



Polycystic ovary syndrome and its disorders: a review

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a common reproductive disorder which leads to infertility in association with several disorders like oligomenorrhea, obesity, type II diabetes mellitus and cardiovascular disorder. It is characterized by an increased level of androgen production and disordered gonadotropin secretion, which results in chronic anovulation. In fact, it is the leading cause of anovulatory infertility. It mostly affects the women of reproductive age. In this review, there is a detailed description about the clinical manifestations, diagnosis, etiologies and treatments.

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Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, present in 5-7% of women of reproductive age.¹ PCOS is a kind of heterogeneous disorder of unknown etiology. The heterogeneity of the ovarian morphology and clinical findings in patients with polycystic ovaries was first recognized by Stein and Leventhal in 1935.² It is characterized by increased level of androgen in serum and disordered gonadotrophin secretion which leads to anovulation. The morbidity may include hyperinsulinemia, insulin resistance, and early onset of type 2 diabetes mellitus, dyslipidemia, cardiovascular disease and infertility.

The polycystic ovary syndrome is originally called as Stein-Leventhal syndrome. PCOS is a common disorder in women in which the ovaries become enlarged with many cysts. The cysts are nothing but small undeveloped follicles. Over the time there is thickening and fibrosis of the ovarian which prevents the follicles from developing and not releasing the follicles later leading to anovulation. PCOS is the leading cause for infertility due to anovulation. The signs and symptoms may vary greatly among the patients having PCOS. The common features of polycystic ovary syndrome are hirsutism, acne, male pattern alopecia, polycystic - appearing ovaries, obesity and acanthosis nigricans. About 50-70% of patients with PCOS expressed symptoms like hyperandrogenism, hirsutism, acne and acanthosis.³ As the condition progresses it may lead to various complications like dysfunctional uterine bleeding, obesity, type 2 diabetes, endometrial cancer, high cholesterol and cardiovascular disease.⁴

Other names of polycystic ovary syndrome are Polycystic Ovary Disease (PCOD), Functional Ovarian Hyperandrogenism, Stein-Leventhal syndrome, Sclerocystic Ovary Syndrome and Ovarian Hyperthecosis.

Prevalence

The prevalence of PCOS has not been definitely established, because PCOS is inconsistently defined from one literature to other. In general population, the prevalence of PCOS among the women of reproductive age is estimated to be

4-12%.⁵ Not surprisingly, the prevalence of PCOS is higher i.e. 37-90% in patients who are having menstrual abnormalities and there is also increase in the presence of certain disease.^{6,7} According to a comparative study, the prevalence of PCOS is higher in patients with epilepsy than the patients without epilepsy.^{8,9,10}

Clinical Manifestations

The PCOS is characterized by a wide range of clinical manifestations which varies from one individual to other. Apart from the hallmark features like hyperandrogenism and anovulation, other conditions like type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease and malignancies including endometrial, breast and ovarian cancer are associated.

Hyperandrogenism

Hyperandrogenism is one of the principle features of PCOS where it can be detected by serum concentration of androgens like testosterone, androstenedione and the precursor of androgen, dehydroepiandrosterone sulphate (DHEA - S). The etiology of hyperandrogenism is unknown but it may be due to the abnormalities like inborn defects in the ovarian steroidogenesis, excessive steroidogenesis by the ovary due to hyperinsulinemia and LH stimulation due to excessive steroidogenesis by the ovary. LH stimulation plays a vital role in the etiology of hyperandrogenism in PCOS.¹¹ Abnormal production of gonadotropin - releasing hormone can cause a primary defect in the hypothalamus and also for the abnormal circulating levels of estrogen, androgen or insulin in PCOS.

Menstrual problems and infertility

Oligomenorrhoea and amenorrhoea are commonly present in PCOS patients.¹² Up to 10% of patients with PCOS have primary amenorrhoea and 75% of them have secondary amenorrhoea. Even though anovulation is a defining characteristic of PCOS; the more accurate feature is oligomenorrhoea because some of the patients of PCOS will ovulate occasionally.

Obesity

There is a worldwide public health emergency due to the increasing epidemic of obesity and its related diseases.¹³ Obesity

is one of the characteristic features of PCOS but it is not seen in all PCOS.¹⁴ Obesity has profound effects on both the pathophysiology and clinical manifestation of PCOS. Compared with normal weight women with PCOS, those with obesity had poorer menses, worsened hyperandrogenic and metabolic state and poorer pregnancy rate. Obesity is thickly associated with PCOS. Although the cause is unknown, but obesity is present in nearly 30% of cases and in some cases the percentage is even higher like 75%.¹⁵

Type 2 diabetes and insulin resistance

The association between glucose intolerance and hyperandrogenism was first made by Achard & Thiers (1921) and called 'the diabetes of bearded women'.¹⁶ Insulin resistance may be defined as reduced glucose response to a given amount of insulin. The insulin resistance can be brought about by peripheral target resistance, decreased hepatic clearance or increased pancreatic sensitivity. The link between PCOS and insulin resistance and type 2 diabetes has been observed independent of obesity.^{17,18} There is a decreased insulin sensitivity in PCOS patients, when compared with the non-obese PCOS patients.¹⁹ The prevalence of type 2 diabetes is found to be higher in PCOS patients 15-33%, compared with patients without PCOS 2-24%. Insulin resistance is an important factor in the pathogenesis of hyperandrogenemia and anovulation. Excessive serine phosphorylation of insulin receptor is a possible mechanism for insulin resistance in at least 50% of PCOS suffers. A finding suggests that insulin resistance and elevated LDL levels cluster in families with PCOS, where these traits have their genetic component.

Blood Lipid Abnormalities

Patients with PCOS are at a high risk for dyslipidaemia due to elevated level of androgen, body fat distribution and hyperinsulinaemic resistance. Patients who suffer from PCOS have high levels of total cholesterol, LDL cholesterol, very low density lipoprotein cholesterol and triglycerides. They have a low level of high density lipoprotein (HDL) and HDL₂ when compared with normal healthy women.²⁰ Some studies shows that PCOS patients have atherogenic lipoprotein profile where there is a high concentration of atherogenic small, dense LDL III relative to body mass index of normal women. Even there is an increased hepatic lipase activity in PCOS patients. There is an increased circulating level of plasminogen activator inhibitor, PAI-1. The elevated PAI-1 activity levels are linked to insulin resistance and increased thrombotic vascular events, which may leads to atherosclerosis.

Cardiovascular Disease

Women who are suffering from PCOS constitute risk factors for cardiovascular disease.²¹ Some retrospective studies say that there is a link between PCOS and cardiovascular disease. Birdsall *et al.* (1997) carried out a survey regarding PCOS patients.²² He carried out a pelvic ultrasound scan for 143 PCOS patients undergoing cardiac catheterization. There was no significant difference in the prevalence of polycystic ovaries in patients with coronary artery lesions and normal arteries. However, PCOS patients were affected more. Various studies have been done on other aspects of endothelial functions and its association with PCOS. According to a report, there was a lower cardiac flow velocity, higher resting forearm flow during reactive hyperaemia and lower incremental forearm flow in the PCOS patients rather in normal control women of same age. Moreover there was thicker carotid artery and coronary artery calcification seen in PCOS patients when compared to the

normal women of same age group, which shows the presence of atherosclerosis.²³ Although these evidence support that PCOS increases cardiovascular disease risk, PCOS patients does not experience a higher risk of cardiovascular disease when compared to normal women. Results of a UK report say that there was no correlation between the cardiovascular disease and PCOS. So, further research studies are needed for more and better understanding.

Cancer

There are many evidences proving a link between PCOS and cancer. Mostly, infertility predisposes towards cancer in PCOS patients. The association between infertility and cancer was proved in epidemiologic and also in single case reports. There are many gynaecological cancers prevailing among women. Among that endometrial cancer is the most common especially in developed countries including North America, Europe, Australia, New Zealand and Japan. According to a study, patients who are suffering from chronic anovulation have three times higher risk of endometrial cancer.²⁴ There are many possibilities of getting endometrial cancer, one potential risk is pre existing PCOS and others are consequent exposure of endometrium to oestrogen, which is unopposed by progesterone. The endometrium of PCOS patients have a high concentration of estrogen receptors²⁵ and they also show greater CYR61 protein expression, which is an angiogenic factor.²⁶ Not only this, the CYR61 protein is also an apoptosis regulator and is associated with tumourogenesis.²⁷ Ovarian cancer is also associated with PCOS. According to a report there is 2.5 fold risk of getting ovarian cancer in women who are affected with PCOS.²⁸

Genetic factors and genes involved

Many studies suggest that genetic factors play a vital role in the etiology of PCOS but the mode of inheritance remains unknown.^{29,30} The recent studies depicts that PCOS could be a complex trait.³¹ This shows that PCOS is caused due to the interaction of many genes which is stimulated or provoked by the environmental factors.³² At the same time, biochemical parameters like fasting insulin levels or hyperandrogenemia seems to be highly heritable parameters which could be transmitted as autosomal dominant³³ or X linked dominant mode of inheritance³⁴, but genetic studies have not yet revealed the pattern of hereditary.³⁵ The inheritance of PCOS is as complicated as type 2 diabetes and cardiovascular disease. On the other hand a positive family history appears to be one of the risk factors in the development of PCOS.

It has been confirmed that there is an association between PCOS and X chromosome aneuploids and polyploids as well as other cytogenetic abnormalities. Studies show that there is a large deletion of the long arm of chromosome 11 in the patients of PCOS³⁶ but more cytogenetic studies are required to identify karyotype abnormalities.

Hypothalamic – pituitary abnormalities

In PCOS patients, the normal pulsatile secretion of luteinizing hormone (LH) is increased at the same time follicle stimulating hormone (FSH) is unchanged or muted. So there is a high LH level and the FSH: LH ratio can even be increased to 2.5. The abnormal secretion of gonadotropins may be due to the abnormality of gonadotropin releasing hormone pulse generator in the hypothalamus. The reason behind the process is unclear.

Elevated prolactin level is also a cause for PCOS. Nearly 25% of patients of PCOS has a high level of prolactin. Drastic increase of prolactin can stimulate adrenal production of DHEA-S. There is a decrease in the level of estradiol whereas there is

an increase in the estrone level.^{37,38} It is due to the extra glandular conversion of androstenedione in adipose tissue which further stimulates LH and inhibits FSH, causing hyperplasia of the ovarian stroma and theca cells which finally leads to elevated androgens.

Signs and Symptoms

The common symptoms of PCOS are oligomenorrhea, amenorrhea (absence of menses), anovulation, hirsutism (excess body hair), hyperandrogenism, alopecia, male pattern baldness, acne, oily skin, seborrhea, obesity, elevated LH level and decreased FSH level, depression, deepening of voice and infertility.

Histological features of PCOS

The histological features of PCOS include, Ovarian hypertrophy, thickened capsule (> 100µ), scarcity of corpora lutea or albicantia, increased number of sub capsular follicle cysts, hyperplasia and fibrosis of the ovarian stroma, premature luteinization of theca cells.³⁹

Diagnosis

The diagnosis of PCOS is primarily clinical. The National Institutes of Health (NIH) in 1990 proposed certain criteria for the diagnosis of PCOS. The diagnostic criteria were revised by the Rotterdam European Society of Reproductive Medicine (ASRM) - sponsored PCOS consensus workshop group in 2003, where the following criteria were established: oligo/amenorrhea, clinical and biochemical signs of hyperandrogenism and sonographically confirmed PCOS. The features are hyperandrogenism with chronic anovulation after identifiable causes are excluded. Menarche may be normal or delayed, and amenorrhea, oligomenorrhea or dysfunctional uterine bleeding may occur. There is no need of all the criteria to be present for the diagnosis.

There are many ways to diagnose the PCOS condition. Each symptom will change from one person to other. The patients must be subjected to laboratory investigation to exclude hyperprolactinemia, late onset congenital adrenal hyperplasia and androgen secreting tumours of the ovary or adrenal gland. Polycystic ovary can be sonographically diagnosed by ultrasound of the pelvic region. There will be atleast 10 subcapsular follicular cysts measuring 2 to 8 mm in diameter, which is arranged around or within thickened ovarian stroma giving the appearance of a 'string of pearls'.

Some of the serum analysis is also helpful in the diagnosis of PCOS condition. Elevated level of androgens including androstenedione, testosterone and DHEA -S is observed in the patients. Other tests in the serum, like concentration of LH and FSH are also done, where the level of LH will be higher and the FSH will be lower in concentration in the PCOS affected patients. Common assessments include fasting biochemical screen and lipid profile. Oral glucose tolerance test is also performed.

Biochemical Basis

The biosynthesis and/ or metabolism of androgen act a vital role in the cause etiology of PCOS. Nearly 50-70% of the patients who are suffering from PCOS had signs of androgen excess.⁴⁰ Enhanced possible mechanisms of the pathogenesis of PCOS are 5α-reductase activity, dysregulation of 11α-hydroxysteroid dehydrogenase type 1 activity and increased total adrenal steroid production. When CYP 17 gene is silenced in the rat ovary, there was a decrease in androstenedione, 17α-hydroxyprogesterone and testosterone production and also there was reduced progesterone levels.⁴¹ According to in-vitro studies

there was an increased level of steroidogenic enzymes in the theca cells when LH and insulin was administered, thus leading to steroidogenesis.⁴² In PCOS patients, majority of the androgens are secreted from the ovaries but according to a statistical study, approximately half of the patients had excessive production of adrenal androgens.⁴³ On the other hand the cause for the adrenocortical disturbances is still remains unclear.

DHEA-S is a metabolite of dehydroepiandrosterone which is an adrenal androgen which is produced by the adrenal cortex and it is also considered as a marker of adrenal androgen production. Around 25% of PCOS patients have supranormal levels of DHEA -S.⁴⁴ The enzyme called DHEA sulfotransferase (SULT2A1) helps in the sulfonation of DHEA mainly in the adrenal cortex and in turn the sulfonate is removed in DHEA -S by steroid sulfatase (STS), an enzyme that is expressed in many tissues, regenerating DHEA that can be later metabolized to active androgens or estrogens. According to a previous study the variation in SULT2A1 was associated with DHEA -S in PCOS patients.

Some studies have proved that hyperandrogenemia and hyperestrogenemia in PCOS like conditions is due to the deficiencies in the steroidogenic enzyme deficiency such as 3 β hydroxysteroid dehydrogenase type II and aromatase. An increased production of testosterone and insulin in the PCOS patients directly down regulate sex hormone binding globulin (SHBG) synthesis by the liver which makes a low SHBG level, a good indicator of insulin resistance.⁴⁵ SHBG has a very strong binding affinity towards testosterone and dihydrotestosterone thus controlling androgen availability in serum.⁴⁶ Reduced level of SHBG results in the increased level of bioavailable of testosterone. Since serum bound testosterone is the most frequent androgen which is measured to diagnose hyperandrogenemia.

Knochenhauer *et al.* (1998) showed that only 18% of PCOS patients had abnormally elevated level of thyroxine (T4), which is blunted by high testosterone level.⁴⁷ Insulin binds to insulin like growth factor 1 (IGF-1) receptors on the theca cells with significantly higher affinities than IGF-1.⁴⁸ Hepatic IGF-1 binding protein secretion is also inhibited in PCOS patients, leading to excessive free IGF-1, which is supposed to play a vital role in the abnormal androgenesis of the theca cells along with high LH. IGF-1⁴⁹ and insulin additionally increase mRNA of P450c17 which leads to increased androgen biosynthesis in ovary and adrenal glands.⁵⁰

Treatments

Polycystic syndrome is one of the most common disorders in women and the manifestations may vary from individuals. Each patient may need a special treatment according to their symptoms. Non pharmacological measures like diet, exercise and weight reductions are universally accepted. Weight loss in obese patients increases the endocrine profile and also the chance of ovulation and pregnancy. When 5% of the weight is reduced from the initial body weight, there was a lot of improvement in the ovulation and menstrual cycle. Diet and exercise plays an important role in PCOS patients because they improve the metabolic consequences like reduction in hyperinsulinemia, P450c17 activity in ovary, plasminogen activator inhibitor activity and triglycerides and an increase in the HDL level. In PCOS patients, anovulation is due to low follicle stimulating hormone and the arrest of follicle growth in the final stages of maturation and this can be treated with medications like clomiphene citrate, tamoxifen, aromatase

inhibitors, metformin, glucocorticoids or gonadotropins or surgically by laproscopic ovarian drilling. If other options fail, then in-vitro fertilization is the last option for getting pregnant. Alternative medicines like kinesiology, herbalism, homeopathy, reflexology, acupressure, acupuncture and massage therapy are emerging and they are very useful in the treatment. One of the most common modality is the acupuncture. It helps in the regulation of periods.

Conclusion

Polycystic ovary syndrome is the leading cause of anovulatory infertility. It is a serious problem prevailing in the women of their reproductive age. PCOS is a syndrome which is curable at early stage and if it is ignored, then it leads to very serious conditions like endometrial cancer and ovarian cancer. Changes in the life style and diet habit can bring some changes in PCOS. When compared to all therapies natural therapy is always good and also there are no side effects. Herbal drugs have an eminent role in the treatment of PCOS with minimal side effects. Herbal supplements, may take some time to cure but the disease can be treated from its root. PCOS is an enigma, where the exact cause for the occurrence is not known. So, more sophisticated study is needed for better understanding of the disorder.

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