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POLYCYSTIC OVARY SYNDROME (PCOS) – A REVIEW

Ritu Kainth*, Gurneet Kaur and Baljeet Kaur

Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar (Punjab).

Corresponding Author: Ritu Kainth
Assistant Professor, Department of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar (Punjab).

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous condition which is related to an endocrine reproductive disorder of females. It affects females of 18–44 ages. Women with polycystic ovarian syndrome (PCOS) have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production. PCOS can result from abnormal function of the hypothalamic-pituitary-ovarian (HPO) axis. The clinical presentation of polycystic ovary syndrome is widely variable, with complaints encompassing oligomenorrhea, infertility, obesity, hirsutism, endometrial cancer, and diabetes. The persistent hormonal disbalance leads to the complexities such as numerous cysts, an irregular menstrual cycle that ultimately leads to infertility among females. Many candidate genes have been identified to be one of the causes of PCOS. Different studies have been carried out to find the genetic correlation of PCOS. It is essential to carry out such studies that identify the clear cause of PCOS and its genetic association and hormonal disbalance. Androgen excess has been implicated as a distinct risk factor, with several studies showing circulating androgen burden to correlate closely with surrogate markers of metabolic risk, independent of body mass index (BMI). PCOS is also a common and treatable cause of infertility. This review has highlighted different genes and their correlation with PCOS that leads to hormonal disbalance. Yet not in-depth but an attempt to study the genetic predisposition of PCOS.

KEYWORDS: Adolescent, Heterogeneous, Hormonal, Infertility, Hirsutism, Steroidogenesis.

INTRODUCTION

Polycystic Ovary Syndrome **(Stein Leventhal Syndrome)** is a health condition that affects about 10 million people in the world. It is considered a hormonal problem. Genetics and environmental factors are believed to be involved in the development of PCOS.[1] It is leading cause of female infertility and is responsible for a numbers of symptoms that can affect the body physically or emotionally.[2] Despite the name many people do not have cysts on their ovaries .Common to all women with PCOS is an irregularity in the menstrual cycle and the presence of excess male hormone (androgen). The condition was named because of the finding of enlarged ovaries containing multiple cysts POLYCYSTIC OVARIES.[3,4] Polycystic ovary syndrome (PCOS) increases serious complications among females. One in every 5–6 female is facing serious complications regarding infertility and irregularity in their menstrual cycles. Stress, obesity, fluctuation in hormonal level is the major cause worldwide.[5] Globally it affects 5–15% of females.[6]

It is the most common endocrine abnormality in reproductive aged women affecting. The classic triad of this syndrome consists of chronic ovulation dysfunction, hirsute (male pattern hair growth) and obesity. It is often associated with psychological impairments included depression and other mood disorders and metabolic derangements chiefly insulin resistance which is recognized as a major factor responsible for altered androgen production and metabolism.[7]

If there is a constant disturbance of hormonal level in females then it will disturb ovary functioning which leads to the formation of a cyst inside the sac of an ovary. Whereas androgen which is a male hormone elevated beyond its normal range in females affected with PCOS.[8]

Poly cystic ovaries containing a large number of harmless cysts that are no bigger than 8mm each. More than 12 cysts are present in the ovary. About 70% of females are infertile because of this condition.[9,10] Normal ovaries have only about half this number of cysts. The cysts are egg containing follicles that have no developed properly because of hormonal imbalance many women have polycystic ovaries without having the syndrome. Some women have the symptoms, but have normal looking ovaries on ultrasound.

Research suggests that 5 to 10 % of females 18 to 44 years of age are affected by PCOS, making it the most common endocrine abnormality among women of reproductive age in the U.S. Women seeking help from care professionals to resolve the issues of obesity, acne, amenorrhea, excessive hair growth and infertility.[11]

SYMPTOMS OF PCOS[12] String of pearl cysts on ovaries

1. Insulin resistance
2. High testosterone causing excessive hair growth , male pattern baldness and acne
3. Suppressed ovulation
4. Excessive weight gain
5. Dark thick patches on the skin
6. Pelvic pain
7. Anxiety or depression
8. Irregular menses
9. High BP
10. Infertility
11. Type 2 diabetes
12. Sleep apnea

Diagnosis

There are three major guidelines for the diagnosis if this condition that are:

1. Rotterdam criteria i.e. irregular menstrual cycle, elevated androgen level and the presence of cysts.[13]
2. National Institutes of Health Criteria i.e. hyperandrogenism and menstrual irregularity.[14]
3. Androgen Excess-PCOS Society Criteria i.e. hyperandrogenism, menstrual irregularity or Polycystic Ovaries on Ultrasonography.[14]

Pathophysiology

The abnormal findings in PCOS are a result of ovarian hyperandrogenism[15] insulin resistance.[16] Evidence suggests that the ovarian hyperandrogenism in PCOS is a result of primary ovarian dysfunction and is secondary to disordered gonadotropin activity.

While not included in diagnostic criteria for PCOS, the elevated level of serum luteinizing hormone (LH) in affected patients due to inappropriate secretion has long been recognized.[17] LH is the ligand for the LH receptor on the ovarian theca cells responsible for ovarian androgen production. Genome-wide association studies conducted on hyperandrogenic subjects with PCOS revealed genome-wide significance for a locus mapping to chr 11p14.1 in the region of the follicle-stimulating hormone beta polypeptide (FSHB).[18] This single-nucleotide polymorphism was associated with LH levels that result in the elevated LH: FSH ratios often seen in PCOS, providing further support for the hypothesis that dysregulated gonadotropin secretion in PCOS leads to secondary hyperandrogenism. This gonadotropin imbalance favors an exaggerated intraovarian androgen environment under the influence of LH, and impaired folliculogenesis resulting in anovulation due to a relative FSH deficiency. Evidence also suggests that the ovarian hyperandrogenism seen in PCOS is primary, with abnormal ovarian steroidogenesis through overexpression of the *CYP17* gene being responsible for androgen biosynthesis, as well as increased expression of the LH receptor, which would potentially render the ovarian theca cells more sensitive to LH stimulation.[19,20] The ovarian hyperandrogenism appears to play a role in the appearance of the polycystic ovary on ultrasound and the follicular arrest and anovulation that is prevalent in PCOS. The ovarian phenotype may result from either endogenous or exogenous androgens. Androgens, as demonstrated in the similar ultraosonographic findings and gene expression profile studies on the ovaries of women with PCOS and the ovaries of androgen-treated femaleto- male transgender individuals.[21] Evidence for the role of insulin resistance in the pathophysiology of PCOS and ovarian hyperandrogenism is demonstrated indirectly by the findings of hyperandrogenism in female subjects with type A insulin resistance syndrome, a disorder characterized by a mutation in the insulin receptor gene.[22] Insulin contributes to the biochemical and clinical hyperandrogenism by directly enhancing theca cell ovarian androgen production in concert with LH.[13] and indirectly by lowering sex hormone-binding globulin, the carrier protein responsible for reducing circulating free testosterone levels.[23] The high prevalence of impaired glucose tolerance and type 2 diabetes in women with PCOS has led researchers to consider the role of insulin sensitizers in treating PCOS.

PCOS progression and severity increases with the increase in insulin level as well as an androgen. Hyperinsulinemia affects ovarian theca cells and raise androgen level. This condition reduces the hepatic biosynthesis of SHBG and IGFBP-1. Elevated androgen level, on the other hand, stimulates visceral adipose tissue (VAT) that generates free fatty acids (FFA's) which contributes in insulin resistance Fig. 1.[24] Genetic predisposition with PCOS, a pathway describes hyperandrogenism in Fig. 2.

Fig. 3 depicts a pathway that describes how steroidogenesis enzyme affects the theca cells of an ovary. 5α-reductase activity increased that elevates 5α-androstane -3, 17 Dione concentrations and inhibit the activity of aromatase in the granulosa cells. In the case of PCOS, LH and progesterone are expressed in the granulosa cells which results in high androgen level and reduced estrogen level.[25]

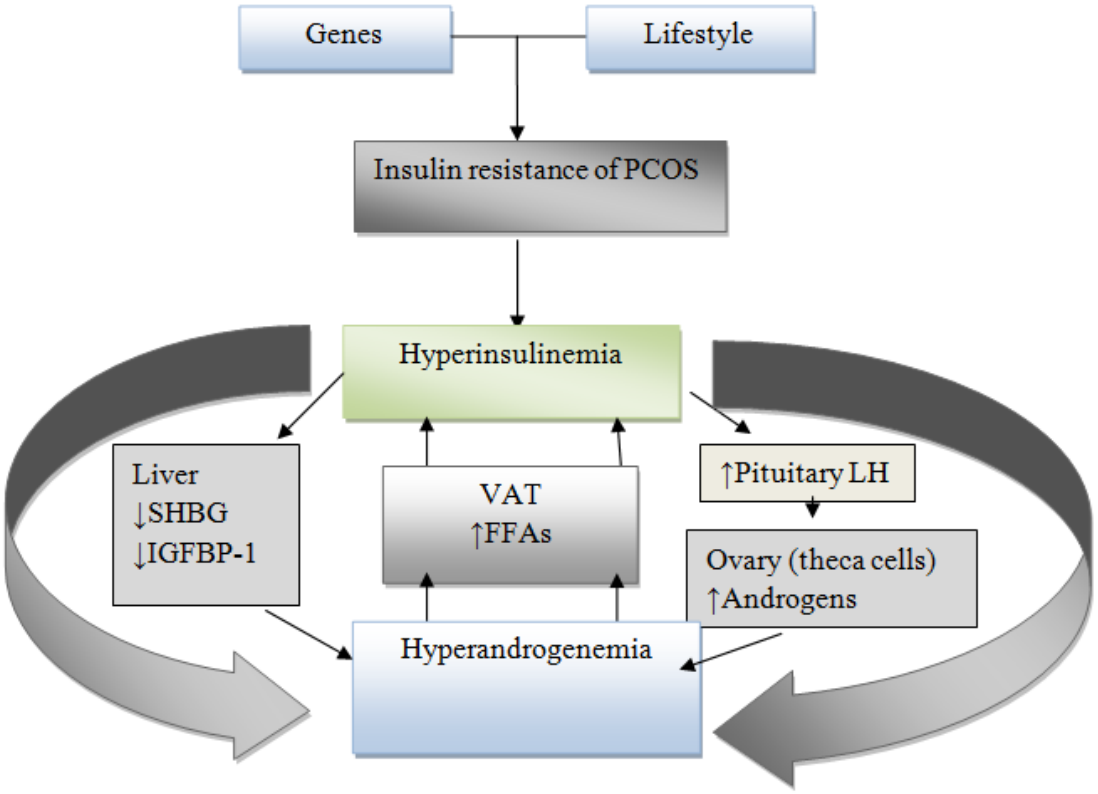

Fig. 1: Show insulin resistance affects the ovarian theca cells and perturbs its functioning.[25]

SHBG=sex hormone-binding globulin, IGFBP=insulin-like growth factor, VAT= visceral adipose tissue, FFAs= free fatty acids, LH= luteinizing hormone.

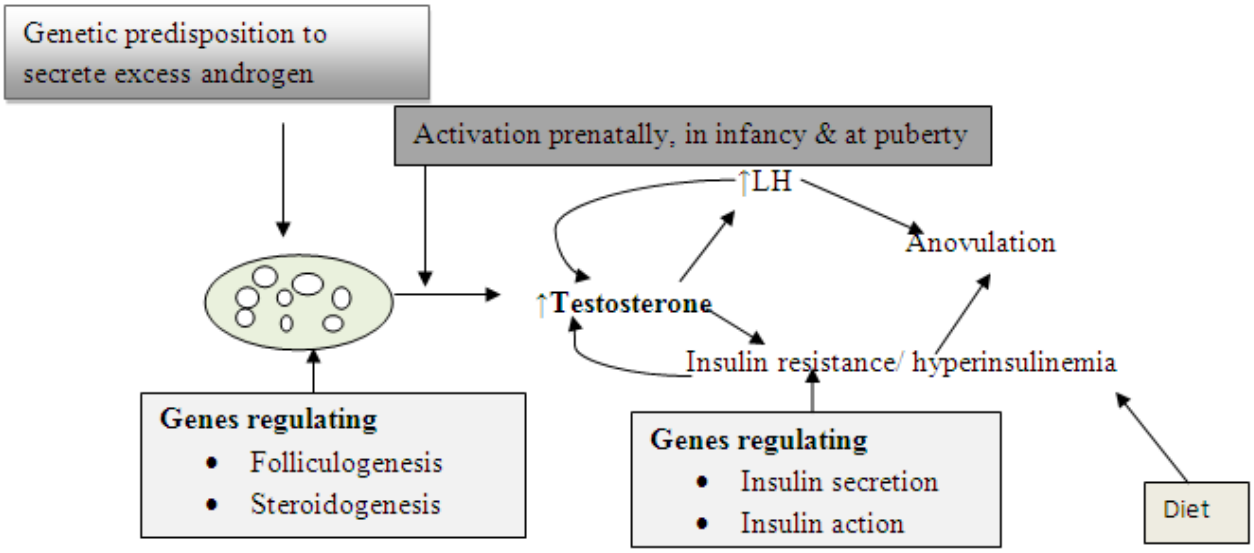

Fig. 2: A defect in the pituitary axis elates testosterone and LH. It also leads to insulin resistance. Together insulin resistance and high level of androgen subsidize in the pathway of an ovulation.[26]

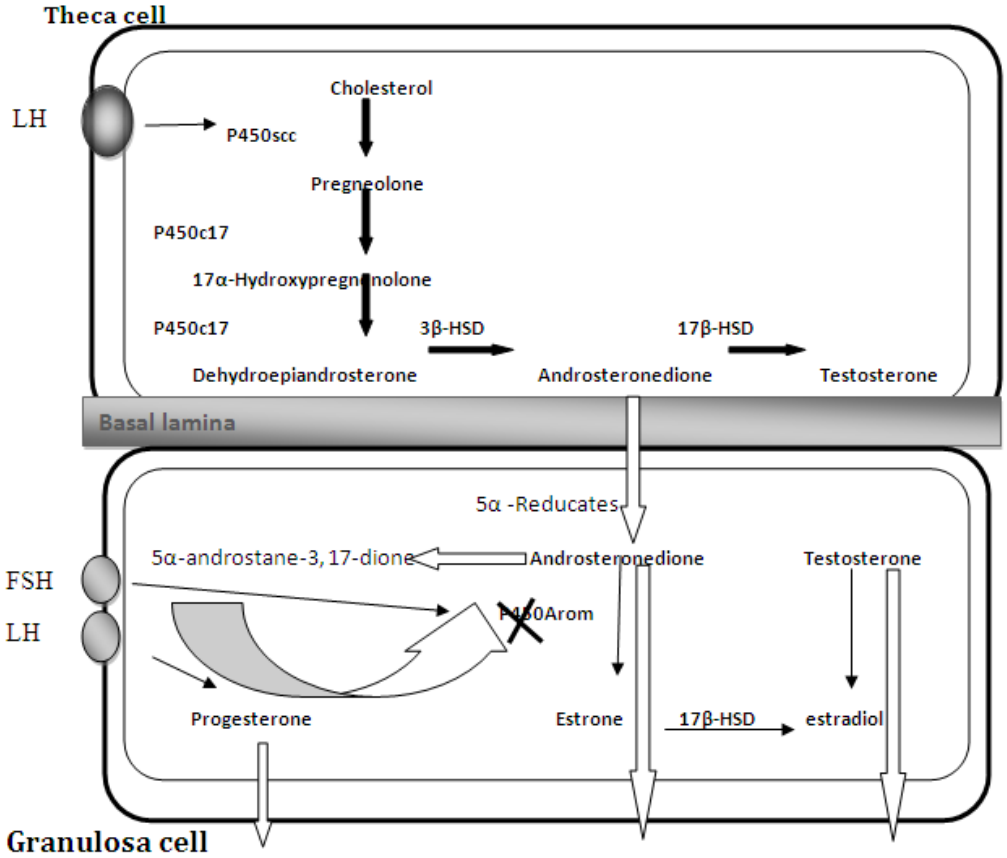

Fig. 3: Effect of steroidogenesis enzyme and theca cells of an ovary.HSD=beta hydroxysteroid dehydrogenase, FSH=follicle-stimulating hormone

Pregnancy Complications and Life Style Modification in PCOS Women's

Ovarian cyst: - The definition of a cyst is a fluid filled sac. Cysts can occur anywhere in the body with PCOS, women can develop cysts due eggs not being released over time. The follicles keep growing and form multiple cysts. These may be described as appearing like a **string of pearls in an ultrasound images.** These cysts are described as functional because they often develop during menstrual cycle. There are two types of cysts:-

1. Follicular cysts - These usually go away on their own in 1 to 3 month. These form when an egg does not get release as expected, so the follicle keeps growing.

2. Corpus luteum cysts – The growth after follicle ruptures and release the egg (ovulation). The follicle release and fluid starts to build up within it. They can enlarge and cause pain, bleed, twist the ovary. Ovarian cysts can also relate to endometriosis or form the outer surface of ovary (cystadenomas) or formed with non ovarian tissues.

1. Miscarriage

Women who have PCOS do appear to be at a slightly higher risk for having a miscarriage, though the cause for this relationship is unclear. Researchers believe that a few factors may be to blame. First, women with PCOS tend to have longer menstrual cycles, meaning that ovulation occurs later on. This exposes the developing egg to lots of hormones, possibly damaging it.

Second, there is a known relationship between uncontrolled blood sugar and miscarriage. Given that women with PCOS tend to have insulin resistance and elevated insulin levels, some researchers hypothesize that this may contribute to poor egg quality and miscarriage.[27]

2. Pregnancy-induced hypertension

Pregnancy-induced hypertension, or PIH, refers to women who develop new-onset high blood pressure after 20 weeks. Preeclampsia is a serious health condition that also develops in the second half of pregnancy and causes protein in the urine, in addition to high blood pressure. The loss of protein in the urine leads to swelling and signals a problem with the kidneys.[28]

3. Gestational Diabetes

All pregnant women are monitored for gestational diabetes with routine blood sugar screening sometime between 26 and 28 weeks. Women with known diabetes, insulin resistance, or who are at higher risk for developing gestational diabetes may be screened earlier. Women who are older than 25, have had gestational diabetes with prior pregnancies, who are overweight, who have prediabetes, or who have close family members who have been diagnosed with type 2

diabetes are at greater risk for developing gestational diabetes.[29]

4. Premature Delivery: - Women with PCOS are also to risk of delivering their body early. The reason behind this again is not clear. Experts also known that preeclampsia is a risk factor for premature delivery and women with PCOS are at higher risk for the preeclampsia.

In addition, experts have found that babies born to moms with PCOS are more likely to be large (called large for gestational age) have a meconium aspiration (when a baby first stool gets into their lungs) and have a low Apgar score at five minutes.[30]

Hormones Involved In PCOS

- **Androgen –** All females make androgen (also reffered to as male hormones), but there are often higher level of androgen in women with PCOS. The excess androgen is produced by the ovaries, but the adrenal glands can also be involved. Excess androgens are responsible for PCOS symptoms including acne, unwanted hair, thinning hairs and irregular periods.
- **Insulin – can cause the body to make androgen .**This hormone allows the body to absorb glucose (blood sugar) into cells for energy. In PCOS the body is not as responsive to insulin as it should be. This can lead to elevated blood glucose level and cause the body to make more insulin. Having too much insulin.
- **Progesterone –** In PCOS, lack of progesterone contributes to irregular periods. Progesterone resistance implies a decreased responsiveness of target tissue to bioavailable progesterone, and such an impaired progesterone response is seen in the endometrium of women with PCOS.[31]

Advances and challenges in PCOS understanding

Advances researches defined PCOS as the presence of any two of three features: **hyperandrogenism** (clinical or biochemical), **ovulatory dysfunction** (often manifested by menstrual irregularities) and **polycystic ovarian morphology** (PCOM**)** by ultrasound.[32]

Anti – mullerian hormone (AMH) is a gylcoprotein secreted by the granulosa cells of pre – antral amd small antral follicles. AMH plays an essential role in sexual differentiation and gonadal function, besides central effects on the hypothalmic – pituitary gonadal axix. A straight forward experimental study demonstrated that AMH receptor is expressed in gonadotropin releasing (GnRH) neurons and that intracerebroventricular administration of AMH increases GnRH – dependent LH pulsatile release.[33] There is accumulating evidences that GnRH pulsatility is preturbed in women with PCOS, leading to increases LH pulsatility, which plays an important role in PCOS pathophysiology.[20] serum AMH levels are typically increased in PCOS and therefore AMH dependent regulation of GnRH release could be involved in PCOS.[34]

PCOS at different stages of life

1. PCOS in childhood: - The interaction between a genetic predisposition and some prenatal and postnatal environment factors seems to take part in pathophysiology of PCOS. Intrauterine growth retardation or small for gestational age and high level of androgen during the intrauterine period could lead to an increase production of glucocorticoids which may induce epigenetic modification and increase risk of PCOS.[35]

2. PCOS in aldoscence: - PCOS is often diagnosed in aldoscence. Menstrual irregularity, acne and hissutism are the major finding in this age group. Family history of PCOS, overweight or low birth weight, exposure to androgens during gestation, precocious puberty, obesity and IR are risk factors to development or syndrome. Dietary orientation, stimulation to physical activity and self care should be part of integral care for adolescent girls.[36]

3. PCOS in postmenopausal women: - Women with PCOS persist with hyperandrogenism even after menopausal transition and continue to manifest metabolic alterations and with increase risk of cardiovascular disease.[37]

Management of PCOS

The medications used PCOS aim to alleviate the symptoms of the disease while there is currently no cure for PCOS, you can minimize the impact of the disease by maintaining a healthy lifestyle and managing symptoms with selective use of drugs.

Approach considerations – Certain life style changes such as diet and exercise are considered first line treatment for adolescent girls and women with PCOS. Pharmacological treatments are reserved for so called metabolic de-arrangements such as an ovulation, hirsutism and menstrual irregularities. Medications for such conditions include oral contraceptives, metformin, prednisone, clomiphene, spironolactone.[38]

Life style modifications:- The American college of Obstetricians and gynecologists (ACOG) and Society of obstetricians and gynecologist of Canada (SOGC) indicate lifestyle modifications such as weight loss and increased exercise in conjunction with a change in diet consistently reduce the risk of diabetes. This approach has been found to be comparable to better treatment with medication and should therefore be considered first line treatment in managing women with PCOS. These modifications have been effective in restoring ovulation cycles and achieving pregnancy in obese with PCOS. Weight loss in obese women with PCOS also improves hyperandrogeic features.[39]

Medical management

The oral contraceptive pill (OCP)

The oral contraceptive pill (OCP) remains the first-line therapy for hirsutism because of its effect on androgen production.[40] First, the estrogen component of the OCP increases sex hormone-binding globulin levels, resulting in greater androgen-binding capacity, and reducing circulating free testosterone levels. Second, the progestin component suppresses pituitary LH production, reducing the stimulation of ovarian theca cell androgen synthesis under LH stimulation. Certain OCP progestins such as drosperinone and cyproterone acetate function as androgen receptor antagonists, and have a theoretical advantage over other progestins. OCP use offers the additional benefit of reducing acne, if present, and provides protection against endometrial cancer and menstrual cycle irregularity. Oral contraceptive use has consistently been found to reduce risk of endometrial cancer. OCP use appears to provide a risk reduction of approximately 50%, and the protective effect seems to last up to 20 years after stopping OCP use.[41] Additionally, relative reduction of endometrial cancer risk seems to be approximately twofold lower in women who have used the OCP for 12 years compared with women using it for 4 years.[42]

Insulin-sensitising agents

Metformin

Anti diabetic medications, statins, hormones and hair growth inhibitors. Birth control pills to regularize periods, medications called metfoemin to prevent diabetes statins to control high cholesterol hormones to increase fertility and procedures to remove excess air. Metformin improves insulin sensitivity in women with PCOS.[43] It has also been shown to decrease fasting insulin levels, but this benefit was restricted to non-obese women with PCOS (BMI <30 kg/m2).[44] There is no robust evidence for the use of metformin to merely ameliorate insulin resistance associated with PCOS, and its use to combat the same in normoglycaemic women is not recommended by any international organisation.

Inositol

Inositols are compounds with insulin-mimetic properties, particularly the isomers myoinositol (MI) and d-chiroinositol (DCI). MI and DCI are involved in downstream signalling pathways following the activation of insulin receptors and are considered mediators of insulin action.[40]

Various studies have demonstrated that administration of DCI leads to decreased basal insulin levels, an improved lipid profile and reduced systolic blood pressure.[45,46]

Anti-obesity agents

Orlistat

Orlistat, rimonabant and sibutramine have been used in the pharmacotherapy of obesity in PCOS. Sibutramine and rimonabant have been withdrawn over safety concerns. Orlistat is an irreversible gastric lipase inhibitor that prevents the breakdown of dietary fat and thus, its absorption. In PCOS, orlistat induces significant and sustainable weight loss with similar efficacy to metformin. Its use is also associated with an improved lipid profile, including significant reductions in the levels of total cholesterol, low-density lipoprotein and triglycerides. Based on available evidence, orlistat can be considered for the treatment of overweight and obese women with PCOS for whom lifestyle modifications are insufficient.[47] Patients take 60–360 mg of orlistat per day, divided between two to three doses. Its use is associated with mild to moderate gastrointestinal side effects including steatorrhoea and abdominal pain, which potentially affects compliance to treatment.

Statins

In women with dyslipidaemia, the use of statins results in significantly and consistently improved lipid profiles. Furthermore, reduced levels of markers of endothelial dysfunction and systemic inflammation suggest a decrease in cardiovascular risk factors.[48]

For infertility, clomiphene is first line treatment.[49]

Surgical treatment

Laparoscopic – Laparoscopic ovarian drilling is a relatively simple procedure performed by minimal access and usually an outpatient basis. It provides an alternative treatment option for PCOS patients an ovulatory to clomiphene citrate. The MOA of laparoscopic ovarian drilling is unclear its beneficial effect is apparently due to destruction of androgen producing stroma. The procedure appears to have little or no effect on insulin sensitivity and lipoprotein profile. The PCOS patients who are clomiphene citrate resistance ovulate after drilling and at least half of them go on to achieve a pregnancy.[50]

Clinical significance of PCOS in normal women

1. PCOS are the morphological ovarian phenotype ovary syndrome.[51]
2. The morphology of the polycystic ovary was defined as an ovary with 12 or more follicles measure 2-9 mm in diameter and for increased ovarian volume.[52]
3. It is interesting also to note that presence of PCOS is a marker for increased ovarian aging.[53]
4. It has been found that some women with hypogonadotropic hypogonadism (HH) also have polycystic ovaries detected by pelvic ultrasound and when these women were treated with GnRH to induce ovulation they had significantly higher serum LH concentration than women with HH and normal ovaries.[54]

Herbal treatment of PCOS

- Cinnamon extract has been shown to reduce insulin resistance by increasing phosphatidyl ionsitol, 3 – kinase activity in the insulin signaling pathway.[55]

- Recent research in Turkey has revealed that the spearmint tea has antiandrogenic properties in females with hirsutism.[56,57]
- Aloe Vera gel formulation exerts a protective effect against the PCOS phenotype by restoring the ovarian steroid status and altering key steriodogenic activity.[58]

Besides those factors that are involved in the etiology of PCOS, due to unknown single cause there is no such treatment that overcomes this condition. Whereas the symptoms and severity of this condition can be reduced to some extent. Adopting a healthy lifestyle is the first and foremost method of controlling PCOS severity. The severity of symptoms can be reduced if affected females lose weight. Losing weight up to 5–10% control the symptoms.[51] PCOS woman should follow a balanced and healthy diet that includes low fat to moderate proteins. Fiber-rich containing food, fruits, vegetables, cereals should be taken along with regular exercise. High-caloric food should be avoided.[59] Medicines like Oral Contraceptive Pills OCP, Metformin, Cyclin Progestin are recommended to PCOS patients to reduce PCOSprogression.It also regulates the menstrual cycle and hyperandrogenism.[60] For hirsutism and acne, laser and cosmetic treatment are recommended. For infertile woman invitro fertilization IVF and gonadotrophins are recommended.[61] Prevention of insulin resistance using certain drugs: a flow chart is represented in Fig. 4.

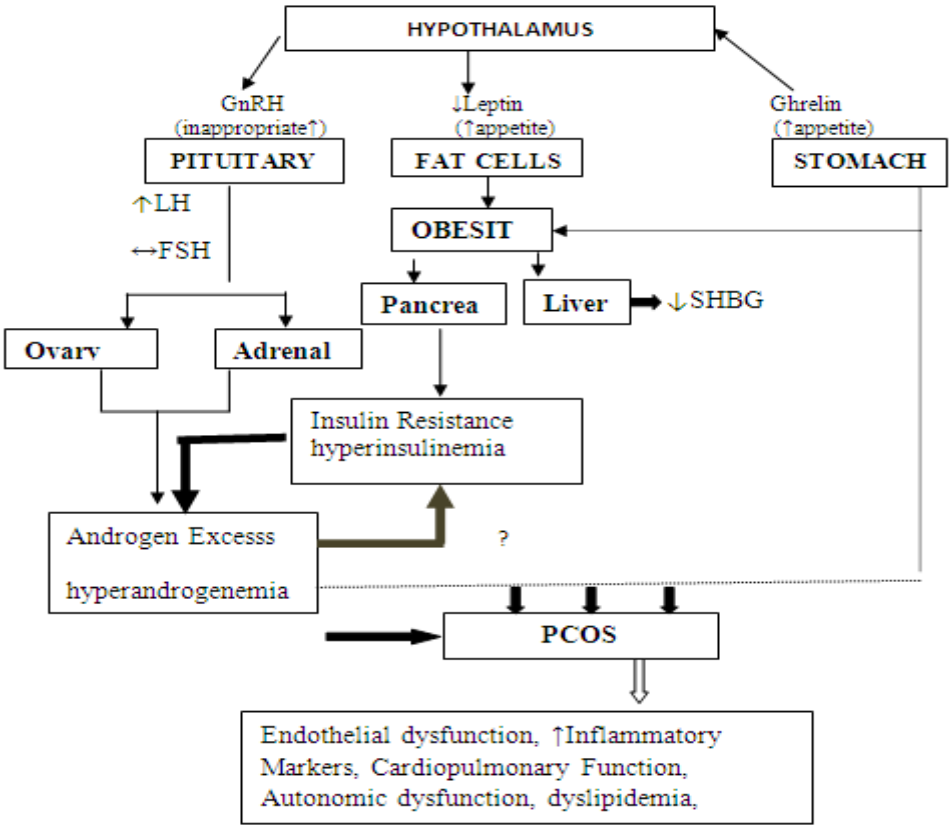

Fig. 4: Flowchart that illustrates how insulin resistance leads to elevated level of androgen. It also explains decrease level of androgen that can be possible by using drugs that prevents insulin resistance.

CONCLUSION

Apart from the environmental factors, many candidate genes are involved in the etiology of the PCOS, alteration in the metabolic pathway due to the defect in gene leads to the progression of PCOS and ovary dysfunction. The severity can only be reduced when follows proper preventory measures that is weight loss, healthy diet and medications.

DECLARATION OF COMPETING INTEREST

We hereby declare that we have no conflict of interest related to this article.

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