مروری بر درمان دارویی سندرم تخمدان پلی کیستیک(PCOs) و تداخلات دارو و غذا

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تابستان۱۳۹۹

Polycystic Ovary Syndrome:

Variable spectrum of symptoms/conditions

- Hyperandrogenism
  - hirsutism, severe acne, male pattern alopecia
- Menstrual irregularity(cycles less than 21 days or more than 35 days)
  - oligo or amenorrhea, irregular bleeding
- Polycystic ovaries
- Central obesity

➢Infertility with changes in endocrine hormones including increased levels of androgens, estrogen, prolactin and decreased levels of progesterone

➢Metabolic disorders such as insulin resistance, obesity, hyperlipidemia and type 2 diabetes

Patients with polycystic ovary syndrome:

- Due to risk factors such as obesity, hyperinsulinemia, hyperandrogenism, insulin resistance and dyslipidemia, they are exposed to other diseases such as cardiovascular and thrombotic diseases.

- Obesity and especially abdominal obesity is seen in 75% of patients with this syndrome.
- According to scientific research, losing 5 to 10 percent of body weight makes it possible to resume ovulation and get pregnant without medical intervention.

- **Diagnosis of polycystic ovary syndrome:**

- Ultrasound evidence of polycystic ovary (increase in ovarian volume to more than 9 ml, presence of 2-8 cysts 10 mm or more in each ovary and an increase in uterine stromal density (endometrial hyperplasia).

- Metabolic disorders such as elevated serum levels of LH, testosterone, insulin, prolactin and insulin resistance are common in this disease.

❑ Treatment :

- Treatment for polycystic ovary syndrome depends on the patient, some patients need oral contraceptives while others use ovulation induction. Sustained treatment of hyperandrogenism and hirsutism can be done simultaneously.
- However, control of hirsutism may not be possible in patients who wish to become pregnant. The types of treatment methods are as follows:

1- Weight loss: is the first recommendation in obese patients; Weight loss during the 6-month period significantly reduces testosterone and in 75% of women causes ovulation to resume.

2- Oral contraceptive pills (OCP): reduce the production of steroids in the ovaries and adrenal glands and reduce hirsutism in two-thirds of patients.
Contraceptive pills that contain new progestins minimize androgen activity.
Contraceptive use alone may be ineffective in treating hirsutism in women with polycystic ovary syndrome (less than 10%).
In these patients, insulin resistance also increases due to the use of these drugs.

Oral contraceptives and risk assessment in PCOS

- **Combined estrogen-progestin oral contraceptives (COCs)** are the mainstay of pharmacologic therapy for women with PCOS for managing hyperandrogenism and menstrual dysfunction and for providing contraception.
- COCs are associated with an increased risk of **venous thromboembolism (VTE)** in all users but particularly in obese women. There have been concerns that the presence of PCOS per se may represent an additional independent risk factor for VTE, but available data do not support this concept.
- We currently suggest **using caution** if COCs are prescribed to obese

3. Depomedroxyprogesterone or medroxyprogesterone acetate: This drug is successfully used to treat hirsutism. 150 mg every three months depomodorex progesterone or 20-40 mg oral medroxyprogesterone acetate 95% reduces hair growth.

4. Gonadotropin-releasing hormone agonist: Suppresses steroid production from the ovary. Luprolide acetate treats hirsutism every 28 days. Adding a contraceptive or estrogen to the gonadotropin-releasing hormone prevents bone loss and other complications of atrophy and atrophy.

5. Dexamethasone: Used to treat patients with adrenal hyperandrogenism or a mixture of it with the ovary.

6. Ketoconazole: This drug reduces the concentration of androstenedione and free testosterone at a low dose of 200 mg per day.

7. Spironolactone: A diuretic that preserves potassium and lowers testosterone. Reduces the daily linear growth rate of sexual hair and the diameter of the hair shaft. 100- 25 mg twice a day has the maximum effect.

** The most common complication is menstrual irregularities,

8. Cyproterone acetate: It has strong anti-androgenic properties that are used in severe cases of hirsutism and acne. Concomitant use of this drug with estrogen is more effective.

9. Metformin (glucophage): using dose of 500 mg three times a day to significantly improve Hyperandrogenism

Pharmacotherapy for hyperandrogenism management in PCOS women.

Drug	Administration	Safety, limit and side effects
COCs	Low-dose COCs containing EE2/	Avoid progestin with high androgenic power (i.e., LNG)
DRSP	antiandrogenic progestins are administered	COCs employment was not related to a significant impairment on
CMA	since the 1 day of	glucose tolerance
Cyproterone	menses for at least 6 months.	Products containing third-generation progestins, DRSP or
acetate	DRSP 3 mg combined with EE2 20 or 30 μg	cyproterone acetate represents a safe treatment in PCOS patients
	CMA 2 mg plus EE 30 μg	with regular CV risk. Clinician should pay attention to patient characteristics before starting any hormonal therapy, especially in adolescents, hypertensive women and smokers
Antiandrogens		Spironolactone induces polyuria, nicturia, iperkaliemia,
Spironolactone	Daily dose of 200 mg	hypotension
Finasteride	Daily dose of 5 or 7.5 mg	Flutamide induces gynecomastia, breast pain, dry skin, fatal liver
Flutamide	Daily dose of 250 – 500 mg	toxicity
		All antiandrogens have a teratogenic effect on genital of fetus (feminization of male foetuses)
Eflornithine	Topic application at the formulation of 13.9%	Efficacy disappears just after 8 weeks; skin irritation, stinging, burning, tingling and erythema
ISDs	Daily dose 1500 – 2250 mg	Metformin assumption induces gastrointestinal symptoms
Metformin		(diarrhea, nausea, vomiting, abdominal bloating.
Thiazolidinediones		Thiazolidinediones increase body weight

COCs: Combined oral contraceptives; CMA: Chlormadinone acetate; CV: Cardiovascular; DRSP: Drospirenone; EE2: Ethinylestradiol; ISDs: Insulin-sensitizing drugs; LNG: Levonorgestrel.

Pharmacotherapy of polycystic ovary syndrome (Drug -Nutrient Interactions)

Clomiphene Citrate:

- use in polycystic ovaries has excellent results.
  In some study populations, 80 to 85 percent of women ovulate and 40 percent become pregnant

** The first line of treatment to stimulate ovulation is clomiphene citrate, and resistance to this drug is common with obesity and hyperinsulinemia due to peripheral insulin resistance, and the dose should be increased in overweight individuals.

❑ Side Effects

Ovarian hyperstimulation syndrome
flushing ("hot flashes")
Nausea
Feeling of pain in the breast and discomfort in the pelvis (breast tenderness)
Stomach upset
headache
dizziness

Spironolactone:

When potassium-sparing diuretics are used, a high intake of potassium-rich foodstuffs such as licorice, bananas, kiwis, oranges, spinach and other green leafy vegetables, and salt substitutes may result in hyperkalaemia.

In particular, severe hyperkalaemia with serious cardiac arrhythmia has developed after excessive use of potassium-containing salt substitutes in patients treated with spironolactone.

Analysis of possible food/nutrient and drug interactions in hospitalized patients, Everton Moraes Lopes et al.2010

Spironolactone Side Effects

- Drowsiness, dizziness, lightheadedness, stomach upset, diarrhea, nausea, vomiting, or headache may occur. To minimize lightheadedness, get up slowly when rising from a seated or lying position.

- increased thirst, signs of kidney problems (such as change in the amount of urine), mental/mood changes, unusual fatigue/weakness, muscle spasms, menstrual period changes, breast pain, breast enlargement (gynecomastia) in men, sexual function problems, signs of infection (e.g., fever, persistent sore throat), severe stomach/abdominal pain, persistent nausea/vomiting, vomit that looks like coffee grounds, dark urine, yellowing of the eyes/skin, easy bruising/bleeding.

Metformin:

- By reducing hepatic gluconeogenesis and increasing peripheral glucose uptake, it decreases plasma insulin levels and also induces normal menstruation by reducing serum LH and androgen levels.

- Clinical studies show that the ovaries respond better to stimulation of ovulation with clomiphene if metformin is used concomitantly.

- In obese patients with PCOs, weight loss along with the use of metformin can show positive effects, and in people with this disease who are normal weight, the use of metformin

❑Side Effects:

Nausea, vomiting, stomach upset, diarrhea, weakness, or a metallic taste in the mouth may occur.

Metformin does not usually cause low blood sugar (hypoglycemia).

Low blood sugar may occur if this drug is prescribed with other diabetes medications.

Metformin reduces the absorption of vitamin B12 in up to 30% of patients, decreases the serum concentration of this vitamin in 5-10% of patients and rarely causes megaloblastic anemia and peripheral neuropathy .

**In one study, the reduction in the absorption of this vitamin was corrected by administration of a calcium carbonate supplement (1·2 g daily).

In another study, taking a daily multivitamin supplement reduced vitamin B12 deficiency.

Diabetics should avoid excessive alcohol consumption during treatment with metformin.

Concurrent symptoms include: lactic acidosis, restlessness, severe muscle pain, irregular heartbeat, drowsiness, abdominal discomfort

❑ Metformin drug interactions:

Cimetidine, amiloride, calcium channel blockers, digoxin, morphine, procaine amide, quinine, ranitidine, triamterene, trimethoprim, and vancomycin excreted by renal tubular transport, Increase the plasma concentration of metformin and interfere with renal clearance.

- Insulin-sensitizing drugs:

Metformin and thiazolidinediones are insulin-sensitizing drugs (ISDs), which act by improving insulin sensitivity with following reduction in serum androgen concentration.
All guidelines do not suggest insulin sensitizers to treat hirsutism. however, several studies evaluated their employment in hyperandrogenism reduction .

Thiazolidinediones (pioglitazone and rosiglitazone) improve peripheral action of insulin. Available data.

have shown a reduction in Ferriman--Gallwey score and androgen serum levels in adult and young PCOS women, without significant difference in terms of Ferriman--Gallwey scores compared with metformin .

However, glitazones do not have any role in PCOS treatment nowadays because of the serious side effects (such as CV and ischemic and bladder cancer risks)

Non-hormonal treatments for polycystic ovary syndrome

Myo-inositol:

Deficiency of myoinositol causes insulin resistance, and with its administration, insulin resistance decreases.

It can also improve fat profile and regularize menus.

The duration of treatment varies in different articles and has been reported between 3 to 6 months and even up to 5 years. (If gastrointestinal side effects do not occur) and usually has no side effects.

Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials, Vittorio Unfer et al.2017
Myo-inositol in patients with polycystic ovary syndrome: A novel method for ovulation induction, Papaleo - 2007

Vitamin D:

Decreased vitamin D by impairing aromatase gene expression as well as decreased calcium levels and increased parathyroid hormone levels promotes endocrine disorders in polycystic ovary syndrome.

Modifying vitamin D levels improves menstruation, builds dominant follicles and ovulates, and reduces insulin resistance.

Effect of vitamin D supplementation on polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials Fang Fang et al.2017

Chromium:

Chromium is involved in homeostasis and insulin. Administration of chromium at a dose of 800-200 micrograms for 8-12 months reduces fasting insulin levels and weight loss.

Chromium supplementation and polycystic ovary syndrome: A Systematic Review and Meta-Analysis. Siavash Fazelian et al.2017
Chromium supplementation does not improveweight weight loss or metabolic and hormonal variables patients with polycystic ovary syndrome: A systematic review, Vahid Maleki et al.2017

L-Carnitine:

Administration of L-carnitine at a dose of 250 mg per day can improve fat profile, reduce fasting sugar and reduce abdominal fat.

Omega-3 supplements:

Omega3can lower androgen levels in women with PCOS. One study found that women with PCOS who received three grams of omega-3s daily for eight weeks had lower testosterone levels and were more likely to have regular periods than those who took placebos.

Supply of micronutrients zinc, magnesium, cobalt, selenium and copper in polycystic ovary syndrome helps to improve the disease

Vitamin B6 helps to improve the symptoms of this syndrome.

Blood Trace Element Concentrations in Polycystic Ovary Syndrome: Systematic Review and Meta-analysis, Poli Mara Spritzer et al·2017

N-acetyl cysteine and PCOD:

N-acetyl cysteine (NAC) inhibits oxidative stress and prevents hyperglycemia-induced insulin resistance .

PCOS patients with hyperinsulinemia, treatment with NAC results in improvement of insulin sensitivity and a significant decline in plasma testosterone and lipid levels.

Melatonin and PCOD:

Not only anovulation but also decreased oocyte and embryo quality may be a cause of infertility in women with PCOS. The reactive oxygen species–induced oxidative stress may be responsible for poor oocyte quality. Studies have demonstrated that there are increased lipid peroxidation products both in serum and in follicular fluids.

high concentrations of melatonin in serum, women with PCOS have a deficiency of this indoleamine in their ovarian follicles.

Increased serum melatonin in PCOS may be a feedback response to the deficient levels of melatonin in the ovary

The high levels of melatonin in the FF are essential for follicle growth, ovulation, and oocyte quality, whereas reduced follicular melatonin concentrations may be responsible for anovulation and poor oocyte quality in PCOS.

Acarbose and PCOS:

Acarbose is an oral tablet used in the management of type 2 diabetes.

Acarbose reduces the postprandial rise in both serum glucose and insulin levels by inhibiting aglucosidase, an enzyme responsible for the intestinal absorption of carbohydrates, and hence decreases the serum androgen concentrations in hyperinsulinemic premenopausal women. Dose-related adverse effects, including flatulence, diarrhea, and abdominal distention, may be minimized by titration. Unlike other antidiabetic drugs, acarbose does not cause hypoglycemia because it does not stimulate insulin release. Acarbose exhibits a low systemic absorption profile. Various studies have demonstrated that acarbose therapy improves various clinical manifestations of PCOS, including insulin resistance, signs and symptoms of hyperandrogenism, menstrual irregularity, obesity (in women with BMI > 30 kg/m2), and infertility

Acarbose should be consumed between meals (not more than half an hour before or after meals)

Lifestyle change is the most important therapeutic principle in polycystic ovary syndrome. A good low-calorie, high-fiber diet is the best nutritional advice for these people. Eliminating simple sugars and limiting sugars from the diet will reduce insulin resistance. In general, low carbohydrate diet with moderate to high fat percentage and increased physical activity and exercise are ways to treat this syndrome.

Regular exercise (at least 4 hours a week) that causes sweating and increased heart rate has a significant effect on controlling symptoms in these people. Weight loss of 5-10% with a reduction of 30-35% of peritoneal fat reduces androgen synthesis and control symptoms and reduces cardiovascular complications.

Thank you for your attention