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AN UP TO DATED OVERVIEW ON POLYCYSTIC OVARY SYNDROME (PCOS); CURRENT STATUS OF TREATMENTS IN VARIOUS SYSTEMS OF MEDICINES

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex metabolic, endocrine and reproductive disorder affecting 5-10% of women of reproductive age. Irregular periods, acne, excessive hair growths are the common symptoms of PCOS. Prevalence of PCOS varies depending on the diagnostic criteria used. Insulin resistance, genetic factors, hormonal imbalance, high maternal androgen are the common predisposing factors associated with PCOS. PCOS is a multifaceted metabolic disorder that shows a high association with insulin resistance leading to hyperinsulinemia. The main risk factors for PCOS include obesity, family history of infertility, diabetes & other psychological factors. Metabolic syndrome, cardiovascular complications, oncology, infertility are the complications associated with PCOS. PCOS can be managed through diet, exercise therapy, lifestyle modifications. National institutes of health criteria (NIH) defined in 1990, later in 2003 the Rotterdam criteria used to diagnose PCOS. Allopathy, Ayurveda, Siddha, Homoeopathy and Acupuncture are the various systems of treatments used for PCOS. Allopathy does not cure PCOS, but helps in managing and controlling effects while in Ayurveda and Homoeopathy can be considered as best cure and promising treatment with no side effects. PCOS is becoming a more prevalent disorder among women of reproductive age with lifelong complications. In the future, research in the area of genetics and pathophysiology of PCOS is needed to determine preventive risk factors as well as successful treatment modalities for this syndrome.

Keywords: Polycystic ovary syndrome, Diabetes, Insulin, Allopathy, Ayurveda, Siddha, Homoeopathy, Acupuncture.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex metabolic, endocrine and reproductive disorder affecting 5-10% of women of reproductive age [1]. PCOS is also called as polycystic ovary disease (PCOD), Stein-Leventhal Syndrome, Ovarian hyperthecosis and sclerocystic ovary syndrome. PCOS means the ovaries containing a large number of small cysts that are not bigger than 8mm and develop to 12mm or more follicles, increased ovarian volume (>10ml) [2]. The cysts are the egg containing follicles that do not develop properly because of hormonal imbalance [3]. PCOS consider as a lifestyle disorder affecting 22-26% of young girls in their reproductive age in India [4]. The characteristics of PCOS include polycystic ovaries, hyperandrogenism, irregular menstrual cycles, and metabolic abnormalities such as hyperinsulinemia and obesity. PCOS adversely affects health related quality of life and increased risk of depression and anxiety [5,6].

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SIGNS AND SYMPTOMS

Symptoms like irregular periods with in 3 or 4 years of starting menstrual lighter very heavy bleeding during period weight gain, excessive hair growth to varying degrees on face, chest, and lower abdomen, abdominal discomfort during periods, acne, and excessive skin growth or in armpit also called as skin tags [3]. Bone pain

(arthralgia)and hair loss (alopecia), constipation, hidradenitis suppurativa (chronic inflammatory skin condition), indigestion, skin dryness, increased androgen level, triglyceride problems, infertility, imbalance of lipids, improper cholesterol level, excessive weight gain around hip and stomach, pregnancy problems are the common symptoms of PCOS [5]. In some patients due to insulin resistance a dark coloured band like skin lesion may be developed at the back of the neck, inner thighs and axilla called as acanthosis nigricans [**7**]. Depression and anxiety are the other symptoms of PCOS [5].

PREVALENCE

Prevalence of PCOS varies depending on the diagnostic criteria used. The prevalence estimate using the Rotterdam criteria are two to three times greater than those obtained using the NIH/NICHD criteria. The prevalence of PCOS was 40.5% in the type 1 diabetes group and 2.6% in the control group. In case of type2 diabetes PCOS was extremely common, occurring in 82% of women. The prevalence of PCOS in type2 diabetes using the NIH/NICHD criteria has been estimated to be 26.7% [8]. According to Ferriman- Gallwey (F-G) method the prevalence of hirsutism varied from 2–8% with no significant difference between white and black women. Using an F-G score of 6 or more as indicative of hirsutism, 3.4% of blacks and 4.7% of whites had PCOS as defined. These data suggest that PCOS may be one of most common reproductive endocrinological disorders of women. Using ADA (American Diabetes Association) criteria, only 3.2% of PCOS women would have been classified as having diabetes, whereas 7.5% had diabetes by WHO criteria, a difference of 4.3%. The prevalence rate of IGT (Impaired glucose tolerance) is also higher than that in another profoundly insulin-resistant group of reproductive age women. Metabolic syndrome (MS) is a common disorder and is thought to be extremely prevalent in polycystic ovary syndrome (PCOS). Metabolic syndrome is substantially higher in women with PCOS than in the general population, and the prevalence is higher in those women diagnosed by classic criteria. The metabolic syndrome was codified in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. This definition includes fasting glucose, waist circumference, and blood pressure and lipid criteria. The main changes in the modified American Heart Association/National Heart Lung and Blood Institute definition (ATP III) include 1) ethnic specific waist circumference and 2) reducing the threshold for impaired fasting glucose as per revised American Diabetes Association definition. The prevalence of the metabolic syndrome in women with PCOS has wide variations and it ranges from 16.6% to 47.7% depending upon the population studied and the criteria used for the diagnosis of the metabolic syndrome [9].

PREDISPOSING FACTORS

Insulin resistance

PCOS is a multifacted metabolic disorder that shows a high association with insulin resistance leading to hyperinsulinemia, wherein 10% show type 2 diabetes. 30-35% women have impaired glucose tolerance, such a condition leading to increase the production of testosterone thus leading to abnormal or non- existent ovulation. High activity levels of micro RNA named miR-93 in fat cells hinder the use of glucose by insulin contributing PCOS and also to insulin resistance [1, 10]. Women with endocrine syndrome of hyperandrogenism and chronic anovulation appear to be insulin resistant and high risk for glucose intolerance [11]. Insulin also has a direct gonadotrophic action on ovarian steroidogenesis. Insulin will amplify the steroidogenic response of both theca cells and granulosa cells to LH in human ovary [12]. Insulin resistance promote a high hepatic secretion of very low density lipoprotein (VLDL).Insulin resistance also associated with reduced clearance of VLDL particle and chylomicrons. Hepatic content of triglycerides is high, large VLDL particles are produced, which result in the formation of small, dense LDL particles that are poorly cleared and more atherogenic [8].

Genetic factors

PCOS is a genetically determined ovarian disorder and the heterogeneity can be explained on the basis of interaction of the disorder with other genes and with the environment. Gene implicated in the development of obesity is also linked to susceptibility to PCOS. Excessive exposure to androgens during intra-uterine life may have a permanent effect on gene expression leading to PCOS and later in insulin resistance. First degree relatives of patients with PCOS may be at high risk for diabetes and glucose intolerance. An underlying genetic defect conferring insulin resistance and perhaps β-cell dysfunction interacts with environmental factors worsening insulin resistance. PCOS is a complex genetic disorder; the effect of any one gene may be small. The mode of inheritance remains unclear, an autosomal dominant disorder has been proposed, suggesting a single gene effect. PCOS is a complex endocrine disorder involving more than one, and probably several gene [10,11].

Hormonal imbalance

The imbalance of certain hormones is common in women suffering from PCOS. High testosterone levels leading to signs of hyperandrogenism, High luteinizing hormones (LH) disrupt proper ovarian functions, Low Sex Hormone Binding Globulin (SHBG) leading to hyperandrogenism, High prolactin levels. The exact reason for this hormone imbalance is unknown. Hyperinsulinemia may directly or indirectly result in LH secretion that leads to hyperandrogenemia [13].

High maternal androgen

Maternal androgens, in women with PCOS are able to cross the placenta in significant amounts in human pregnancy. The excess androgen in PCOS originates from foetal ovary although the adrenal may also play a role. Foetal ovary is steroidogenically inactive; the ovary has the capacity to synthesize androgen in prenatal life. If the foetal ovary does not produce significant amount of androgen the postulate is that the ovary is genetically predisposed to hypersecrete androgen. Hyperinsulinemia produces hyperandrogenic state by acting as a gonadotropinwith LH. Increasing androgen production by theca cells and by reducing hepatic production of SHBG resulting in higher concentration of free androgens [12].

RISK FACTORS

The main risk factors for PCOS include obesity, family history of infertility & diabetes, high calorie food, stress and other psychological factors, bisphenyl A, sedentary lifestyle. Family history of diabetes, notably an inherited metabolic disorder, also posses significantly high risk for PCOS. The mother's irregular menstruation contributes high risk of PCOS in daughter. First degree relative with diabetes was associated with an increased risk of glucose intolerance in PCOS women [13-15]. More frequent consumption of fast food has 1.7 times greater risk of development of PCOS. Fast food usually contains high amounts of saturated fats and steroids frequent consumption of fast food and irregular eating habits leads to fluctuations in glucose levels, insulin resistance and increases hormonal imbalance such as hyperandrogenism adding to the risk for development of PCOS [14]. Use of pickled food, coarse food, drinks and salty food, with irregular diet leads to PCOS. Lack of physical exercise, leading to uneven distribution of body fat, is an important risk factor of centripetal obesity (13).Obese women are 1.74 times more risk for development of PCOS compared to women with normal BMI. Sedentary lifestyle, access to high calorie food and machineries for all house hold works has been attributed to the higher risk of PCOS [14-15]. Valproic acid, an antiepileptic drug is associated with features of polycystic ovary syndrome when used to treat women with epilepsy. These features include menstrual disturbances, polycystic ovarian morphology, and elevated serum testosterone [8]. Bisphenyl A (BPA), a common industrial compound used in dentistry, plastic consumer products and packaging to be a probable cause of PCOS. They found a significant positive association between male sex hormone and BPA in women with PCOS suggesting that BPA probably has a role in ovarian dysfunction [10]**.** Majority of women with PCOS were residing near mobile towers or sewage [15]. Increased stress can upset the normal menstrual cycle and causes hormonal changes such as raised level of cortisol and prolactin. Tobacco use is especially unhealthy for women with PCOS.

COMPLICATIONS

Patients with PCOS present not only a higher prevalence of classic cardiovascular risk factors, such as hypertension, dyslipidemia, and type-2 diabetes mellitus, but also of non- classic cardiovascular risk factors, including mood disorders, such as depression and anxiety. Women with PCOS also show an increased risk of endometrial cancer compared to non-PCOS healthy women, particularly during premenopausal period**.**

Metabolic syndrome

PCOS is a common disorder of women of childbearing age and is associated with *metabolic syndrome* (MS).*Non-alcoholic fatty liver disease* (NAFLD) is considered as the hepatic manifestation of metabolic syndrome. PCOS is considered as the ovarian manifestation of metabolic syndrome. Both these conditions can co-exist and may respond to similar therapeutic strategies [16].

Cardiovascular complications

PCOS at any age is characterized by elevated CVD risk markers and these elevated markers can occur without obesity but are magnified with obesity**.** Among the cardiovascular risk factors, T2DM represents one of the most important and PCOS is considered a major risk factor for developing impaired glucose tolerance (IGT) and T2DM.CVD risk factors such as hypertension and hypertriglyceridemia were more prevalent among the PCOS women at postmenopausal stage [17,18].

Oncology

Since PCOS is considered as a lifelong multi-systemic disorder the reproductive and metabolic alterations characterizing the syndrome may be associated with an increased risk of the development of cancers, such as the endometrial, ovarian, and breast cancer [17].

Infertility

PCOS is the most common cause of ovulatory disorder and oligoanovulation is related with increased risk for infertility. Insulin resistance (IR) and obesity were independently related to an increased risk of abortion and to reduce pregnancy and live-birth rates [17].

PATHOPHYSIOLOGY

Various theories have been proposed to explain the pathogenesis of PCOS. They are as follows: An alteration in gonadotropin releasing hormone secretion results in increase of LH secretion, an alteration in insulin secretion; leads to hyperinsulinemia and insulin secretion, Defect in androgen synthesis leads to increase in ovarian androgen production.

LH hypersecretion: Various etiologies introduced for the hypersecretion of LH include hypothalamic dysfunction, reduced pituitary sensitivity to gonadotropin releasing

hormone [GnRH] and increased pulsatality of GnRH. Increase in LH leads to increase in androgen production by theca cells within the ovary. Hyperandrogenism is one of the primary symptoms of PCOS, which is observed in 60 - 80% of women with PCOS [3]. The majority of patients with PCOS have insulin resistance and/or obesity. Hyperinsulinemia increases GnRH pulse frequency, LH over FSH dominance, increased ovarian androgen production, decreased follicular maturation and decreased SHBG binding. All these factors contribute to the development of PCOS [19]. Insulin resistance further leads to development of Type 2 diabetes mellitus. Insulin acts collaboratively with LH to enhance androgen production in the ovarian theca cells. It also decreases hepatic synthesis and sex- hormone binding globulin [SHBG] secretion, a hormone which binds testosterone therefore increasing the amount of free testosterone which is biologically available. All these factors contribute to the development of PCOS [3, 20].

DIAGNOSIS

The diagnosis of PCOS is based on hyper androgenic or chronic anovulation in the absence of specific pituitary and or adrenal disease. The criteria for diagnosis have been proposed, National institutes of health criteria (NIH) defined in 1990 later in 2003 the Rotterdam criteria used polycystic ovarian morphology on ultrasound as a new criteria [21]. Various diagnostics are**;** History and physical examination, Ultrasonography, USG (Determination of B/L enlarged ovaries with multiple small follicles), Testing of hyperandrogenemia [22, 23].

Laboratory tests for diagnosis of PCOS

FSH (follicle stimulating hormone) will be normal or low with PCOS, LH (luteinizing hormone) will be elevated, prolactin level also elevated. Estrogens may be normal or elevated, Lipid profile-low HDL and high LDL, Glucose test-Fasting and or a glucose tolerance test. Insulin often elevated, TSH (Thyroid stimulating hormone) check thyroid function, any abnormality chances for PCOS. Free cortisol and creatinine levels, Dehydroepiandrosterone-sulphate (DHEA-S) values may be normal or slightly elevated in PCOS.DHEA-S valueswarrant consideration of an adrenal tumor [24, 25].

MANAGEMENT

PCOS can be managed through diet, exercise therapy, lifestyle modifications.

Diet

Eucaloric and Ketogenic diet are followed to manage the PCOS. Insulin inhibits the production of SHBG (sex hormone binding globulin) and stimulates the androgen production. Eucaloric diet enriched with MUFA (Monounsaturated fatty acids) or low in concentrations of carbohydrate would decrease insulin concentration and androgen production. Small decrease in body weight following the low carbohydrate diet contributed observed reduction in fasting insulin. Eucaloric low carbohydrate diet, which was relative low in carbohydrate and cholesterol, high in fibre, and 45% fat improved metabolic profile of women with PCOS within 16 days. This information may allow clinicians to modify treatment regimens [26]. Ketogenic diets are characterized by reduction in carbohydrate (less than 50g/day) and increase fat and protein proportions. Low carbohydrate diet can lead to improvement in metabolic pathways and have beneficial health effects. Ketogenic diet reduces the insulin like growth factors-1 (IGF-1) &reduction in blood insulin level.

Exercise therapy

Aerobic exercise & regular exercise are used to control PCOS [27]. Aerobic exercise without weight loss improves insulin sensitivity and ovarian morphology in women with PCOS. In comparison to dietary restriction, aerobic exercise led a 40% higher rate of ovulation and greater improvement in SHBG and testosterone. Aerobic exercise results in a greater reduction in fasting insulin and insulin resistance (28,29). Exercise induced change in visceral fat and ectopic lipid in non- fatty tissues. Exercise appears to have beneficial effects, with reports of improvements in fitness, body composition, fasting insulin, IR, ovulation, quality of life scores and depression. The combination of exercise and dieting has been extensively reported to substantially increase weight loss compared with dieting or exercise alone. With addition of exercise providing better long term weight maintenance. Menses frequency and ovulation rate were higher in the exercising group with a trend for higher pregnancy rates and greater improvement in hormonal profile. Regular moderate intensity aerobic exercise over a short period improves reproductive outcomes including ovulation and menstrual cycle regulation in addition to reducing weight and IR in young overweight women with PCOS [29,30].

Lifestyle modifications

Lifestyle (diet and exercise) intervention improves the level of FSH, SHBG, total testosterone, androstenedione and FAI (free androgen index) and FG (Ferriman- gallwey) scores in women with PCOS. Exercise alone improves all these outcomes except FAI and LH. Lifestyle intervention or exercise alone showed a favourable improvement in hirsutism [31]. Metformin and lifestyle appears to offer benefits in weight loss and menstrual cyclicity [32].

CURRENT STATUS OF VARIOUS SYSTEM OF TREATMENTS FOR PCOS

Allopathy, Ayurveda, Siddha, Homoeopathy, Acupuncture are the various system of treatments used for PCOS.

Allopathy

Metformin (oral antihyperglycemic agent- Biguanide)

It alter the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation & endometrial growth. Daily dose is 500mg with food. Lactic acidosis, nausea, diarrhoea are the common side effect. The use of metformin is associated with increased menstrual cycle, improved ovulation, reduction in circulating androgen levels.

Rosiglitazone (oral antihyperglycemic agents)

It improving the insulin sensitivity, daily dose is 8mg. Edema, nausea, dry skin, vomiting is the common side effect. The use of rosiglitazone is associated with improve ovulation& increase pregnancy rate.

Clomiphene citrate (Estrogen receptor antagonist)

Interferes with negative feedback of the estrogen-signaling pathway, resulting in increased availability of FSH.50-150mgare administered for 5 days. Stomach pain, bloating, blurred vision are the common side effects. Used to treat infertility in women & first line treatment for ovulation.

Dexamethasone (Glucocorticoids)

It decreases androgen secretion with no adverse antiestrogenic effect. Daily dose is 0.25-0.5mg at bed time. It helps to induce ovulation. Nausea, stomach pain, spinning sensation is the common side effects.

Letrozole (Aromatase inhibitors)

Inhibit estrogen production in the hypothalamus-pituitary axis which implies an increase in gonadotropin-releasing hormone & FSH.

Oral contraceptive pills, Antiandrogens, Glucocorticoids, GnRH agonist, Insulin-lowering agents, and Laser technique are used for hirsutism. Both oral contraceptive pills and antiandrogens have been used in the treatment of acne. Oralcontraceptive pills, androgen blockers, Cyproterone acetate has had some effect on alopecia (33). Nowadays, the use of antioxidant in management of women with PCOS has attracted lots of interests. Antioxidant supplementation has been shown to improve insulin sensitivity and other health threating conditions in women with PCOS. Antioxidant supplements include calcium and vitamin D, N-Acetyl cysteine, Zinc, Folic acid&Soybeans [34].

Ayurveda

Allopathic medicines have mild to severe side effects, so now Ayurvedic medicines are mainly used. Ayurvedic treatment protocol for PCOS include:- Shodhanachikitsa, Shaman chikitsa, Lifestyle management,Yoga and pranayama therapy. Shodhanachikitsa include Basti (Enema of medicated oil or decoction is given through rectum), Uttar basti (It help to purification & clears the AartavaVahaSrotas, improve follicular maturity), Virechan (drugs eliminate the bowel movement& eliminate body toxins), Vaman (Vaman procedure purifies internal toxins, this balance hormonal system).Shaman chikitsa, wide range of medicinal herbs are used like; Shatavari, Kumari, Ashoka, Lodhra, Guduchi, Triphala& Dashamoola [35]. ShilajatuRasayana, Nastapushpantaka Rasa, Shatapushpachurna are the herbal formulation used for PCOS [35, 36]. Weight loss is the most essential part of the treatment. Several Yoga postures aid in weight loss, relieve stress and improve the ovarian blood supply. Different Asanas like; Sarvangasana**,** Ardhmatsyendrasana**,** Mandukasana, Surya namaskara,Paschimottan asana. Different pranayama like; Kapalabhati**,** Ujjayi**,** Anuloma- Vilomaare used for PCOS [4].

Siddha

Siddha medicine is a treatment which is followed by an ancient tamilians. It has no side effects and cost efficient. Siddha treatment based up on the patient symptoms; for the endometrium problem Nochi is used, for amenorrhea *Raphanussativa* (mulangi), *Nigella Sativa* (Karunjeeragam), *Trigonellafoenumgracaum*(venthayam), *Daucuscarota*(wild carrot) are used, for menorrhagia *Saracaindica*, *Symplocosracemose*, *Glycyrrhizaglabra*, *Cynodondactylon* are used. For other symptoms Kalarchikari, *Aloe barbadensis*, *Cadabaindica*, thipili are used [37].

Acupuncture

Acupuncture are mediated through endogenous opioid peptides in the central nervous system, particularly β-endorphin (38). Because these neuropeptides influence gonadotropin secretion through their action on GnRH and acupuncture may impact on the menstrual cycle through these neuropeptides. Besides its central effect, the sympatho inhibitory effects of acupuncture may impact on uterine blood flow. Physiological responses produced by acupuncture vary depending on site, intensity and duration of stimulation [36, 39].

Homoeopathy

Sepia, Pulsatilla, Calcarea Carb, Thuja Occidentalis, Lycopodium are the homoeopathic medicines used for PCOS [3].

FUTURE PERSPECTS

PCOS is becoming a more prevalent disorder among women of reproductive age with lifelong complications. In the future, research in the genetics and pathophysiology of PCOS is needed to determine preventative risk factors as well as successful treatment modalities for this syndrome.

Diagnosis

Hyper androgenism testing is the most promising diagnostic criteria for PCOS which may be inaccurate or yield unreliable results. Since such a high percentage of

PCOS patients display hyperandrogenism, a better method of evaluating and testing symptoms must be formulated.

Immunology

Women with PCOS have increased levels of inflammatory mediators includes, TNF-α, IL-6, IL-1, IP-10, CRP and IL-18. Women with PCOS often exhibit low levels of progesterone, causing anovulatory complications. The absence of progesterone in PCOS patients may lead to overstimulation of the immune system, inducing autoantibodies [40].

Insulin resistance

Future research should aim at assessing the insulin resistance includes following: how to best measure insulin sensitivity, standardization of insulin measurements, identification of strong surrogate biomarkers of insulin resistance etc.

Treatment

Recent studies reported that Metformin promotes apoptosis and inhibits the growth of uterine serous carcinoma in endometrial cancer. Metformin along with an oral contraceptive pills (OCP) is a new treatment option, which can reduce risk of endometrial cancer by 50-70% in the PCOS populations. On the other hand, OCPs also have a risk of cardio-metabolic effects, which are already heightened in women with PCOS, especially if they are obese [40] .Standardisation and fixed study protocols, where all patients receive the same treatment will increase the validity of treatment studies in future [41].

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Nil

CONFLICT OF INTEREST

Nil

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