POLYCYSTIC OVARY SYNDROME, A COMPLEX ENTITY INVOLVING REPRODUCTIVE AND METABOLIC IMPAIRMENTS: A SYSTEMATIC REVIEW

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POLYCYSTIC OVARY SYNDROME, A COMPLEX ENTITY INVOLVING REPRODUCTIVE AND METABOLIC IMPAIRMENTS (Abstract): We attempt to synthesize main data in what concerns pathogenesis, signs and symptoms, diagnosis and management of polycystic ovary syndrome PCOS. The issue was the systematization of main data regarding different features of PCOS and stressing its peculiar association with characteristics of metabolic syndrome, main diagnostic criteria and most important therapeutic options, finally contouring an updated general picture of PCOS. We pointed also on associated morbidities, such as endometrial cancer, insulin resistance and need for individualized therapy, including changing in lifestyle, especially weight loss.

Keywords: POLYCYSTIC OVARY SYNDROME (PCOS), INSULIN RESISTANCE, ANOVULATION, HYPERANDROGENEMIA, GLUCOSE TOLERANCE TEST (GTT).

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome or hyperandrogenic anovulation is characterized by irregular menstrual periods or amenorrhea, hirsutism, acne, infertility and acanthosis nigricans (1).

The syndrome was first described in 1935 by American gynecologists Irving F. Stein and Michael L. Leventhal, giving the initial name of Stein-Leventhal syndrome. The earliest description of the disease dates back from 1721 in Italy (2).

In 2010, World Health Organization has estimated the syndrome being present in 116 million women all over the world, 3.4% of the female population.

Ultrasonography has found polycystic ovaries in 8-25% of normal women (3, 4).

ETIOLOGY AND PATHOGENESIS

Genetic factors are strongly involved in the genesis of the disease. Evidences include: hereditary features of PCOS, familial clustering and greater concordance in monozygotic than in dizygotic twins (5).

The disease is transmitted on an autosomal dominant way; in women with the allele, the phenotype is revealed by high androgen levels originating in the theca cells of the ovarian follicles. The precise affected genes have not yet been identified, but accumulated data suggest that the syndrome is a complex multigenic disorder (6).
The severity of the PCOS symptoms seems to be related to obesity and features of metabolic syndrome, since symptoms of PCOS are partially reversible, thus supporting the overlapping with main traits of metabolic syndrome (3).

The cysts in the ovaries are a symptom of the disease and not its primary cause; recent data is featuring the syndrome as a multisystem disorder with primary hypothalamic hormonal dysregulation. The term of disease is used to describe the situation in which ovarian cysts are evident in ultrasonography, while the term of syndrome is rather describing a complex condition with a wide spectrum of symptoms and presenting ovarian cysts in only 15% of the cases (7).

Main pathogenic issue is represented by the overproduction of androgens, especially testosterone generated by the high levels of luteinizing hormone (LH) and hyperinsulinemia, in women whose ovaries are peculiarly sensitive to insulin (6, 8).

The increase of hypothalamic GnRH pulses results in an elevated LH/FSH ratio. Most PCOS cases show insulin resistance and/or obesity. Elevated insulin levels are triggering features of PCOS since are increasing the frequency of GnRH pulses. Increased LH/FSH ratio is inducing ovarian androgen overproduction, decreased follicular maturation and low SHBG binding, leading to the development of PCOS. Aromatase present in the adipose tissue is converting androstenedione into estrone and testosterone into estradiol; obesity is responsible for both overproduction of androgens (causing hirsutism and virilization) and estrogens (inhibiting FSH secretion) (9).

Chronic inflammatory mediators are believed to be involved in the development of different symptoms of PCOS, such as anovulation (10).

**DIAGNOSIS**

Diagnosis of polycystic ovary syndrome is based on two of the three criteria: anovulation, high androgen levels and ovarian cysts in ultrasound examination (Rotterdam criteria established in 2003).

Common signs and symptoms of PCOS are represented by: menstrual disorders, more often oligomenorrhea or amenorrhea, but other menstrual disorder may also be present; infertility caused by chronic anovulation; high levels of androgens resulting in acne and hirsutism, sometimes determining hypermenorrhea, alopecia or other symptoms; metabolic syndrome with central obesity and signs of insulin resistance (3, 11).

Diagnosis may be established exclusively on clinical signs, such as the history of menstrual pattern, obesity, hirsutism and acne (12).

Ultrasonography should demonstrate presence of small ovarian cysts resulted from the so called follicular arrest, in which several follicles reach a size of 5-7 mm, but they do not develop furthermore. No follicle reaches the pre-ovulatory size of at least 16 mm.

Recent studies support the opinion that at least 25 such follicles should be present in an ovary, in women aged 18-35 years, to confirm the ovarian morphology of PCOS. The cysts must appear in periphery of the ovary, showing the aspect of a string of pearls (13).

An ovarian volume of at least 10 ml is also considered a criterion for the PCOS morphology, besides the presence of cysts. Laparoscopy may put in evidence a thickened, pearl-white surface of the ovary.

Plasma elevated androgen levels (androstenedione and testosterone) is also a common finding in the polycystic ovary
Polycystic ovary syndrome, a complex entity involving reproductive and metabolic impairments: a systematic review

Polycystic ovary syndrome. 60% of PCOS patients show high free testosterone levels.

Free androgen index: ratio of testosterone to sex hormone-binding globulin (SHBG) is correlating to the degree of obesity. Among obese PCOS cases, low levels of SHBG are common. Anti-Müllerian hormone shows high levels in PCOS; this may become a diagnostic criterion (14).

Insulin resistance demonstrated by abnormal two-Hour oral glucose tolerance test (GTT) is present in 15-33% of women with PCOS; insulin resistance is appearing in overweight, as well as in normal weight subjects. Diabetes is associated in approximately 65% of women with the disease.

Elevated insulin levels are a common finding; insulin resistance in such cases is revealed at GTT (GTT insulin levels) by higher insulin levels and lower blood glucose, than in fasting condition.

Glucose tolerance test is a better diagnostic tool than fasting glucose in PCOS, since while fasting glucose may be normal, oral glucose tolerance is impaired in 38% of the asymptomatic cases (15).

Differential diagnosis should consider different other causes of amenorrhea and virilization: hypothyroidism, congenital adrenal hyperplasia (21-hydroxylase deficiency), Cushing’s syndrome, androgen secreting tumors or hyperprolactinemia.

**MANAGEMENT AND PROGNOSIS**

Therapy includes changing in lifestyle, medications and surgery.

Main aims of the therapy are consisting in reducing insulin resistance, recovery of fertility, therapy of hirsutism and acne; obtaining regular menstruation and prevention of endometrial hyperplasia and endometrial cancer.

Significant controversies are ruled out in what concerns optimal therapy, especially because of the lack of therapies comparing large-scale clinical trials. Weight loss is the most effective method in restoring normal ovarian function (ovulation, menstruation). Unfortunately, many women found it difficult to achieve. There are studies which are pointing on low glucids diets, which are bringing greater benefit in what concerns regular menstruation (16).

Medications used in the treatment of PCOS are especially oral contraceptives and metformin (oral hypoglycemics).

Oral contraceptives are increasing SHBG levels and thus the binding of free testosterone. In this way are improved symptoms of hirsutism and normal menstruations are appearing. In many cases besides treating insulin resistance, metformin is effective in restoring ovarian function and normal ovulation. Spironolactone is also used for its antiandrogenic effects (17).

For anovulation (cause of infertility in PCOS) besides recommended weight loss, ovulation inducing medications are used: clomiphene-citrate and FSH (19). Metformin was also used in the treatment of anovulation but was found to be less effective than clomiphene; an important aspect in what concerns the use of metformin is that is not increasing the risk of birth defects (18).

In vitro fertilization may be used in case of non-responsiveness to clomiphene therapy.

Laparoscopic procedure consisting in puncturing 4-10 small cysts using electrosurgery or laser, known as ovarian drilling is used for its result in restoring normal ovulation, yet there are controversies in what concerns the long-term effect of this
surgical procedure (19).

Anti-androgen drugs, such as flutamide and spironolactone are used to treat hirsutism. At the same time, metformin may reduce hirsutism possibly by diminishing insulin resistance, for this being used in the treatment of associated conditions such as diabetes and obesity (17).

The risk of endometrial hyperplasia and endometrial cancer through hyperstimulation of the uterine lining by estrogens, might be induced also by associated conditions such as obesity, hyperandrogenemia (20).

Insulin resistance and type II diabetes are commonly associated with PCOS, even in the cases with normal body mass index (7, 21).

Other associated conditions in PCOS are including: dyslipidemia non-related to insulin resistance; depression and anxiety; cardiovascular disease; hepatic steatosis; acanthosis nigricans and autoimmune thyroiditis (22, 23).

CONCLUSIONS
In our evaluation, besides its direct related pathology, PCOS is drastically affecting life quality; the need for changes in lifestyle (diet, physical exercise) does not need any more to be stressed; however, the difficulty in adopting different living habits makes from PCOS a subject of continuous challenge for patients, as well as for physicians.

REFERENCES