**A Review On Polycystic Ovarian Syndrome (PCOS)**

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**Abstract:**

**Polycystic ovarian syndrome is a diverse condition in that it can impact numerous bodily systems and be influenced by a wide range of circumstances. Numerous mental illnesses, such as anxiety and depression, have been associated with a higher prevalence of polycystic ovarian syndrome. There is a dearth of study on the socioeconomic impact that these conditions may have on PCOS patients and society at large. The relationship between PCOS and mental health is now the subject of various theories. According to some, PCOS patients' hyperactive hypothalamic-pituitary-ovarian and hypothalamic-pituitary-adrenal axes may change their hormonal profile and play a role in the emergence of mental illnesses.**

**Key point: PCOS, epidemiology, factors, complication, pathophysiology, non-pharmacological treatment**

**Introduction :**

 **Polycystic ovarian syndrome (PCOS) is currently considered as possibly the most frequent cause of female infertility, Stein-Leventhal syndrome and functional ovarian hyperandrogenism are the other name of PCOS . eight percent of reproductive age woman will be diagnosed with polycystic ovarian syndrome .1 It is a one very common hormonal, metabolic, and reproductive disorder . In this provide a rationalized overview of the longstanding health effects, pathophysiology, diagnosis and therapy and treatment of PCOS.2 Compared to women without the illness, those who have it are more likely to experience cardiometabolic difficulties. Although adverse cardiometabolic indicators differ amongst PCOS affected individuals, they are tangentially related to both fertility and the results of conception.3**

 **PCOS is a complex illness with a broad spectrum of symptoms that affects not only teenage girls and women going through menopause, but also females in the reproductive stage of life. Due to the nature of the condition, PCOS has a detrimental effect on women's reproductive health and fertility. Furthermore, it is a significant contributor to metabolic and cardiovascular morbidity because of its association with other lifestyle conditions. Even though many theories have been put up, ranging from genetic susceptibility to exposure to the environment during both prenatal and postnatal life, the precise etiology and pathophysiology of PCOS are still being investigated.4**

 **Epidemiology of PCOS :-**

 **The impacts of PCOS in India have been the subject of very few studies, and much of the sampling was done so for convenience rather than accuracy in recreating the true incidence of PCOS in the society. Tested early adolescent females in Tamil Nadu, an experimental cross-sectional study found an 18% prevalence of PCOS.5 The results of a Lucknow study that examined college students who were studying menstrual irregularities and hirsutism within the age range of 18 to 25 years showed that the participants' predicted prevalence, as determined by the NIH criteria, was only 3.7%.6**

 **Additionally, they found that women in cities had a larger chance of developing PCOS than women in rural areas. Similar to this one, an urban community-based study conducted in Mumbai found that the prevalence of PCOS was 22.5% by the Rotterdam criteria and 10.7% by the Androgen Excess Civilization criteria.7 A study was conducted among medical professionals at a private medical facility in India using the modified Cronin questionnaire.8 6% of Chennai's female residents who live in both rural and urban communities have PCOS, according to the Rotterdam criterion.9 In a different Andhra Pradesh study, 9.13% of the young women enrolled in a residential college satisfied the Rotterdam criteria for PCOS.10 International surveys indicate that between 4 and 10% of women who are fertile have PCOS.11 The prevalence of PCOS has been found to differ according on the criteria used in this study, making it difficult to reach a clear conclusion. This variance in prevalence estimates among studies from India and other nations may possibly be directly related to this variable. Thus, it is possible to estimate that between 3.7 and 22.5% of Indian women have PCOS based on the limited evidence that is currently available.12**

**Sign & Symptoms :-**

**Pathophysiology:**

 **PCOS's pathogenesis is most likely complex, combining metabolic, endocrine, genetic, and environmental factors. Hormonal concentrations follow predictable cyclic patterns in a normal menstrual cycle, but patterns of gonadotropin and sex steroids are altered in chronic anovulation. The release of gonadotropin-releasing hormone (GnRH) is changed in women with PCOS, leading to an increase in the frequency of luteinizing hormone (LH) pulses and a decrease in the secretion of follicle-stimulating hormone (FSH), which impairs follicular growth. Theca cells can produce more ovarian androgen due to the elevated LH pulse frequency. Insulin resistance in women with PCOS causes elevated amounts of circulating insulin, which in turn causes hyperandrogenemia in two ways:**

**1. By inhibiting sex hormone binding globulin by the liver**

**2. By stimulating ovarian androgen production**

**In PCOD, ovarian dysfunction is a result of abnormal gonadotropin secretion patterns, persistent hyperandrogenism, and insulin resistance.13**

 **When comparing women with PCOS to normal controls, the ovaries of PCOS patients have more developing follicles and antral follicles that prematurely stop growing around 5 to 8 mm. This higher follicular density seems to contribute to ovarian dysfunction in PCOS patients by obstructing the start of follicle activation. Concentrations of antimullarin hormone (AMH), produced by granulosa cells of preantral and antral follicles, correlate with the number of these small antral follicles. An unusual environment with elevated levels of LH, insulin, testosterone, and AMH, and insufficient levels of FSH, is presented to the developing follicle. Ovarian dysregulation in PCOS is a result of these skewed interactions between the endocrine, paracrine, and autocrine systems that control follicular maturation.14**

 **The role of genetics and epigenetics in PCOS increasingly is researched. Multiple studies have showed have revealed greater prevalence of PCOS in siblings and parents of women with PCOS as well as hyperandrogenemia and hyperinsulinemia in first-degree relatives, suggesting a genetic vulnerability.15 Genes implicated in PCOS have started to be identified by genome-wide association studies, which presently account for 10% of heredity.16 Additionally, some developmental programming models propose that the condition is influenced by environmental variables that promote obesity, such as the Western diet, and androgen-induced epigenetic alterations.17 To fully manifest the phenotype, there may be a need for both genetic predisposition and an obesogenic environment.18**

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**Diagnosis:-**

 **According to the widely recognized Rotterdam criteria, a diagnosis of PCOS necessitates ruling out other endocrine conditions with symptoms similar to PCOS (such as congenital adrenal giantism, hyperprolactinemia, Cushing syndrome, and androgen-secreting tumors), as well as at least two of the following traits: polycystic ovarian morphology, clinical or biochemical hyperandrogenism, or oligo/anovulation.19**

**The four distinct PCOS phenotypes generated by the Rotterdam criteria, with two of the three features required for analysis, are**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Phenotype 1** | **Phenotype 2** | **Phenotype 3** | **Phenotype 4** |
| **Biochemical and clinical hyperandrogenism (HA)** | Present  | Present  | Present  | Absent  |
| **Ovulatory disfunction (OD)** | Present  | Present  | Absent  | Present  |
| **Polycystic Ovarian morphology (PCOM)** | Present  | Absent  | Present  | Present  |

**The characteristics of cardiac metabolic dysfunction in these groups are compared throughout a large study corpus. According to most of the data, compared to people with "nonclassical" phenotypes (Phenotypes 3 and 4), females with the Standard phenotypes (those with both OA and HA; Phenotypes 1 and 2) have higher body mass indices and a higher incidence of cardiovascular risk factors. Ovulatory PCOS patients (Phenotype 3) tend to have a lesser degree of cardiac metabolic dysfunction, which is nevertheless better than that of normal controls, whereas non-hyperandrogenic PCOS patients (Phenotype 4) have the most impressive endocrinologic and metabolic profile.20,21  Among contrast, Phenotype C + D (non-classic PCOS) was more common among women with PCOS discovered in unselected groups (53% vs. 35%; p = 0.001).22 Consequently, it is clear that PCOS has a sizable referral bias. Subjects from referral communities are often more obese and have more severe illness manifestations than unselected populations.23,24**

 **Patients who were recommended by their doctors participate in the great majority of PCOS research. As a result, it's likely that most PCOS sufferers won't be affected by the specific research' conclusions regarding the long-term impacts. There are also notable differences in how PCOS traits manifest themselves between different ethnic groups. It seems that the primary reasons of the ethnic differences in PCOS are metabolic disorders such obesity, diabetes, and Met’s , as well as excessive hair growth.25 For instance, the frequency of PCOS in Middle Eastern girls is complex, and their hirsutism is more severe in those with Mediterranean and Hispanic ancestry. On the other hand, girls from Southern Eastern Asian backgrounds who have PCOS have a lower BMI and a lessened hyperandrogenic phenotype. However, they are more prone to central obesity, which raises the risk of IR, diabetes, and Met’s. Black and Hispanic women with PCOS are heavier and have a worse metabolic profile.26**

 **overall, while assessing the likelihood of long-term consequences in specific individuals, it's critical to take into account the differences in different PCOS phenotypes linked to clinical, hormonal, and metabolic factors as well as the consequences of ethnic variety and referral status.27 Androgen misuse can disrupt hormone balances by increasing the frequency of GnRH pulses, which alters the LH to FSH ratio and results in dysplasia and follicular arrest.28 Due to their effects on oxidative stress, hyperandrogenism, hyperinsulinemia, and irregular periods, these factors raise the chance of developing metabolic syndrome. The term PCOS was coined after an ultrasound identified several ovarian cysts, or undescended follicles, associated with the disorder. Since the follicles were descended from primitive follicles, their development was disrupted by ovarian function, which caused them to stop developing early.29**

**FACTORS , SOURCE AND ROLE IN PCOS DEVELOPMENT :**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Sr. No** | **Factor**  | **Source** | **Function in PCOS development** | **Reference** |
| **1** | **Stress** | anxiety, depression , severe mental health issues. | Stress is one of the main causes in the development of PCOS. | **30** |
| **2** | **Life style modification** | Obesity, weight increase cause metabolic abnormalities that result in insulin resistance. A sedentary lifestyle, diet deficient in nutrients also play role in the development of PCOS. | A desk job, fried food, processed meats, sausages, hot dogs, diet high in fat, carbohydrates, including excessive sugar ,fizzy drinks, all contribute to obesity, insulin, hormone imbalances, which in turn trigger PCOS by stimulating androgen receptors outside of the ovary. | **31** |
| **3** | **Ethnic background and Race** | PCOS affects people of all races and ethnicities, although black women are disproportionately impacted when compared to other ethnic groups. | 6.3% of women in Asian nations have been diagnosed with PCOS. residing in the Indian subcontinent are 52% Asian women , African women make up 8.0% of Black women and 4.8% of White women. | **32** |
| **4** | **Change in diet** | consumption of processed meat, sugar-filled beverages , refined calories | Each of these components causes off the onset of PCOS.Inhibition of aromatization of androgen into estrogen & progesterone in theca & granulosa cells | **33** |
| **5** | **Genetic variations** | The CYP11a, CYP21, CYP17, and CYP19 genes are involved in PCOS, which is a genetic syndrome**.** | Inhibition of aromatization of androgen into estrogen & progesterone in theca & granulosa cells | **34** |
| **6** | **Xenobiotic exposure** | The main causes of this condition are a weaker immune system, a bad diet, a family history of PCOS, and various chemicals including pesticides, bisphenol A (BPA) or phthalates. | DCs have the ability to engage with receptors and serve as agonists or antagonists of hormones. BPA directly inhibits oogenesis through interactions with GPCR30, the non-classical membrane ER, and the estrogen receptor (ER) | **35** |
| **7** | **Oral contraceptives** | Pills to prevent pregnancy and other non-prescription medications | disturbs the hypothalamic-pituitary-ovarian axis and hormonal balance. | **36** |

**Complications Associated With PCOS :-**

**Menopause :-**

 **As women age, they naturally go through a physiological stage called menopause, which can cause health issues that last a lifetime. The hormonal milieu that changes during the menopausal transition leads body fat to redistribute in favour of belly obesity, even though menopause itself is not associated with weight gain.37 He inability of the ovaries to produce estrogen is associated with increased IR, an additional unfavorable lipid profile, the start of chronic inflammation, the RAS system, endothelial dysfunction, and oxidative stress.38 The lifelong health effects of PCOS that continue into post-menopause are still being studied. Although it is believed that PCOS may substantially impact postmenopausal women’s health, given the disorder’s pathophysiology, this may exacerbate the recognized hazards of the postmenopausal period itself.**

**Hypertension :-**

 **A higher occurrence of high blood pressure has been found in several investigations in PCOS females.39 Patients with PCOS exhibited greater rates of hypertension than control subjects, according to a recent meta-analysis. Menopausal women with a history of PCOS were not seen to have this at this time; only females of reproductive age were discovered to have this. In comparison to control females with regular periods, ladies with PCOS (average age: 45 years) had higher incidences of hypertension and body mass index. Furthermore, analyses matched by age, BMI, and ethnicity showed that this was still the case.40 Compared to controls, significant increases in both systolic and diastolic blood pressure have been noted in PCOS populations collectively. Furthermore, hyper-androgenic women with PCOS ≥ 39 were shown to have higher levels of hypertension and body mass index-adjusted SBP, even though the average values in both groups were within normal ranges.41 It is noted that hypertension is more common in women with PCOS, despite other research finding no discernible variations in the prevalence of the condition between the general population and older females with PCOS.42 Women who have PCOS are frequently more likely to develop hypertension. Further research is currently needed to regulate the risk of hypertension in older female PCOS patients who have gone past menopause.43**

**Diabetes mellitus :-**

**Numerous long-term research have linked the risk of diabetes mellitus to PCOS.44  Women with PCOS are more susceptible to diabetes because they have metabolic abnormalities, such as insulin resistance, that persist after menopause. Numerous studies have examined the relationship between PCOS in older women and diabetes mellitus.45 discovered in the CARDIA study that over the course of 18 years, girls with PCOS had a two-fold increased risk of acquiring diabetes. In the evaluation of weight-matched healthy controls, normal-weight girls with PCOS had a three-fold increased risk of diabetes mellitus prevalence. The likelihood of acquiring diabetes was highest among women with persistent PCOS who met the NIH parameters at baseline and during follow-up (probabilities ratio (PR) 7.2, assurance interval (AI) 1.1–46.5).46 According to certain research, women with PCOS were more likely to experience IGT during pregnancy and to develop diabetes mellitus during the perimenopausal period. It is currently recommended that all ladies with PCOS have their first visit examined for diabetic mellitus, regardless of age or body mass index.47**

**Dyslipidaemia :-**

 **One of the most common metabolic disorders associated with PCOS, dyslipidemia, affected about 70% of women with the condition.48 A organized appraisal and examination of 30 studies involving participants below age limit of 45 found that women with PCOS had lesser levels of HDL cholesterol and increased levels of low-density lipoprotein cholesterol (LDL), non-high-density lipoprotein cholesterol, and triglycerides in comparison to controls. LDL and non-HDL cholesterol levels were greater in PCOS patients even when BMI was matched.49 Only a few studies address the incidence of dyslipidemia in older women with PCOS. In cross-sectional studies, there were no variations in serum lipid levels between perimenopausal PCOS women and controls.50 Comparing females with PCOS and controls, there was no statistically significant difference in the probability of developing dyslipidemia beyond the age of 40. Similar to this, the authors of the retrospective cohort study found that blood lipid levels in PCOS subjects and controls (mean age: 46.7 years) were similar between the ages of 45 and 50.51**

**Cancer :-**

 **Female PCOS patients have risk factors for EC, such as obesity, nulliparity, and prolonged unopposed estrogen. It has been demonstrated that women with PCOS have a significantly increased risk of endometrial cancer, but not of ovarian or breast cancer. After studies with individuals older than 54 years old were removed from the data, the risk for endometrial cancer and ovarian cancer increased significantly for females with PCOS, but no significant risks were detected for breast cancer.52 Further more, following a diagnosis of PCOS, a group of 786 women with PCOS (average age: 55) underwent average 30-year follow-up (range: 16–55). Compared to the control group, women with PCOS experienced a higher incidence of endometrial cancer (2.2% vs. 0.5%; p = 0.001).53 Using information from The Danish National Patient Register, the author calculated an overall 4-fold increased risk of EC; however, she found no connection between PCOS and either ovarian or breast cancer. In conclusion, women with PCOS and healthcare professionals should be aware of a 2 to 6 times increased risk of endometrial cancer, even if the small records of occurrences included limit this research.54**

**TREATMENT OF PCOS DEVELOPMENT :**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Name of drugs** | **Effect of drug** | **Side effect/ ADR** | **Reference** |
|  | **Clomiphene citrate**  | An agonist of estrogen receptors is thought to be the best treatment option for PCOS patients in order to induce ovulation. stimulates the development of ovarian follicles to start ovulation, and the pituitary gland in the brain secretes FSH & LH. | smoking and clotting history, and obesity, hypertension | **55** |
|  | **Tamoxifen** | inhibits the hypothalamic oestrogen receptors, resulting in ovarian stimulation. | Hot flashes, nausea , dizziness, depression, headache | **56** |
|  | **Aromatase inhibitors** | Very potent in inducing ovulation Aromatase is necessary for production of follicles | hyperandrogenism | **57** |
|  | **Gonadotropins** | These aid in the induction of ovulation, the appropriate development and maturity of oocytes, and their readiness for fertilisation. | Multiple pregnancies & follicles development, & ovarian hyperstimulation syndrome | **58** |
|  | **Metformin** | agent that lowers testosterone levels less effectively and is an antidiabetic for type II diabetes weight loss. It lowers androgen levels and enhances ovulation. insulin sensitivity rises when insulin levels are lowered. | Diarrhea , Belly pain Constipation, Little appetite | **59** |
|  | **Troglitazone**  | Having promising effects on testosterone levels | Infection, headache , runny & stuffy nose, UTI , Diarrhea | **60** |
|  | Spironolactone | Treatment with a single medication reduces hirsutism upto 40%. When used with oral contraceptives, the effects are increased upto 75% and hirsutism is decreased upto 45%. | nausea or menstrual irregularities | **61** |
|  | Flutamide | Nonsteroidal antiandrogens inhibit the activity of both endogenous and exogenous testosterone. | Both teratogenicity and dry skin | **62** |
|  | **fenasteride** | Endogenous & exogenous testosterone , Combining flutamide & metformin has a synergistic effect | Teratogenicity | **63** |
|  | **statins** | endocrine support , Reduces inflammation and decreases lipid levels and hyperandrogenism | Teratogenicity | **64** |
|  | *Linum usitatissimum**L.(flaxseed)* | Reduced T, E2, LH, and insulin levels promote follicle development and reduce inflammation, leading to a positive effect on PCOS | Not one | **65** |
|  | ***Cinnamon (Cinnamomum verum)*** | This treatment effectively reduces insulin resistance by activating the insulin signaling system through increased P13-K activity. | Not one | **66** |
|  | Berberine | decreases level of LDL, triglycerides, cholesterol, glucose, insulin and insulin resistance levels as well as increased HDL and SHBG | Not one | **67** |
|  | *Oenothera biennis l.(evening primrose oil)* | This treatment effectively reduces insulin resistance by activating the insulin signaling system through increased P13-K activity. | Not one | **68** |
|  | *Camellia sinesis (L) kumtze (Green tea)* | It has been shown to reduce IR and weight , improve ovarian shape, and reduce the number of cysts in the ovaries, making it a popular herbal weight loss therapy. | Not one | **69** |

**Nonpharmacological treatment:-**

 **For PCOS control, many nonpharmacological therapies are also employed. These include weight loss, dietary adjustments, nutritional supplements, resistance and aerobic training, yoga, acupuncture, osteopathic manipulative medicine, and so forth.70**

**Conclusion:-**

 **There is compelling evidence that females with PCOS are at a higher risk of developing obesity, dyslipidemia, cancer, and mood disorders during their first reproductive years, in addition to having prediabetes, diabetes, and other cardiometabolic risk factors. On the other hand, nothing is known about PCOS's long-term impact on health beyond menopause. According to current research, PCOS phenotype improves with age, and between perimenopause and post-menopause , the differences in cardiac metabolic dysfunctions risk profiles between females with PCOS and controls become less significant. The similar risk of cardiovascular disease observed in females with PCOS and controls may be attributed to these factors, even if there is limited data on CVD risk in later age groups. Further research is needed to determine whether females with diverse PCOS phenotypes or ethnic backgrounds are subject to the same risks for lifelong health effects. It is currently unknown whether the elevated risks associated with other comorbidities, such as cancer, obesity, and mood disorders, continue through the premenopausal years. To address these questions, more substantial community-based cohort studies wherein together, well-phenotyped PCOS affected females and healthy controls are surveyed from premature reproductive years until late menopause are needed.**

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