

# Polycystic Ovary Syndrome: A Comprehensive Review of Pathogenesis, Management, and Drug Regimen

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## Abstract:

PCOS Polycystic ovary syndrome is an ailment that is associated with the endocrine system of the body that usually affects the females of Reproductive age. In addition to this it is also known as an Infertility disorder. It has significantly affected a wide range of female population all around the Globe. Furthermore, PCOS is a multifactorial complex disease with ample number of side effects for instance Acne, Obesity, Insulin resistance, Infertility, Cardiovascular disorders as well as various other health disorders. Subsequently, in this modern contemporary era PCOS is a globally concerned emerging issue that needs to be resolved in the near future. Additionally various Therapeutic actions are used in order to eradicate this ailment for example the usage of Oral Contraceptives, regular changes in routine lifestyle habits, drugs like metformin, surgical methods, Laparoscopic ovarian drilling, etc... However, these modes of elucidation of the disease come with additional adverse effects and certain complicated health conditions. PCOS is directly or indirectly associated with not only the disorders of the reproductive system but also the, metabolic disorders such as Glucose intolerance, Dyslipidemia, Diabetes Mellitus, Hypertension etc... The PCOS: - Polycystic Ovary syndrome usually is known to also manifest the menstrual Dysfunction and hormones mal function in the suffering females.

**Keywords:** PCOS, Endocrine disorder, oral contraceptive pills, menstruation, Insulin resistant

## Introduction:

Plethora of Diseases is specific to the gender. Gynecological disorders involve the disablement in reproductive as well as the organs which are controlled by estrogen hormone in women[1, 2]. While some of these female issues maybe curable, the others are chronic, as well as fatal. Ample of these disorders hamper the fertility. With the upswing in the annexation of, and vulnerability to chemicals, that are to a wider extent endocrine disruptors, the instances of hormonal imbalance are on the quick rise[3, 4]. Some of those commonly-encountered reproductive and hormonal abnormalities that consist of amenorrhea, endometriosis, polycystic ovary syndrome, fibroids, infertility, ovarian cancer, miscarriage, ectopic pregnancy, preterm delivery etc....[5, 6]. Polycystic ovary syndrome (PCOS), an amalgamation of symptoms, that affect a woman of child- bearing age is presuming epidemic proportions. This ailment a

yield of imbalance in sex hormones of females, that results into formation of cysts into the antral follicles of ovary. A cyst can be referred to a sac filled with water that contains egg, which could have been functionally discharged for probable fertilization. The formation of the egg into a cyst, can be entitled as as 'functional cyst', which stopn ovulation. As ovulation is prevented, it leads to the disruption of the menstrual cycle, which further leads to 'amenorrhea'. When a lot of cysts are formed in the follicles of ovary due to the hormonal imbalance, it can be called as. Due to the cysts that are water retained, some of them can be a big with widened of 10 mm, the size of ovary may increase, up to 10 cm in the width. Negliible ovulation as well as irregular menstrual cycle prevents fertilization, and conception, henceforth pregnancy becomes strenuous[5, 6, 7]. Nevertheless, these cells in PCOS patients are hyper- responsive to the bracing effects of insulin, so they increase rapidly, causing ovarian hypertecosis. Insulin resistance exaggerate the androgenic potential in the theca cells, aggravating PCOS[8]. As the human body is a multiplex system and the metabolites are functionally-interlinked, disruption in one can exert an influence on the others as well. Knock over in the level of a number of hormones (prolactin, antiMüllerian hormone (AMH), cortisol, androgen), neurotransmitters (dopamine), peptides, lipid, protein, and glucose are correlated with the manifestation of PCOS. Hyperprolactinemia convict's hypogonadotropic hypogonadism, characterized with amenorrhea, galactorrhea (abnormal milk production from the breasts), as well as osteoporosis[9]. According to the studies conducted in cohorts of mono and dizygotic pair of twin, the history suggested that PCOs is neither an autosomal dominant nor a monogenic disease but it is an x linked polygenic disorder. It has been proved by conducting a twin study[10, 11].

### **Sign and Symptoms of PCOS :-**

Anovulation or oligovulation is a customary symptom of PCOS. Some of the cysts produce androgens, which result in sequel the virilization or the expression of male-like characters in the females. Henceforth, PCOS accelerates the outward form of a gamut of masculine symptoms or 'hyperandrogenism'. Detectable signs of hyperandrogenism include weight gain, abdominal and subcutaneous fat, hirsutism (facial and body hair), male-pattern alopecia (hair loss), clitoromegaly (enlargement of the clitoris), deep voice, seborrhea (oily skin), acne etc. [12]. Apart from these geomorphological features, modification in metabolic profile transpires. Insulin resistance is a major indicator of PCOS. It aggregates in hyperinsulinemia, and can lead to diabetes mellitus<sup>4-10</sup>. High insulin level is accountable for the accumulation of fat all over the abdomen or central adiposity. In a seniority of females with PCOS, the body mass index (BMI) is 30 or greater than 30. In addition to that, hypertension, cardiovascular issues, dyslipidemia, etc. are chronicities of PCOS [13]. A normally healthy blood pressure for women is 120 over 80 or less than that. PCOS patients are at a lofty risk for the enlargements of early-inception of cardiovascular disease. Moreover, The PCOS patients frequently exhibit sweet sugary cravings, recurring urination, delayed healing, fatigue, blurred vision, tingling sensation, mood swing, anxiety, and depression occurrences. It is comprehensible, as these conditions are related to diabetes as well. The patients usually feel pelvic pain, fever, nausea, vomiting, urinary conditions, constipation etc. Pressing of the giant cysts against the bladder or rectum is responsible for the anomalous urinary and bowl movement. Sleep apnea (it is a disorder of in which breathing stops in a repetitive manner and starts) is another symptom of PCOS, that arises due to altered levels of sex steroid [14]. Ovarian hyperstimulation syndrome (OHSS) is a circumstance of accumulation of fluid in the abdomen and chest (ascites and pleural effusion), which results due to obstacles in ovulation induction. This transfer of fluids into the third space i.e., abdominal and pleural cavity is because of the vascular hyperpermeability [15]. OHSS is classified on the basis of

indications of signs and symptoms. It can be compassionate, leading to weight gain, abdominal pain, nausea and vomiting, bloated abdomen due to ovarian expansion (from 5 to 12 cm), low urinary sodium excretion, oliguria etc. Although at times, the condition maybe critical, manifesting to difficulty with breathing; ionic imbalance; deep vein thrombosis; hypovolemia, rupture of a cyst in an ovary expedite to consequential bleeding; ovarian torsion; pregnancy loss from miscarriage, or termination by the virtue of complications; pulmonary embolism, kidney failure and more. Ovarian torsion is a medical extremity, which potentially can cut off blood to the ovaries, causing immense pain and bleeding. In serious cases, casualty may occur because of hypovolemia, hypercoagulation, respiratory, also circulatory collapse [15].

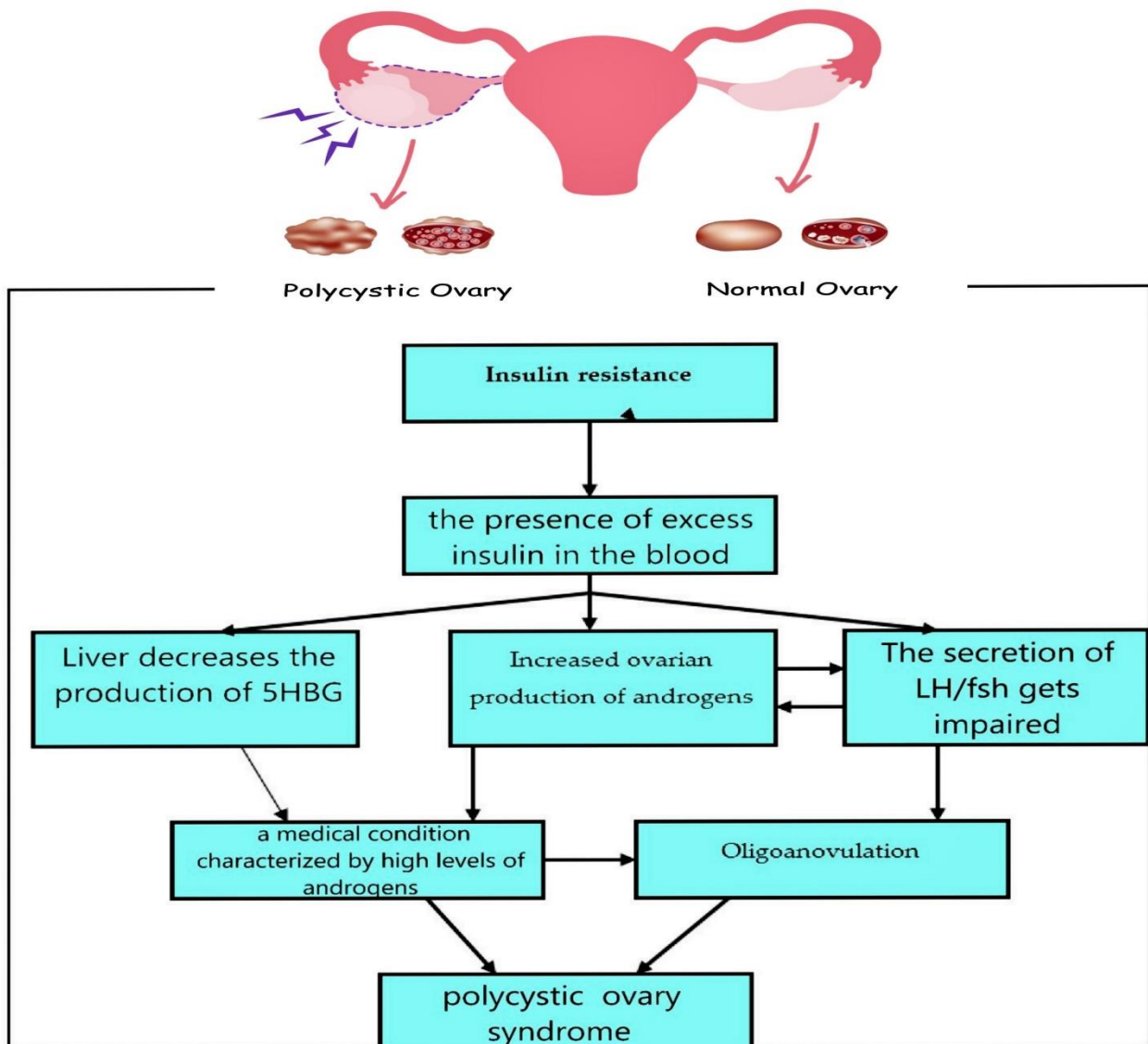
### **Etiopathogenesis of PCOS :-**

The components which cause PCOS are conglomerate. Genetic, or lifestyle mistakes, also their combinations can lead to PCOS. Thyroid dysfunction, hyperprolactinemia, androgen-secreting tumors, Cushing's syndrome (a syndrome correlated with surplus cortisol levels), and congenital adrenal hyperplasia can navigate PCOS pathogenesis. Chemical exposure has been Self-care products such as perfume, sunscreen, deodorant, Clasp responsible for the enlargement of PCOS. The exposure to a various chemical, accidentally (pesticide, vehicle exhausts, in-dustrial pollutants etc.) or deliberately (cosmetics, household cleaning agents, chemotherapeutics etc.), means are customary in ongoing times. Self-care products such as perfume, sunsceem, deodorant, hair dye etc., which have been the core and quintessential grooming ingredients, are major offenders behind the rebelling examples of PCOS. A majority of the users are not aware about the fact that these harmless -seeming hygiene products are responsible for disrupting endocrine. These chemical products maye possess phthalates, parabens, isopropanol, glutaraldehyde, benzophenones, turpentine oil, metals like (nickel sulfite, cobalt chloride), benzophenones and a lot more [16, 17, 18]. Certain not only genetic but also environmental factors play a vital role in the pathophysiology of PCOs[19]. Moreover as a part of factors related to PCOs pathology there may be increased Lh and androgen levels as well as insulin resistance[20].

### **Current scenario :-**

Currently Polycystic ovary syndrome (PCOS) is the most customary Endocrinopathy in the age of reproduction affecting 5 – 10% of Women, and is the major yield to the ovulatory dysfunction[21].

Figure : 1



Adopted from: Kamenov Z, "Inositols in PCOs", Nov 2020[22].

### PCOS Diagnosis :-

Early detection can be helpful in avoiding the intensification of PCOS[23]. Gynecologist can diagnose PCOS by the described symptoms of the suffer ants (for instance the history of oligomenorrhea), as well as the morphological features (hirsutism). Although, PCOS detection is based on certain deliberated points of suffer ants (blood pressure, cycle duration), and ultrasound (follicle count, mean ovarian volume) parameters, endocrine (SHBG, testosterone, free androgen index (FAI), FSH, AMH, thyroid function tests), and lipid profiles can indicate PCOS. Glucose tolerance test (GTT), and prolactin test may also designate PCOS circumstances. Normal prolactin levels are not more than 500 mIU/L in women. Ultrasound is an illustrating technique which is able to diagnose PCOS. Not only Transabdominal but Wilson vaginal ultrasound are able to show the cysts[24].

### Therapies :-

The options for the therapeutic actions of PCOS can range from pharmacological therapeutics to surgical therapeutics. The PCOS cysts are functional cysts that are able to resolve by themselves. Although, some cysts may burst and also may bleed, which yields to certain critical pain in the lower abdominal region. Oral contraceptive pill (OCP) can be taken for 6 months, ameliorate hyperandrogenism and regularize menstrual cycles, by conquering ovulation, and fend off cyst formation. Although, it may increase the risk of a condition known as venous thrombosis [25]. In addition to this, it can reduce serum 25-hydroxy vitamin D levels, which may affect health of the bones. This therapy elevates plasma ICAM-1, MCP-1, and TNF- $\alpha$  levels in the PCOS suffering females. Although these cytokines may be inflammatory, they regularize the metabolic parameters, which includes plasma glucose, lipids, and insulin. Metformin, is an insulin sensitizer, which elevates the quality of life in females suffering with PCOS, by lowering the increased parameters as insulin, androgens, circulating free T levels, while elevating SHBG (sex hormone-binding globulin) and IGFBP (insulin-like growth factor-binding protein) levels and androgen level has a reaction which is inversely related. Metformin treatment before and during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in females with PCOS decreased the risk of OHSS [26]. Metformin works on the adipocytokines such as IL-6, IL-8, angiogenic proteins (VEGF), and metabolic regulators (for instance adiponectin, leptin). Moreover, this drug decreases the hyper-reactivity of platelets in PCOS sufferers, by causing an improvement in mitochondrial integrity. Exenatide and liraglutide (glucagon-like peptide-1 (GLP-1) receptor agonists), either as monotherapy or in combination with metformin, can decrease PCOS patient weight [27]. Amalgamated therapy with exenatide and metformin upgrades menstrual cyclicality, hormonal parameters, metabolic profiles, and inflammatory markers in overweight, insulin resistant oligoovulatory women with PCOS. Although, the adverse effects of metformin consist of lactic acidosis, fatigue, dizziness, severe drowsiness, cold skin, muscle pain, dyspnoea breathing, slower irregular heartbeat, stomach pain, nausea, vomiting, as well as diarrhea [28]. Antiandrogens for instance spironolactone, cyproterone acetate, flutamide, and finasteride are operated to treat androgenism. N-Acetyl-cysteine and other insulin sensitizers are administered to handle the resistance of insulin. The antiestrogen medication clomiphene citrate is administered to cure anovulatory infertility [29]. Metformin along with clomiphene citrate was useful in clomiphene-resistant PCOS patients. Gonadotrophins stimulation is also engaged to treat clomiphene resistance. Henceforth, all of the above-enlisted therapeutic actions are potentially effective upon certain extent, however not completely. Moreover, these therapeutic methodological aspects aren't adverse-effect free. The relevance and the risk of therapeutics depend on the morbidity factors. Long term consumption of these hormone stimulating agents causes obesity, cancer, psychiatric issues, and ample other problems. If the cysts do not get eradicated after multiple months, and they cause the risk of ovary torsion, which needs to be removed by surgical eradication. This can be gained by laparoscopy and laparotomy. Laparoscopic ovarian cauterization (drilling) has been found working effectively for treating PCOS [30]. Using a laparoscope, the cyst is eradicated by incisions made near the pubic hair line. For larger cysts, laparotomy can be a way. In crucial cases, not only ovaries, but also the uterus, omentum (a fold of fatty tissue), and some lymph nodes have to be removed. Hyperprolactinemia as well as PCOS, can cause women infertility, and result several clinical features, so they are considered to be correlated. Although, a study report states that the correlation of both conditions does not prove the pathologic dependence on each other [31]. DOPA. This dopamine precursor, L-DOPA, accompanied with monoamine oxidase-B (MAO-B), as well as ergot alkaloid derivatives, are among the therapeutic options to hold back neural pathologies operated by the deficiency of estrogen. These agonists



are capable of activating signaling pathways by the means of trimeric G-proteins and B-arrestins, eventually yielding to changes in transcription of the gene. Cabergoline, an ergot derivative, is a formidable dopamine receptor agonist on D2 receptors. However, it has been linked with an elevated risk for the development of heart valve defects in patients suffering from Parkinson's disease using it as a therapeutic action. Extreme lower doses of the drug (0.5 mg twice a week) can be required in the cure of hyperprolactinemia. Extreme dopamine causes schizophrenia, so dopamine antagonists can be used in the medication of the psychiatric disease[32]. Insomnolence in sufferers of PCOS is habitually observed. As melatonin helps with sleep, its favorable actions in PCOS are comprehensible. Not only, this hormone which is secreted from the pineal but also the neurotransmitter, safeguards the skin against oxidative stress also. Furthermore, the correlation indicates - be it any organ the ovary, or the skin, or even the brain, the disruptions in their functions always may arise from not only oxidative stress but also inflammations[33]. Pertinence, of acupuncture in PCOS has got some acceptance. Circulating GnRH and adiponectin system can stimulate by the means of acupuncture. Moreover, in an RCT which is randomized controlled trial, electroacupuncture an increment in the frequency of menstruation can be compared with the group of no intervention. In the regards to this, additional RCTs must be performed for the assessment of the relevance of acupuncture for diagnosis and treating the ovulation disorders of the ovulation in PCOS women[34]. Transcutaneous acupoint electrostimulation on serum sex hormone level in PCOS patients conditioning was assessed. The studied report found a low endocrine and reproductive mal-function in PCOS patients, most possibly by modulating sympathetic nerve activity, and sex steroid synthesis[35]. Abdominal fat loss can be potential to lowering the inflammation, which also reduces androgen level, which may also induce ovulation, and also be able to restore functions of metabolism. Loss of excess weight can be achieved by glucagon for instance peptide-1 receptor agonists (GLP-1RA), though the latter has adverse effects for instance nausea[27]. Although, it is better to indulge into physical exercises, and to cohere to healthy dietary changes habits, to reduce Body Mass Index in patients with excessive weight having the disease condition of PCOS. Reduction of excessive fat and weight has been marked to sort a majority of adverse reactions of PCOS. Physical straining exercises training can ameliorate the cardio metabolic profile in PCOS patients. Although, dreadful exercise can yield to activation of platelet and finally yields to cardiovascular complications. Moreover, human body is usually very sensitized to fluctuations of energy, so strainous exercise, and heavy dietary changes is discern as a threatening remark to survival chances, and hormones may go crooked and imbalanced again. Instead, methodological, modest physical exercises are Advocate for PCOS eradication. Plethora of phytochemicals that belong to vivid classes have marked curative effects in animal suspects of PCOS. The flavonoid rutin have effects of restoration against not only the metabolic, biochemical but also hormonal disturbances in rat suspects of PCOS[36]. However, herbal drugs are not standard recorded. They can exasperate the condition, by inducing further hormonal imbalance and mal function. Moreover, their plant origin does not spare them from their adverse effects. They can interfere with ion channels, neural receptors, or thrombocytes, which may to serious fall outs. However, PCOS can be said to be a hormonal disease its manifestation is more compound. All the three critical constituents of neural-immune endocrine axis, play a vital role in PCOS pathology. It not only an autoimmune disease as well, but also the prevalence of autoimmune thyroiditis, anti-thyroid antibodies, and goiter is found at peak rates in PCOS women[37]. The acuteness of PCOS differs among women, and oscillates with not only age but also comorbidities.. PCOS patients have wide risk of cardiovascular diseases because of the situations for instance dyslipidemia, hypothyroidism, and insulin resistance, all become apparent due to hormonal Disruption. However, the

actual examples of cardiovascular diseases, and strokes is not easy to trace. The connections may not direct but fraught with complex interactions. Although PCOS is a disease associated with reproductive age females, it can exert its pathological effects beyond menopause. Moreover, not only Hyperandrogenism, susceptibility to type 2 diabetes, but also increased risk of cardiovascular disease are some of side effects connected to PCOS[38]. Furthering, the connection between multiple sclerosis (MS) and PCOS is not studied Completely, although considering their common characteristics of inflammatory parameters for instance oxidative stress, CRP, interleukin-18 (IL-18), as well as MCP-1, they are probable to be comorbidities. Hypothalamic-pituitary, ovarian as well as adrenal factors are associated with PCOS evolution. Studies have reported the hepatic facets of this disease as NAFLD (non-alcoholic fatty liver disease) is usually present in PCOS sufferings' may not be a surprise, as all organs are functionally dependent on each other as well as interconnected. In fact, persuasive number of reports have shown the inter-relation between diabetes and PCOS. Perturbed glucose metabolism and utilization, the central hallmark of diabetes, is also a activating factor of Alzheimer's disease[39]. It draws attention towards the correlation between PCOS and the neuropathology as well. The association of altered glucocorticoid receptor function as well as depression, a PCOS co-morbidity, has arisen[40]. The activated renin-angiotensin-aldosterone system, a Paramount inflammatory pathway, plays a vital role at some r the other situation in the metabolic circuitry of PCOS[41]. Considering the increment incidences of PCOS, women must be aware of its risk factors, and should gain knowledge on how to deal with them, without much dependence on medications, because there are no drugs without its adverse reactions and side effects. As PCOS is a manifestation of hormonal Disruption, the drugs which are prescribed are hormonal, which come with much unwanted trunks of situation. Being dependent on drugs is a short-term solution with side effects. The patients and vulnerable women should be persuaded lifestyle and should avoid offending, inflammatory agents. Processed foods, smoking, alcohol etc. must be strictly prohibited. Most importantly, minimized usage if chemical consisting self-care products must be made a necessity. Females must make sure to educate themselves and should try to mitigate the causes, not the symptoms[42]. An analysis of FDA (Food and Drug Administration)'s Adverse Event Reporting System FAERS Reported that a majority of the undesirable topical or systemic reactions are marked up to be from the usage of self-care products, and the dominant of the side reactions included issues of ovaries and reproductive system. Beauty artist who works in salons are often exposed to metals, fragrances, hair colourants, bleaching agents, as well as corrosive solutions. Those chemicals may cause a series allergic condition for instances contact dermatitis, urticaria, angioedema, photodermatoses, conjunctivitis, respiratory tract diseases, as well as asthma. With constant exposure, these inflammations increase to ovarian as well as urinary tract diseases, inclusive of Pcos Insulin resistance is a part of PCOS, rice consumption is not beneficial however wheat, that is a staple grain can cause gluten intolerance as well as gut inflammation. In such cases it isn't an optable by any means. The human body functions as a dependent on each other entity, so, gut inflammation is associated to ovarian inflammation. It can be raised as acidification of the body as well as higher inflammatory enzymatic activities[43]. Females of reproductive age are more likely to be affected to triggers of hormone disturbance, leading to PCOS[44].

### **PCOS Genetics:-**

PCOS is an exceedingly heterogenetic and crucial disease. The genetic inheritenc3 of PCOS is different between families and within families but is related to a common pathway. Due to severity as well as heterogeneity single gene or related genes in a single family have not been observed. The genetic

susceptibility of ample genes is different in suffarants from the same family[45].Genome conceal to search for a subject gene in a complex disease like PCOS is Impractical. Linkage analysis in such families usually yield with negative results. In such anailment, case- control studies of larger population size and genome-wide association studies may come in handy to find possible associations. Parental analysis in such ailments is often impractical; although, known risk of disease can be estimated[46].

#### **Present Day Treatments prevailing :-**

PCOS is a disease that can never be completely eradicated however, to assist Women seeking conception, treatment modalities are Prevailing.

#### **Therapies including dietary factors :-**

Obesity has been reported in around 1/3 Rd of PCOS patients. The symptoms of PCOS can be considered to be recovered by dietary therapies including insulin resistance, annulations, and irregular menstruation[47].However, dieting habit and physical straining exercise do not show longer periodic results; henceforth, bariatric surgery was introduced to get more beneficial results[48].

#### **Oral contraceptives:-**

Combination of oral contraceptive pills can be considered the treatment in resolving PCOS. These drugs regulate multiple endocrine abnormalities that include not only hirsutism but also acne[49].Oral contraceptives are safe when compared to other therapeutic actions because of the low risk of endometrial cancer[50].These pills include a mixture of progestogen and estrogen, that increases SHBG which decreases LH and FSH, which in turn decreases free T and ovarian androgen production[51].Hence, a lower dosage of progestogen is preferable in oral contraceptive pills. Some adverse effects may also be observed with Oral contraceptive pills for instance, hyperglycemia, impaired glucose metabolism, insulin resistance, and diabetes mellitus[52].

#### **Laparoscopic Drilling of Ovaries:-**

When clomiphene citrate therapy is not potential to produce ovulation, other methods of ovulation can be used. Laparoscopic ovarian drilling is used for ovulation since the time when ovarian wedge resection surgery was not successful. Laparoscopic ovarian drilling was successful in majority of women not only improves ovarian androgen production insulin resistance[53]but also increases the levels of SHBG[54].

#### **Assisted Reproductive technology:-**

Various methods are prevailing for the treatment of fertility in PCOS suffarants. Assisted reproductive technology is the most often used. In this method, the ovaries are stimulated along with exogenous gonado tropine that is responsible for production multiple follicles. However, exogenous gonadotropin van be responsible for ovarian hyperstimulation syndrome OHSS in these patients[55].Because of this treatment the modality, in vitro maturation must be used. According to various studies that have been conducted in order to asses ART efficacy are compared to traditional IVF techniques[56].

#### **Futuristic outlooks in the treatment :-**

In the Prevailing times, COPS are used in the treatment PCOS as the first priority of treatment. These consists of multiple medicines that increase ovulation rates. Combinations of drugs can be used to treat the underlying associated pathology, that increase conception chances[57].However these include a lot of other side effects such as Diabetes Mellitus as well as depression and anxiety[58].To reduce the risk of associated pathological conditions interventional procedures were adopted. Those procedures included IVF, IVMfertilization, and laparoscopic drilling. Those procedures are also accompanied by a series of disease that come secondarily[59].



**Conclusion :-**

Henceforth, PCOs ( polycystic ovarian syndrome ) is an ailment which is usually associated with the endocrine system of the body and it affects the female in their reproductive age. PCOs is a multifunctional complex disease that has various symptoms like acne, obesity, infertility, insulin resistance etc. In addition to this PCOs further leads to ample other complications such as metabolic disorders, glucose intolerance, diabetes mellitus, hypertension etc. order to overcome the massive ailment of PCOs there are multiple therapeutic actions used such as oral contraceptives, dietary changes, drug like metformin etc. Not only these but there are various surgical methods such as Laparoscopic ovarian drilling that may be used to eradicate PCOs. Moreover PCOs can be conventionally managed by controlling symptoms and making certain lifestyle changes.

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