inhibits thecal cell androgen production.

In women with PCOS, metformin appears to improve the cardio metabolic parameters by increasing insulin sensitivity, lowering blood glucose and androgenemia, but these effects are more obvious if there are associated with lifestyle changes. Metformin may normalize appetite in obese women with PCOS through normalization of neuropeptide Y, which is low in women with PCOS.

Some studies have shown that patients with PCOS and hyperinsulinemia treated with metformin benefited from a significant decrease in total cholesterol, LDL-C and TG and increased HDL-C, but these benefits have not been demonstrated in patients with severe obesity. Metformin appears to improve some atherogenic factors: endothelin-1, adhesion molecules, CRP, advanced glycation products (AGE).

Other drugs that increase insulin sensitivity are thiazolidinedione (glitazones), which act by binding to and activating the PPAR-gamma receptor (peroxisome proliferator-activated receptor gamma). Pioglitazone is the only one that can be used in Europe today. There is insufficient evidence of the metabolic benefits in women with PCOS, although pioglitazone monotherapy in obese women with PCOS improves the lipid profile (13) and decreases the serum PAI-1 and CRP levels.

4. OTHER THERAPEUTIC METHODS. Statins act by the selective inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is involved in the biosynthesis of cholesterol. In
women with PCOS, statins have different effects, other than reducing lipids (especially LDL-C): they reduce the thecal production of androgens and steroidogenesis (14) and the effects of RI and associated hyperinsulinemia, have antioxidant and anti-proliferative effects, and appear to improve the cardiovascular morbidity and mortality associated with PCOS. However, they are teratogenic and cannot be used in women with PCOS who are planning a pregnancy.

As to the use of acupuncture in women with PCOS, although clinical trials are lacking, animal studies show that electro acupuncture could improve the cardio metabolic abnormalities in PCOS: it activates muscle fibers (which increase blood flow, peripheral insulin sensitivity and peripheral glucose utilization), stimulates the release of neuropeptides in the central nervous system (β-endorphins) and could reduce sympathetic activity, which results in lower levels of circulating testosterone (15).

In women with PCOS, low levels of vitamin D are associated with IR, obesity, IGT and MS, suggesting a possible role of this vitamin in the pathogenesis of PCOS (16). Administration of vitamin D in PCOS improves the lipid profile and IR, but further studies are needed.

It has been shown that the administration of vitamin B12 in patients with MS decreases IR. In women with PCOS, IR, obesity and elevated serum homocysteine levels are associated with low serum concentrations of vitamin B12 (17), suggesting a possible role of this vitamin in the treatment of PCOS.

**CONCLUSIONS**

Polycystic ovary syndrome is characterized by multiple metabolic abnormalities and has significant long-term implications. The therapeutic strategy encompasses numerous approaches and drugs, as the physiopathogenesis of the syndrome is being better understood.

In our opinion, the treatment should be individualized, must not address a single sign or symptom and should also take into account the possible side effects. We believe that further studies are still needed to determine the benefits and risks of medicines that are now available to the practitioners, as well as the long-term cardiovascular implications. Given the complexity of the syndrome, we advocate a multidisciplinary treatment approach (gynecologist, endocrinologist, cardiologist, nutritionist).

**REFERENCES**


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**NEWS**

**CLINICAL AND MICROBIOLOGICAL EVALUATION OF SCALING AND ROOT PLANING PER QUADRANT AND ONE-STAGE FULL MOUTH DISINFECTION ASSOCIATED WITH AZITHROMYCIN OR CHLORHEXIDINE**

Conflicting data about the protocol of choice for non-surgical periodontal therapy with adjuvant use are still reported. The study realized by a group of brazilian researchers aimed to evaluate, through clinical and microbiological parameters, the systemic use of azithromycin as adjuvant to non-surgical periodontal treatment performed by one-stage full-mouth disinfection within 24 hours or conventional quadrant scaling in four weekly sections. In the randomized controlled trial, 85 patients diagnosed with chronic periodontitis underwent different treatment protocols, divided in 6 groups: 3 full-mouth disinfection groups (with no adjuvants, with chlorhexidine and with azithromycin) and 3 weekly sections groups (with no adjuvants, with chlorhexidine and with azithromycin). Clinical periodontal parameters, total and quantitative bacterial counts of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, and *Streptococcus oralis* were measured through real-time polymerase chain reaction at baseline, 90, and 180 days after treatment. In all groups, it was observed a significant reduction in the % of periodontal diseased sites, gingival index, plaque index, and clinical attachment level gain at 90 days of treatment, demonstrating effectiveness of the treatment, independently of the adjuvant. The full-mouth disinfection with chlorhexidine group showed higher reduction in probing depth and % periodontal diseased sites, as well as lower total bacterial count than all the other groups at 180 days. In conclusion, the adjuvant use of azithromycin did not provide any significant benefit, independently of the treatment protocol. The adjuvant use of the chlorhexidine showed a more expressive and significant improvement on clinical and microbiological parameters, especially in the full-mouth disinfection protocol, followed by weekly sections (Campideli Fonseca D, Cortelli JR, Cortelli SC, Miranda Cota LO, Machado Costa LC, Moreira Castro MV, Oliveira Azevedo AM, Costa FO. Clinical and Microbiological Evaluation of Scaling and Root Planing per Quadrant and One-Stage Full Mouth Disinfection Associated With Azithromycin or Chlorhexidine: A Clinical Randomized Controlled Trial. *J Periodontol.* 2015 ; 7: 1-16).

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