December 30, 2020

PharmacologyOnLine

Special issue • 2020 • vol.3 • 214-221

PCOS AND INSULIN RESISTANCE: THE ROLE OF KETOGENIC DIET

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Abstract

Polycystic ovary syndrome (PCOS) is a hormonal disorder of reproductive age characterized by irregular menstrual periods and excessive levels of male hormones (androgens), representing one of the most common causes of infertility in women. Excess insulin might increase androgen production, causing difficulty with ovulation and seems to play an important role in PCOS pathogenesis.

The purpose of this review article is to provide an overview of the polycystic ovary syndrome (PCOS) and hyperandrogenism determined by the insulin resistance and reaffirm the role of correct rules, as proper nutrition and adequate physical activity, in order to prevent weight gain and counteract insulin resistance, improving the metabolic and hormonal picture and favoring the restoration of physiological conditions.

Keywords: *Polycystic ovary syndrome, Hyperandrogenism, insulin resistance, therapy, ketogenic diet.*

Introduction

PCOS is an endocrine disorder characterized by anovulation and hyperandrogenism, involving 5-10% of the female population in reproductive age.
Insulin resistance and compensatory hyperinsulinemia are important features of PCOS and seem to play a role in the pathogenesis (1). This acquisition leads to a new view of PCOS as a metabolic pathology that manifests itself primitively as a reproductive endocrinopathy. In around 50% of women with PCOS there is present an android-type obesity, characterized by a fat distribution in the central part of the body.

Diagnostic Criteria

The syndrome manifest a variety of signs and symptoms leading to a considerable confusion in diagnosis and clinical trial. In 1990 the National Institutes of Health identified the presence of:

- Chronic anovulation,
- Hyperandrogenism
- Polycystic ovaries morphology

PCOS represents a higher risk for cardiovascular, metabolic and other comorbidities and appropriate evaluation and interventions need to be done.
In 2003 the Rotterdam ESHRE (European Society of Human Reproduction and Embryology) / ASRM (American Society of Reproductive Medicine) proposed a revision of the diagnostic criteria, defining as PCOS the presence of at least two of the following criteria (1,2):

- Oligo-anovulation hyperandrogenism (clinical or laboratory signs);
- Polycystic ovary (morphological sign found on ultrasound examination) with the exclusion of congenital adrenal hyperplasia, Cushing's syndrome and androgenic adrenal or ovarian tumors.

At the ultrasound examination the most sensitive criteria for the diagnosis were the increased volume (> 10mL) and the presence of at least 10 follicles with a diameter of 2- 9mm, evaluated both in longitudinal and transverse scanning (3).

The peripheral distribution of the follicles and ovarian stroma hypertrophy may be present, but they are not necessary for diagnosis, the measurement of the ovarian volume has in fact proved to be a good surrogate for the quantification of the stroma in clinical practice. It should be emphasized that:

- These principles do not apply to women in estroprogestinic therapy;
- The finding of polycystic appearance in a single ovary is sufficient for diagnosis;
- The ultrasound examination should preferably be performed transvaginally and in the follicular phase.

The single morphological criterion does not establish PCOS diagnosis. Thereby PCOS remains a syndrome and as such the presence of a single diagnostic sign is not sufficient to make a diagnosis (3). To establish the diagnosis of PCOS, it is important to exclude other disorders with a similar clinical presentation, such as congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors.

The main clinical manifestation linked to hyperandrogenism appears to be hirsutism, present in 70% of women, but often the evaluation is subjective and few clinicians use standardized score methods (4). Some researchers think that hirsutism may be less prevalent in Asian women and adolescents (5,6). The presence of acne or androgenetic alopecia alone may be an indicator of hyperandrogenism, but the exact prevalence of excess androgens in these patients is unclear (7). Excess of circulating androgens is present in 50-90% of cases. The level of total testosterone alone may be a poorly sensitive marker, whereas free testosterone seems to be more effective. Some authors reported lower levels, in PCOS women, of active fraction of testosterone not linked to SHBG transport proteins (8-10). The free testosterone index, ie the ratio (decimal or percentage) between total testosterone/SHBG is another value closely related to the androgenic state. Sometimes there may be evidence of an isolated increase in dehydroepiandrosterone sulfate (DHEAS), while few data exist on the relationship between androstenedione and PCOS. A high level of luteinizing hormone (LH) can be observed in 60% of women with PCOS, as well as in 95% a high LH/FSH ratio is observed due to increased amplitude and frequency of pulsatile secretion of gonadotropin (11). These parameters are not necessary for the diagnosis of PCOS, but they are very important elements; since

LH used to be higher in thin women, their measurement and the relationship with the ovulatory period as well as the patient's body mass index must be considered (2). For patients with oligo-anovulation the determination of FSH and estradiol levels exclude the presence of hypogonadotropic hypogonadism or early ovarian exhaustion, while the determination of prolactin and 17-OH progesterone are useful to exclude an hyperprolactinemia or a deficit of 21-beta-hydroxylase (12). There is an ample evidence that polycystic ovary syndrome (PCOS) is a disorder characterized by insulin resistance and hyperinsulinemia (13-15).

Insulin resistance

Insulin resistance (IR) is a condition whereby a normal concentration of insulin produces attenuated biological effects. In all cases where pancreatic function is intact, this leads to a compensatory hyperinsulinemia. The presence of IR does not imply a systematic intolerance to glucose and the blood sugar level may be normal. On the other hand, numerous prospective and retrospective observational studies show that at least 40% of women with PCOS have glucose intolerance and that 10-20% will develop type II diabetes mellitus in middle age (16). Before glucose intolerance develops, the defect of insulin secretion can remain latent and reveal itself only in circumstances that increase the IR, for example the onset of gestational diabetes or a glucose intolerance in the course of treatment with corticosteroids. The molecular mechanism responsible for IR in PCOS appears to be unique and specific to this syndrome, a different from that one present in obesity. The most probable mechanism would be an altered phosphorylation of the insulin receptor, with a consequent defect in signal transduction. In women with PCOS, ovarian tissue remains sensitive to the action of insulin, although there is systemic resistance to the hormone. In fact, ovarian stimulation seems to involve a signal transduction system different from that for glucose transport, in particular a different second messenger, probably the inositol phosphoglycan and since insulin belongs to a group of growth factors including insulin, IGF-I, IGF-II, nerve growth factor and relaxin, insulin and IGF-I are important regulators of ovarian function. Consequently they influence directly and indirectly steroidogenesis and androgen status. Insulin acts directly on the cells of the ovary theca, activating the cytochrome P450c17, a key enzyme in the synthesis of androgens, and also enhances the synthesis of androgens induced by the luteinizing hormone (14).

Insulin increases indirectly free testosterone (the bioavailable fraction hormone for tissues) by suppressing the circulating levels of SHBG. Finally, the free testosterone can suppress the hepatic synthesis of IGF binding protein 1 (IGFBP-1), so increasing the bioavailability of IGF-I, an important regulator of ovarian androgen synthesis. It seems possible that insulin may also act at the hypothalamic level by modifying the pulsatile secretion of LH, so influencing gonadal steroidogenesis (17). Women with polycystic ovary syndrome (PCOS) may have different degrees of insulin resistance (IR) up to clinical diabetes (18), mixed dyslipidemia with high levels of LDL, VLDL and low level of HDL (low, very low and high density lipids) (18), high triglycerides, hepatic steatosis (19) and also obesity in 50% of cases, with typical android type fat distribution. PCOS, in fact, has unique interactions with the ever increasing obesity prevalence worldwide as obesity-induced insulin resistance significantly exacerbates all the features of PCOS (20). These alterations increase the risks of developing metabolic syndrome and coronary illness in PCOS women. A link between PCOS and metabolic syndrome has been documented in several studies (21-23), with a prevalence of metabolic syndrome among women with PCOS ranging between 33% and 46%.

PCOS is also considered as a risk factor for diabetes by the American Diabetes Association (24,25). The association with endometrial carcinoma has been observed for some time (26,27).

Pharmacological therapy

The drugs used are classified into the action:

- Direct inhibition of the insulin release from the pancreas (diazoxide and octreotide)
- Improvement of peripheral insulin sensitivity and indirect reduction of insulin secretion (metformin, rosiglitazone and pioglitazone).

Insulin-sensitizing drugs are effective in the treatment of anovulation in women with PCOS, and their use is justified in short term therapies for restoration of fertility (27, 28). They improve

parameters linked to metabolic syndrome but have not indication for this purpose because have not enough studies on their safety and efficacy in long-term therapies (28).

Randomized controlled trials on the efficacy of insulin- sensitizing drugs in the treatment of hirsutism and acne in women with PCOS have shown conflicting results. In a meta meta-analysis, Tang et al. (29) showed that metformin is effective in achieving ovulation in women with PCOS, has a significant effect in reducing fasting insulin levels, blood pressure and low-density lipoprotein cholesterol (LDL). Authors concluded that metformin is a first line agent in the treatment for anovulation in women with PCOS. Previously Dunaif et al. in a clinical study on twenty-five women with PCOS showed good outcomes for troglitazone (30). In multicenter, double blind trial performed on four hundred and ten premenopausal women with PCOS, troglitazone improves the ovulatory dysfunction, hirsutism, hyperandrogenemia, and insulin resistance of PCOS in a dose-related fashion, with a minimum of adverse effects (31). In a 2020 study authors investigated the influence of metformin and rosiglitazone on ovarian and endometrium of polycystic ovarian syndrome patients (32).

The presence of chronic anovulation associated with premenopausal estrogenic levels leads to a condition of relative hyperestrogenism which, over the years, can lead to endometrial hyperplasia and an increased risk of carcinoma. The relative risk has not been precisely quantified and it is also necessary to consider that in women with PCOS there may be obesity and type II diabetes mellitus, both conditions also associated with an increased risk of endometrial cancer. There is not agreement on what kind of behavior to adopt for the prevention of endometrial hyperplasia (33).

The Royal College of Obstetricians and Gynaecologists recommends treatment with gestogens to induce a withdrawal bleed at least every 3 to 4 months, An hysteroscopy or endometrial biopsy in case of ultrasound finding of increased endometrial thickness (34).

Theoretically, even the use of insulin-sensitizing drugs, restoring ovulation, could play a role in the prevention of endometrial adenocarcinoma, but there are no long-term studies in this regard. The possible association between PCOS and risk of postmenopausal breast cancer was evaluated in various observational studies (35-37). The epidemiologic studies of the last 10 years (2010- 2020) on the association between PCOS and breast cancer were reviewed recently (38). The simultaneous presence of factors such as obesity, history of anovulation, infertility, hormonal treatments is frequent and it is difficult to isolate PCOS as an independent risk factor for this type of cancer. At the moment, there is no increased relative risk among women with PCOS compared to unaffected women. The combined oral contraceptives (COC) represent the most widely used therapeutic option for the treatment of menstrual irregularities in women with PCOS that intend to postpone the search for a pregnancy (39).

COCs cause suppression of ovarian secretion of androgens and increase the level of SHBG (sex hormone binding globulin). Individual preparations, differing in combination and dosage, may present a different risk/benefit ratio. The different types of progestins showed variable androgenic effects and on the level of circulating SHBG.

Several observational studies have reported an improvement in hirsutism in women with PCOS who use an oral contraceptive, but the data are not definitive and, in the few controlled clinical trials comparing the different estroprogestinic preparations, there is no one superior to the other in the treatment of this symptom (40).

Therapies combined with an oral contraceptive plus an antiandrogen (eg spironolactone, flutamide, cyproterone acetate) appear to be more effective in treating hirsutism in women with PCOS than in COC alone (41). If the woman takes a COC containing drospirenone, the dose of spironolactone should be reduced and the potassium measured (42). Drospirenone was effective in modulating hormones, insulin and lipid metabolism in women with PCOS, maybe more effective when associated with metformin (43). In the general population, the use of COCs is associated with a lower risk of endometrial adenocarcinoma, but the extent of this effect in women with PCOS is not known.

Although the use of oral contraceptives is not associated with an increased risk of type II diabetes mellitus in the general population, studies conducted in women with PCOS have shown conflicting results

and this risk cannot be excluded. The use of COCs is associated with a significant increase in circulating levels of total cholesterol, HDL, LDL, and triglycerides. Dyslipidemias are a risk factor for cardiovascular events, but no studies are available to estimate this risk in women with PCOS using COC compared to the general population. In conclusion, COCs seem to protect the endometrium from estrogen stimulation and improve hirsutism and acne, but potential adverse effects on insulin resistance, lipidemia and coagulation must be considered.

In a recent review authors reported the emerging role glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1 RA) as a therapeutic option for obese women with PCOS (44).

Interventions

Overweight/obesity and insulin resistance are closely related to each other as the former, by reducing peripheral insulin uptake, induce hyper-production by the pancreas. Circulating insulin, being an anabolic hormone, thus favors the accumulation of fat in adipocytes and weight gain, inducing a vicious self-feeding cycle. Fortunately, there are some measures that can be implemented to break this circle, prevent or treat obesity and thus promote the resumption of physiological ovulatory cycles and fertility. These interventions include:

- Lifestyle changes
- Periodic checks by the specialist
- Pharmacological and/or integrative therapy prescribed by the specialist

Changes in Life Style

This definition is intended to promote the adoption of the most correct rules in order to prevent weight gain and counteract insulin resistance. In the case of polycystic ovary syndrome, it has been shown that weight loss until reaching normal weight, accompanied by proper nutrition and adequate physical activity, improves the metabolic and hormonal picture, favoring the restoration of physiological conditions.

Ketogenic diet and PCOS

The maintenance of good glycemic compensation and the control of risk factors for cancer such as obesity, dyslipidemia, and chronic inflammation are an advisable strategy for all PCOS patients. With this perspective, some dietary approaches (e.g. the ketogenic diet) could have a therapeutic potential as they enable to lower blood sugar level and insulinemia, to improve insulin sensitivity (45), chronic inflammation (46,47) and to reduce body weight which, in turn, is a valuable preventive strategy as well. Ketogenic diet (KD) is characterized by the reduction of carbohydrate intake (below 20 g per day) that induces a metabolic condition named physiological ketosis, it is high in fat and very low in carbohydrates, limits glucose availability and causes a switch to fatty acid metabolism. Most of the women affected by PCOS seems to follow a high carbohydrate diet and a sedentary lifestyle. Yancy and coll. showed that a Low Carbohydrate Ketogenic Diet (LCKD) led to improvement in body weight, % free testosterone, LH/FSH ratio, fasting serum insulin, and symptoms in women diagnosed with PCOS. LCKD decreased stimulation of ovarian androgen production as well as increase SHBG levels, synergistically limiting the amounts of circulating free-androgens in the serum (48). In a systematic review a Sim et al. assessed the effect of weight loss in overweight and/or obese women undergoing assisted reproductive technology (ART) on their subsequent pregnancy outcome. A low carbohydrate diets improved fertility in overweight and obese women with PCOS (49). A period of low carbohydrate ketogenic diet may improve fat oxidative metabolism and therefore reduce body weight. There are many evidences that reducing carbohydrate load can regulate circulating insulin levels (45), improve hormonal imbalance and result in a resumption of ovulation to ameliorate pregnancy rates. Mavropoulos et al. performed a research on 11 women affected by PCOS with body mass index >27 kg/m^2 . They found that after 24 weeks of VLCKD (< 20g CHO/die) there were significant reductions from baseline in body weight (-12%), percent free testosterone (-22%), LH/FSH ratio (-36%), and fasting insulin (-54%). Two women became pregnant despite previous infertility problems (50).

Conclusions

Data reported in literature confirmed that all the treatments aimed to reducing insulin levels, such as weight loss and insulin sensitizers, improve female

and male reproductive health. Ketogenic diet seems to be an effective strategy to control insulin blood levels and to prevent metabolic and endocrine disorders associated with PCOS, by acting on weight loss, insulin regulation and improving fertility outcomes.

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