Review article

Polycystic ovarian syndrome

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Abstract

The most common hormonal disorder in women at reproductive age is the Polycystic Ovary Syndrome (PCOS) and the complex pathophysiology of PCOS and its substantial health repercussions, which include obesity, cancer, cardiovascular disease, diabetes, and psychological morbidities, have made it a major global health concern for women. The aim of the present review article is to summarize the literature available on PCOS and to identify the pathophysiology, diagnosis criteria and the treatments for the disease.

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine and metabolic disorder of heterogeneous nature that affects in women at reproductive age[1]. PCOS was first described by Stein and Leventhal in 1935 as a combination of hirsutism (men like facial hair growth), amenorrhea (absence of menstruation), chronic anovulation, infertility and enlarged cystic ovaries[2]. It is a heterogenous collection of symptoms and signs gathered to form a spectrum of a disorder. Clinical presentation varies from mild to severe form and in an individual this may change over a time[3]. It manifests in a variety of symptoms that are influenced by environmental and genetic variables. However, not all women with polycystic ovaries display the disease's hallmark biochemical and clinical features. Among these traits include irregular menstrual cycles, obesity, hirsutism, acne, and changed metabolic profiles, including increased serum concentrations of estrogen, testosterone, and insulin[4]. PCOS is a lifelong disease with varying phenotypes. In the pre-pubertal and adolescent age group hyperandrogenism predominates and it is the reproductive dysfunction, the main concern in third, fourth and fifth decade of life. Metabolic complications tend to rise in post-reproductive period. Diagnosis of PCOS becomes controversy due to heterogeneous condition with variable phenotype expression. The prevalence of PCOS found to be 5-9% in worldwide based on the NIH 1990 criteria and according to the current Rotterdam criteria, prevalence of PCOS ranges 5.5-19%[5]. In Sri Lanka prevalence rate reported 6.3% based on Rotterdam criteria[6].

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Aetiology and pathophysiology

Pathophysiology of PCOS is complex due to the interaction of several generalities and can be addressed by focusing major defects and the interactions[7]. PCOS reflects interaction of genetic and epigenetic changes, primary ovarian abnormalities, alterations in steroidogenesis, neuro-endocrine alterations and endocrine-metabolic modifiers, inflammatory factors and environmental factors such as diet, physical activity and endocrine disruptors[8].

Hyperandrogenism

Hyperandrogenism is leading cause of PCOS and 80-85% women with clinical hyperandrogenism have PCOS[9]. Increased level of androgen (testosterone, dehydroepiandosterone and androstenedione) disrupts the regulation of luteinizing hormone (LH) and follicular stimulating hormone (FSH) via diminished feedback action of ovarian steroids including estrogen and progesterone [10]. Elevated levels of luteinizing hormone (LH), increased LH: FSH ratio and decreased FSH, coupled with increased levels of androgens manifest as ovulatory dysfunction. Moreover, research indicated excess androgen up regulate the level of anti-mullerian hormone (AMH), secreted by growing follicles in excess. AMH inhibits folliculogenesis by inhibiting gene expression, steroidogenesis and FSH effect. As recent studies reported, higher AMH level was reported in PCOS compared to normal level[11]. AMH play key role in PCOS pathogenesis and available data suggests it could serve as useful and reliable biomarker to indicate risk of PCOS, sensitivity of disorder, monitoring and evaluating prognosis[12-14].

Insulin resistance and hyperinsulinemia

Insulin resistance (IR) and hyperinsulinemia are common in women with PCOS and intrinsically play a role in pathophysiology of PCOS[15]. Among women with PCOS, 50-70% are demonstrating IR[8]. IR has been reported independent to the body mass and even lean women manifest IR; overweight exacerbates IR[16]. The etiology of IR in PCOS remain unclear, the genetic and epigenetic factors, inheritable intra and extra uterine factors and varying adaptations to energy excess likely appear to be the development of IR and hyperinsulinemia in PCOS. However, IR, hyperinsulinemia and hyperandrogenism continuously stimulating each other and assemble as vicious cycle. IR in PCOS women remain tissue selective which leads paradox of insulin signaling [7,15]. Insulin resistance is reported primarily in liver, skeletal muscles and adipose tissue whereas steroid-producing tissues such as ovary and adrenal gland remain insulin sensitivity to insulin action on steroidogenesis. Hyperinsulinemia increased the frequency of gonadotropin-releasing hormone (GnRH) and LH pulse secretion and stimulate androgen secretion by ovarian theca cells while suppressed hepatic synthesis of sex hormone-binding globulin (SHBG) thereby leading to augmented levels of free circulating androgens[15].

Increased LH

Increased levels of androgens disrupts the regulation of FSH/LH. Ovarian volume is correlated with the serum LH level. Higher the LH level higher the risk of subfertility. Higher levels of LH is seen in slim PCOS individuals and they are resistant to treatment[3].

Genetic inheritance

PCOS is multifactorial disorder and literature has reported influence of genetic pre disposition to PCOS development. A number of genes, pathways and mediating PCOS have been identified and genetic variants and mutations of these genes replicated in PCOS patients which accounts[11] approximately 10% of the heritability of PCOS[17]. Studies reported multiple relatives and siblings in families with autosomal dominant inheritance[18]. The prevalence of PCOS in the first degree relative of women with PCOS is reported 20-40% and 70% of heritability is reported [5]. Individual genes, gene-gene interaction or gene-environment interaction have been influenced by the predisposition to PCOS[8,19,20].

Environmental risk factors

Environment is likely play critical role in expression of genetic traits. Environmental risk factors act as triggers and exacerbate PCOS pathology throughout life during the prenatal life to a phenotype of PCOS[21,22]. Both prenatal and post natal environment factors have to be considered in PCOS pathogenesis. However, limited published research evidences are available in literature regarding potential prenatal environmental factors linked to PCOS. Intrauterine environment has been influenced in the early pathogenesis of PCOS. Experimental research data on animal models have identified hyperandrogenism during critical time of fetal development affect the fetal physiology and increased susceptibility of disease after birth but this hypothesis is has not been replicated by human studies in normal and PCOS pregnancies[23].

Post natal environment factors include harmful life style factors including obesity, nutrition, physical activity and environmental toxins. Lifestyle factors likely contribute to the expression of PCOS and exposure to these factors can be lead to PCOS in susceptible females[15,21].

Diagnosis of PCOS

Modified Rotterdam criteria is the current recommendation for the diagnosis of PCOS and according the criteria, presence of two of the following features will confirm the PCOS in the relevant patient.

1) Clinical or biochemical hyperandrogenism
2) Oligo-anovulation
3) Ovarian morphology on ultrasound

Clinical or biochemical hyperandrogenism

Hyperandrogenism is a state of excess production of androgens/ male sex hormones in women and testosterone is the most clinically relevant hormone comes under this category. This can be determined clinically or using biochemical tests.

Biochemical hyperandrogenism – Elevated total or free testosterone measured by laboratory assays like liquid chromatography mass spectrometry and extraction/ chromatography immunoassay.

Clinical hyperandrogenism – Clinical signs of elevated androgen levels in women such as hirsutism, female pattern hair loss and acne.

Oligo-anovulation

A prolonged menstrual cycle brought on by infrequent menstruation is known as oligomenorrhea (cycles >35 days apart or <8 cycles per year). Most common signs of oligo-anovulation are missed or delayed periods.

When a person has an unclear menstrual history, luteinizing hormone testing or mid-luteal serum progesterone evaluation might be used to confirm ovulation. Increased intra-ovarian androgens arrest follicular development.

Ovarian morphology on ultrasound

According to more recent transvaginal ultrasound technology, polycystic-appearing ovarian morphology should be characterized as either ~20 follicles per ovary or an ovarian volume of ~10 cm3 on either ovary, with a transducer frequency of 8 MHZ or greater. According to the latest evidence within 8 years of menarche first two criteria are enough and ultrasound is not recommended as multicystic ovaries are common at this stage[24].

Long-term morbidities

Infertility is a disease of the reproductive system defined by the failure of a couple to achieve a clinical pregnancy after 12 months or more despite more of regular unprotected sexual intercourse[25]. PCOS is the primary cause of anovulatory subfertility and 5-6% of infertility noted related to anovulation[26]. Absence of ovulation and menstrual cycle due to PCOS prevents fertilization and conception ultimately preventing the pregnancy leading to infertility. Infertility was 15-fold higher in women reporting with PCOS and noted by 72% of women reporting with PCOS, compared those not reporting PCOS[27].

Women with PCOS may affect with adverse pregnancy outcomes even pregnancy occurred due to increased androgen, and hyperinsulinemia. Increased the risk of gestational diabetes, pre-eclampsia, multiple pregnancies related to use of fertility therapies, risk of miscarriages and pre mature birth could be resulted[8,20,28].

Besides reproductive abnormalities, PCOS is also associated with range of metabolic comorbidities and psychological consequences and increase long-term risk for additional disorders including impaired glucose intolerance, diabetes mellitus, cardiovascular disease, hypertension, dyslipidemia, malignancy (breast, endometrial and ovarian cancers), obesity and nonalcoholic fatty liver[8,29,30].

Apart from the physiological maladies women with PCOS have an increased prevalence of mood disorders, including depression, negative body image perception, low self-esteem, anxiety, obstructive sleep apnea, binge-eating and impaired health related quality of life[31].

Treatment

Treatment of PCOS must always be unique for the individual patient and often multifactorial to adapt actual needs of the patient[5,20]. Treatment of PCOS is symptom-oriented and so far, no pharmacological treatment has been approved[10]. Lifestyle interventions such as weight loss, dietary habits and physical exercise are recommended as the first-line therapy in all cases to prevent and treat obesity and to improve metabolic

dysfunction and fertility. As evident 40-50% of women have improved ovulation with lifestyle interventions and 30-40% who are able to achieve spontaneous pregnancy. Calorie-restricted diets, behavioral treatment and exercise should be included in lifestyle intervention and should be long-term, dynamic and adapted to the personal needs and expectations.

Medical management of PCOS engaged management of acute issues of hyperandrogenism, oligo-anovulation and IR. Clinical hyperandrogenism with dermatological manifestation of hirsutism, acne and alopecia manage with combination of oral and topical dugs with cosmetic techniques. Combination of oral contraceptives and antiandrogens are commonly used[32]. Androgen receptor antagonists (spironolactone, cyproterone acetate and flutamide, or the 5 alpha-reductase inhibitor finasteride) and oral contraceptives have proven useful overarching effect on reducing the hyperandrogenism and normalizing menstrual cycle[33]. Nevertheless, oral contraceptive pills are suitable only for women who are not attempting to conceive[34]. Among first line treatments mentioned above, flutamide is getting popular since it improves menstrual cycle, reduce hirsutism and acnes, improved the lipid profile with marked reduction in total cholesterol and triglycerides but its possible impact on fertility of the patients desiring to have children. Alternatively, anti-androgens include spironolactone and cyproterone acetate, steroidal angiotensin receptor blockers (AR) blockers have been tested and used in PCOS patients with varying degrees of success[35]. Though many of anti-androgenic compounds are effective in suppressing PCOS symptoms, evidence suggests that anti-androgens have unacceptable hepatotoxicity[34].

In many cases, insulin-sensitizers particularly metformin is used to manage IR and mainly considered in metabolically challenged patients to improve PCOS conditions. Metformin has identified with its effect on decreasing body weight and small improvement in menstrual and ovulatory function. However recent recommendations indicate that metformin should be considered in patients with abnormalities in glucose tolerance due to gastrointestinal side effects of nausea, vomiting and diarrhea. Menstrual dysfunction and subfertility are main consequences of oligo-anovulation[5]. For patients desiring for fertility treated with ovulatory agent such as clomiphene letrozole or clomiphene citrate and letrozole is superior. Gonadotropin ovulation induction or laparoscopic ovarian drilling can be considered if failure on clomiphene or letrozole[20].

All of the above-mentioned drug-based approaches are effective up to certain extent, but not entirely. Moreover, most of first line therapeutics are known to have side-effects. Long-term use of the hormone manipulators can result in obesity, cancer, psychiatric issues and range of other problems[8]. Inositols and glucagon-like peptide receptor agonists (GLP-1 RA) are newer agents in the treatment of PCOS[36]. Ceylon cinnamon also improves insulin sensitivity and lipid profile in PCOS. It increases chances of ovulation and has overall benefit in PCOS[37].

Summary

Polycystic ovary syndrome (PCOS) is a heterogeneous condition characterized by dysfunction in ovarian activity, with its primary manifestations influenced by a combination of genetic and environmental factors. Diagnosis relies on the identification of at least two features from menstrual irregularities, hyperandrogenism, and/or the presence of polycystic ovaries. Insulin resistance and hyperinsulinemia are central to the pathophysiology for many individuals, acting as amplifiers of hyperandrogenism, especially in those who experience weight gain. Contemporary strategies that demonstrate optimal outcomes in PCOS management encompass lifestyle adjustments for weight reduction and the use of insulin-lowering medications, showing notable success in treatment approaches.

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