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Polycystic Ovarian Syndrome: A Review on Etiopathology, Diagnosis and Treatment

Roksana Haque[1*], Md. Mizanur Rahman[2]

[1]Associate Professor, Dept of Obstetrics and Gynecology, Bikrampur Bhuiyan Medical College, Sreenagar, Munshiganj, Bangladesh
[2]Professor (CC), Dept of Medicine, Tairunnessa Memorial Medical College & Hospital, Gazipur, Bangladesh

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***Corresponding author:** Roksana Haque
Associate Professor, Dept of Obstetrics and Gynecology, Bikrampur Bhuiyan Medical College, Sreenagar, Munshiganj, Bangladesh

Abstract **Review Article**

Polycystic ovary syndrome is a heterogeneous disorder of different phenotypes. It is the most common endocrine disorder which increases risk of infertility. It affects 7- 10% of women of reproductive age[1] which is characterized by combination of signs and symptoms of hyperandorogenemia and ovarian dysfunction. As PCOS is associated with many long term Comorbidities, both health professionals and women should be aware of it. There are controversies in etiology, diagnosis and management protocols. This review is an attempt to summarize the updates on etiopathogenesis diagnosis and management of PCOS.

Keywords: Polycystic ovary syndrome, PCOS, hyper androgenemia, obesity.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the common endocrinopathy in the woman of reproductive age with prevalence of approximately 7-10% worldwide [1], and encompasses hyperandrogenism as the central biochemical disturbance which has effects on ovarian function and metabolism [2]. It is a heterogenous collection of signs and symptoms that gathered together to form a spectrum of disorder with mild presentation in some and in others a severe disturbance of reproductive, endocrine and metabolic function. Up to 70% of PCOS women remain undiagnosed [3]. Moreover, menifestations of PCOS include menstrual irregularities, acne, hirsutism and infertility. Obesity is a common finding but it is not the diagnostic criteria. A gain in weight is associated with worsening of symptoms, whereas weight loss reduces blood androgen level and improves endocrine, metabolic profile and clinical symptoms [2, 3]. PCOS women are at increased risk for insulin resistance and develop abnormal glucose metabolism [1, 4, 5]. Insulin resistance and compensatory hyperandrogenism predisposes to high triglyceride level with low HDL, high blood pressure and coronary heart disease [1, 6].

Diagnostic Criteria

PCOS was first recognized as a medical disease or syndrome in 1845 in France [7]. It has also been known by the name Stein-Leventhal syndrome and includes multisystem presentations, having its effects on the skin, hair, bodyweight and endocrine and reproductive systems [6, 7]. In 1990 a national institute of Health conference decided the two most consistent features of PCOS which are hyperandrogenism and chronic oligo or anovulation with exclusion of other causes of hyperandrogenism such as adult onset congenital hyperplasia, hyperprolactinemia, Cushing's disease and androgen secreting neoplasm [7-9]. The definition of the syndrome has been much debated. In 2003 a joint European society for Human Reproduction and Embryology/ American society for reproductive medicine consensus meeting agreed refined definition of PCOS:namely, the presence of at least two of the following three criteria: 1. Oligo and/or anovulation, 2. Hyperandrogenism (clinical and /or biochemical), 3. Polycystic ovaries on ultrasound [2, 10, 7, 11]. The morphology of the polycystic ovary has been redefined as an ovary with 12 or more follicles measuring 2-9 mm in diameter and / or increased ovarian volume (>10 cm^3) [2, 11, 12]. Not all women with polycystic ovaries demonstrate the clinical and biochemical features of PCOS. Dunaif A et al claimed that polycystic morphology is consistent with, but not essential for the diagnosis of the syndrome [11]. The changes can be present in women who are endocrinologically normal. Thus the ovarian morphological change must be

distinguished from the endocrine syndrome of hyperandrogenism and anovulation [11, 13, 14].

Etiopathogenesis

The etiology of PCOS in still unclear due to complexity of disease. Many studies reveal genetic and environmental factors are involved [15, 16]. Genetic susceptibility seems to induce the disease but extrinsic factors certainly modify the clinical course of PCOS [7, 8, 9, 15].

Environmental factors that are related in pathogenesis are: in utero exposure of fetus to androgen excess, tobacco, alcohol, premature puberche, peripubertal stress, obesity, nutrition, Physical activity, environment of ethnic origin, geographical location [15, 16].

Clinical Evaluation

The clinical features of PCOS are heterogenous and may change throughout the lifespan, starting from adolescence to post-menopausal age [7, 17]. This is largely dependent on the influence of obesity and metabolic syndrome which consistently affect most women with PCOS [7, 18] .The ethnicity of patients influences extent of signs symptoms especially hirsutism and obesity [9].

Obesity is a common finding of women with PCOSand many studies show higher prevalence of PCOS in women who are overweight and obese [3]. The obesity is significantly associated with an increased risk of hirsutism, menstrual disturbances, infertility as there is development of hyperandrogenic state. Even those with normal BMI, PCOS Women tend to have android body type with waist to hip ratio greater than 0.8 [11]. Loss of body weight can improve ovulation by reducing blood androgen level [3, 19].

Hirsutism can be graded and given a Ferriman - Galway score by assessing amount of hair in different parts of body (upper lip, chin, breasts, abdomen,limbs.[20]

The characteristic increase in LH relative to FSH release, have long been appreciated in PCOS. Due to their pulsatile release a single test fails to detect increased LH/FSH ratio. So LH /FSH ratio in not included in diagnostic criteria for PCOS [11, 21].

Both Obese & non obese PCOS women are insulin resistant and hyperinsulenemic which are related with hyperandrogenism [11] and predisposes to develop type II diabetes, highplasma triglyceride and a low LDLcholesterol, high BP and coronary heart disease [1, 7].

HYPERANDROGENISM

Androgen in produced by ovaries and adrenal cortex under control of LH in ovary and ACTH in adrenal gland. The clinical signs of androgen excess are the presence of hirsutism, acne and sometimes alopecia [2]. Some studies have found patients with PCOS have evidence of hyperandrogenemia [22] and others have not [23, 24]. Excessive production of androgens is confirmed via laboratory analysis, characterized by elevated values of circulating androgens. Ovary produces excess androgen due to dysregulation of steroidogenesis [2]. In 20-40% of women with hirsutism and polycystic ovaries, Serum level of androgen was not elevated [9]. A measurement of SHBG (Sexhormone binding globulin) can be used to calculate free androgen index.

Treatment of PCOS

PCOS requires multidisciplinary approach for management - Gynecologist, endocrinologist, dermatologist and nutritionist.

Life Style Modifications

The important part of management of PCOS is life style changes. Regular exercise and calorie restricted diet are recommended for weight loss which can improve ovulation, menstrual irregularities, reduce testosterone and insulin levels, decrease acne, hirsutism.

Medical Management

Oral contraceptivepive pills

The easiest way to control menstrual cycle in use of low dose combined oralcontraceptive pills (OCP). OCP decreases LH secretions, increase SHBG and decrease free testosterone levels by suppressinghypothalamo-pituitary-ovarian axis. Thus it controls acre & hirsutism [22, 25].

Metformin

Metformin is an oral anti diabetic biguanide drug. This insulin sensitizing agent is effective in reducing body weight, in attenuating insulin resistance and hyperandrogenemia and in reversing menstrual abnormalities and chronic anovulation [26].

Antiandrogens

Anti-androgens act either by Competitive inhibition of androgen binding receptors or inhibit 5-alpha reductase enzyme which decreases androgen production. OCP should be added to young women to avoid feminization of male fetus when they become pregnant [25].

Infertility Treatment

The first line treatment include ovulation inducing agents. American task force and the PCOS Australian guideline Alliance recommend clomiphene

citrate [25, 27, 28] and American college of Obstetricians and Gynecologist (ACOG) updated the use of a letrozole [29] as ovulation inducing drug. If both drugs fail then exogenous gonadotropin, laparoscopic ovarian surgery are recommended [25]. Laparoscopic procedures that improve ovulation are ovarian drilling, ovarian biopsy, electrocautery [25, 30].

Treatment of Hirsutism

Cyproterone acetate is a progestational antiandrogen which improves hirsutism. Excess hair can be removed by threading, waxing and permanently by electrolysis, laser thermolysis [25, 31].

Treatment of PCOS in Young Adults

Adolescents and young adults are best treated with life style changes and metformin. OCP can be used for regulation of menstruation [27].

Newer Drug Approaches

Metformin combination therapy with new drugs glucagon like peptide receptor agonists 1 is more effective in weight reduction, lowering insulin resistance and improves reproductive functions [25].

As dyslipidemia is associated with PCOS statins can be used. In a study by Celik andAcbay reported 12 weeks statins with metformin reduce testosterone, DHEA-S, body weight,TG and LDL [32].

Studies have shown that fibroblst growth factors are involved in regulation of carbohydrate and lipid metabolism, have cardioprotective activity [25].

Some recent studies showed myo-inositol decreases glycemia, improves lipid profile, reduces secretion of LH, testosterone, restores ovulation and fertility [33].

CONCLUSION

PCOS is a significant public health issue and its prevalence is increasing day by day. As etiopathogenesis in still unclear, many research Works are being carried out.

Adolescent girls and young women develop PCOS more commonly which may reflect their sedentary life style, lack of physical exercise and consumption of junk foods. So it is important to prevent the disease by changing life style. Awareness should be created to general population regarding long term health risks with PCOS.

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