

**POLYCYSTIC OVARY SYNDROME: OVERVIEW**A. Ananya<sup>1</sup>, M. Saikala<sup>1</sup>, D. Sudheer Kumar<sup>2</sup> and P. Kishore<sup>1\*</sup><sup>1</sup>Department of Pharmacy Practice, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal (rural) – 506006.<sup>2</sup>Department of Pharmaceutics, Care College of Pharmacy, Oglapur (v), Damera (m), Warangal (rural) – 506006.**\*Corresponding Author: Dr. P. Kishore**

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**ABSTRACT**

Polycystic Ovary Syndrome is the most common heterogenous complex endocrine disorder. It is affecting approximately 15 % of the women in their reproductive age. The exact cause of the PCOS is unknown, but genetic factors, environmental and endocrine factors plays a crucial role in the etiology of PCOS. Clinical manifestations of the PCOS include hyperandrogenism (hirsutism,acne,alopecia), oligomenorrhea, amenorrhea, anovulation, infertility. Insulin resistance is seen in most of the patients with PCOS which may leads to DM. Hypertension, dyslipidemia, metabolic syndrome, insulin tolerance, DM, gestational DM, infertility are the complications of the PCOS. Diagnosis is made by physical and medical history, blood tests to check the hormones levels, ultrasound. Treatment is based on the individual presenting with PCOS. Weight loss and exercise practise can be treated as the first line treatment. Oral contraceptives are the drug of choice for menstrual irregularities. Anti androgens like spironolactone, finasteride are useful in treating hirsutism. Clomiphene citrate is used in treating the infertility, other treatments include laproscopic ovarian drilling, gonadotrophs. Metformin also plays crucial role in ovulation induction.

**KEYWORDS:** PCOS, Hyperandrogenism, Anovulation, COC's.**INTRODUCTION**

Polycystic Ovary Syndrome (PCOS) is an endocrine metabolic disorder characterized by multiple hormonal imbalances representing diverse clinical presentations dominated by clinical and biochemical signs of hyperandrogenism which results in short and long term consequences in female health. It has a tremendous negative impact on the women's physiology and metabolism leading to metabolic alterations i.e., insulin resistance, hyperinsulinemia, abdominal obesity, hypertension and dyslipidaemia culminating as serious long term consequences such as T2DM, endometrial hyperplasia and CVS diseases.<sup>[1]</sup> The prevalence rate of PCOS in India was found to be 30 %. Teenagers are being most affected. PCOS is described as an oligogenic disorder with an interaction of genetic and environmental factors which determine the heterogenous clinical and biochemical phenotype expression in PCOS women.<sup>[2]</sup> The expression of PCOS is mainly due to polymorphism of genes like FBN-3, LHR, TNF- alpha and IL's. FBN-3 is involved in the regulation of TGF signaling. LHR have a role of LH, T stimulation, follicle development, LH surge induced ovulation in ovaries and LH stimulation of adipogenesis in adipocyte.<sup>[3]</sup> Diet, lifestyle and physical activity also have an influence on women health. LH/FSH ratio is elevated in PCOS women. The three common factors associated with PCOS are anovulation, clinical and biochemical hyperandrogenism (hirsutism,

acne, alopecia) and polycystic ovaries. Insulin resistance, obesity, CVD, cancer, infertility, miscarriage, preeclampsia and gestational DM are commonly developed complications in women with PCOS. Treatment is mainly based on clinical presentation of the patients i.e, menstrual irregularities, hyperandrogenism and anovulation.

**INCIDENCE AND PREVALENCE**

The prevalence of PCOS in India was found to be 30 %.<sup>[4]</sup> In middle east countries( Iran and Turkish), China, North California, Australia, Africa the prevalence of PCOS was found to be 6.1 %, 5.6 %, 0.83 %, 8.7 % and 7.4 % respectively.<sup>[5]</sup> Teenagers are being most affected (50 %).

Almost 75% women with PCOS develop insulin resistance and 10% of them develop diabetes by age 40. Risk of developing DM in PCOS patients is 15.4 %.<sup>[5]</sup> The prevalence of PCOS in women with dysmenorrhea was 40%. The prevalence of PCOS was lower in black women compared to white. According to body weight, the prevalence of PCOS is Under weight (8.2 %), Normal (9.8 %), Over weight (9.9 %), Obese (9 %).<sup>[4]</sup>

**ETIOLOGY**

However the etiology of the disease is not completely understood; PCOS is deemed as an interlacing disorder

with multiple abnormalities i.e; genetic, environmental and endocrinological aspects.

### Genetic Factors

Evidence connotes a strong familial aggregation of women with PCOS as well as its clinical and metabolic manifestations. 20-40 % of first degree relatives of women with PCOS also have the syndrome, suggesting that the disease is partially heritable and clusters in families. Although the genetics of PCOS is not well understood, about 43 proteins are responsible for PCOS.

(i) The focal genes taking part in the pathology of PCOS are those encoding for factors involved in synthesis, transport, regulation and effects of androgens.<sup>[3]</sup>

(ii) Genes those coding for factors involved in insulin metabolism such as insulin receptors, signaling cascade proteins responsible for binding of proteins to its receptor, IGF system, other growth factors and genes encoding for calpain-10 enzyme responsible for insulin secretion and action.<sup>[3]</sup>

(iii) Polymorphism of genes coding for TNF-alpha, IL-6, IL-6 receptor.<sup>[3]</sup>

(iv) Allelic variants of fibrillin 3 (FBN-3) and variants of LH receptors (LHR).

### Environmental factors

Factors such as diet, physical activity and life style modifications have a large impact on the PCOS expression. Extending the other factors, environmental insults may result in clinical phenotype of PCOS who are susceptible.

Diet emerges as a major environmental determinant of PCOS. Overnutrition and high content of food in advanced glycated end products (AGEs) are the detrimental dietary factors.<sup>[6]</sup>

Exposure to environmental toxins trigger the pathogenesis of PCOS. Plasticizers such as bisphenol A (BPA) or phthalates belong to endocrine disrupting chemicals (EDCs) which effect women health by destabilization of the hormonal homeostasis and thus leads to disruption of reproductive functions. They also hinder with metabolic alterations such as obesity, insulin resistance, hyperinsulinemia that can exacerbate PCOS, T2DM and CVS disorders.<sup>[7]</sup>

### Endocrine Factors

Ovarian folliculogenesis is regulated by a flimsy equilibrium between intra and extra ovarian factors. Derrangements in this equilibrium alters follicular development leading to formation of immature oocytes thereby resulting in infertility.

Altered secretion of GnRH and gonadotropins

A high percentage (55 -75 %) of women with PCOS have an elevated LH/FSH ratio (2:1/3:1) presumably due to high levels of LH rather than reduced or normal FSH production. GnRH stimulation causes evidence excessive LH production in PCOS women.<sup>[3]</sup>

**Table 1: Role of Intra and extra ovarian factors.**<sup>[3]</sup>

S.no	Factor type	Role	Levels in PCOS	Altered function in PCOS
1	EGF	Regulation of cell growth, proliferation, differentiation with EGFR	Increased	Follicular growth arrest by inhibiting granulosa estrogen synthesis.
2	IGF'S	Follicle and oocyte development	Increased	Follicular growth arrest
3	NGF	Folliculogenesis and oocyte maturation	Increased	Impaired
4	TGF-Beta (i)AMH	Folliculogenesis	Increased	T, LH increased results in altered oocyte maturation, low embryo quality (low fertilization rates)
	(ii)Activin, follistatin, inhibin	Follicular development, cellular growth, differentiation	Increased	Arrest of follicle growth and reduced oocyte development
	(iii)VEGF	Angiogenesis, follicular vascularisation, intrafollicular oxygenation	Increased	Immature oocyte
	(iv)IL's (1,2,6,8,11,12)	Folliculogenesis, ovulation, corpus luteum function.	Increased	Decreased oocyte maturity, fertilization, pregnancy
	(v)TNF-alpha	Proliferation, differentiation, follicular maturation, steroidogenesis, apoptosis	Increased	Poor oocyte and embryo quality
	(vi)Fas and Fas ligand (Fas L)	Anti and pro apoptotic function	Decreased	Reduced oocyte maturation

**Table 2: Miscellaneous Factors.**<sup>[3]</sup>

Sno	Factor	Observed levels in PCOS
1	Heat shock proteins(HSPs)	Decreased
2	Transferrin	Increased
3	Homocysteine	Increased
4	Leptin	Increased
5	Oxidative stress	Increased

Drugs such as anabolic androgenic steroids, synthetic progestins and antiepileptics induce hyperandrogenism.<sup>[8]</sup>

### PHYSIOLOGY

The key hormones involved in the pathogenesis of PCOS are estrogen, progesterone, androgens, LH and FSH. Secretion of androgens by ovaries and adrenals is responsive to their respective trophic hormones (LH, ACTH)<sup>[9]</sup> where as altered physiology is that theca cells secrete high levels of androgens to an intrinsic activation of steroidogenesis (intraglandular paracrine and autocrine mechanism) even in the absence of trophic factors in PCOS women.<sup>[10]</sup>

### Hormonal regulation and ovulation

Hypothalamic-Pituitary-Gonadal (HPG) axis coordinates reproductive behaviour with ovulation. The primary signal from the CNS is GnRH release from hypothalamus which inturn modulates the anterior pituitary gonadotropes regulating LH and FSH<sup>[11]</sup> by theca cells, granulosa cells respectively whose function is to trigger ovulation and maturation of the follicle. As the ovarian follicle develop, they release estradiol which negatively regulates further release of GnRH and FSH. After attaining peak levels, estradiol triggers GnRH which inturn causes LH release inducing ovulation.<sup>[11]</sup> The ovum then move towards the uterus ready for fertilization. If the ovum is not fertilized, levels of estrogen, progesterone drops and doesn't maintain nutritious lining and thus endometrium get slugged off. In PCOS a decreased sensitivity of GnRH causing perturbations in gonadotropin secretion such as LH hypersecretion which have detrimental effect on oocyte maturity, fertilization, pregnancy and miscarriage rates. In PCOS women, LH levels are far higher than FSH levels. Since the LH levels are already high there is no LH surge, without LH surge ovulation doesn't occur.

### PATHOGENESIS

PCOS is a complex disorder and there is no definite explanation. PCOS is thought to be caused by hormonal imbalance. Women with PCOS show about twice the levels of androgens compared to normal healthy women. There are many research theories for PCOS. Some suggest it as a genetically inherited disease, some express that the ovaries produce too much androgens due to defect in the hypothalamus, some theorize ovarian abnormality, another suggests culprit is hyperinsulinemia which lead to hyperandrogenism.

In PCOS, many physiological events within the ovarian cycle and folliculogenesis are dysregulated. The very

beginning of folliculogenesis is compromised due to high levels of anti mullerian hormone (AMH).<sup>[1]</sup> As there are high levels of AMH in PCOS women, ovarian physiology is disrupted and also results in worse fertility outcome.<sup>[1]</sup>

Theca cells secrete high levels of androgens due to an intrinsic activation of steroidogenesis in the absence of trophic factors. This intrinsic defect in the theca cells also has an effect on granulosa cells which produce four times more AMH levels. Studies also revealed an elevated number of follicles, primarily pre antral and small antral follicles. Together with a defect apoptotic processes in maturing follicle will increase the follicle count in PCOS women.<sup>[10]</sup>

Another typical feature of PCOS are feedback disturbances in hypothalamus- hypophysis-ovary axis (HHOA) increased frequency and amplitude of GnRH and LH pulsatile secretion.<sup>[12]</sup> Higher levels of this hormones induce ovarian theca cells to secrete androgen excess. Hyperandrogenemia inturn causes decrease in feedback sensitivity to both estradiol and progesterone in gonadotropic-hypothalamic cells, reinforcing GnRH and LH hypersecretion.<sup>[12]</sup> Hyperandrogenemia plays a pivotal role in the development and progression of PCOS.

The pathophysiological aspects of PCOS are clearly explained by following- endocrine dysfunction, reproductive dysfunction, metabolic dysfunction and biochemical dysfunction.

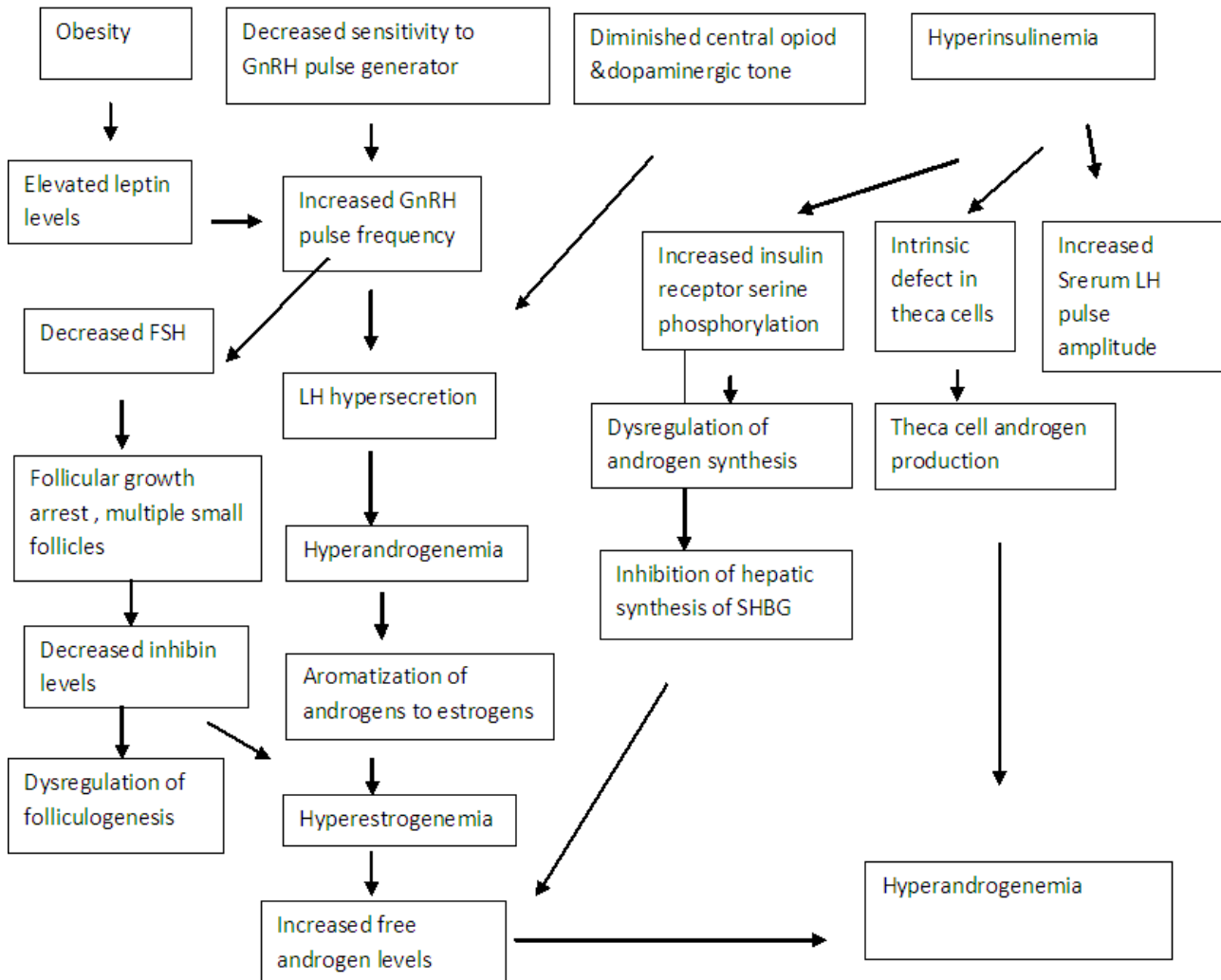
**Reproductive dysfunction:** Women with PCOS frequently present with reproductive dysfunction. The exact pathogenesis of anovulation is not clearly known but many mechanisms like LH hypersecretion, hyperandrogenemia, hyperinsulinemia, obesity, decreased plasminogen activator inhibitor (PAI) activity and endothelial dysfunction are interlinked. Menstrual irregularity is the most common gynecological presentation of PCOS. 85-90% of women with PCOS are oligomenorrhoeic and 30-40% women are amenorrhoeic.<sup>[1]</sup>

Polycystic ovaries display more number of follicles compared to normal ovaries suggesting follicular development disturbances. Perturbations in gonadotropin secretion in PCOS such as decreased FSH and increased LH results in abnormal follicular dynamics manifesting in anovulatory infertility. Decreased FSH levels results in follicular growth arrest at 2-8 mm stage and produce estrogen and inhibin by multiple, small follicles which

in turn inhibit FSH secretory dynamics preventing selection of dominant follicle and thus contributes to impaired follicular development.<sup>[1]</sup>

**Endocrine Dysfunction:** PCOS is marked by abnormalities of both feed forward and feedback

signaling between GnRH /LH and ovarian androgens. The key endocrine abnormalities of reproductive axis include accelerated GnRh pulsatile activity, LH hypersecretion, theca-stromal cell hyperactivity and hypofunction of the FSH- granulosa cell axis.<sup>[1]</sup>



**“Figure 1”. Endocrine dysfunction in PCOS.<sup>[1]</sup>**

### CLINICAL MANIFESTATIONS

The classic symptoms of PCOS are anovulation, clinical and biochemical hyperandrogenism (hirsutism, acne, alopecia), polycystic ovaries.

Obese women may have increased risk of metabolic effects (Type 2 DM, HTN, hyperglycemia, insulin resistance) Pregnant women have a higher chance of miscarriage, gestational diabetes and HTN.<sup>[3]</sup> Patient presentation is variable, ranging from asymptomatic to having multiple gynecological, dermatological, metabolic manifestations.

**Anovulation:** Anovulatory cycles often manifests with oligomenorrhoea, secondary amenorrhea or abnormal

uterine bleeding. Abnormal cycle is usually considered when menstrual cycles are less than or equal 8 per year.

43 % Oligomenorrhoea- infrequent menstruation

21 % Secondary amenorrhoea- Absence of menses for more than 3 months

7 % polymenorrhoea-more frequent cycles with an interval of less than 24 days

95 % Amenorrhoea.<sup>[3]</sup>

Polycystic ovaries: presence of morphological changes in the ovary i.e; 12 or more follicles of diameter 2-9 mm and/ an ovarian volume of more than 10 ml in follicular phase and increase in stromal tissue.<sup>[3]</sup>

### Hyperandrogensim

The manifestations of hyperandrogenism are hirsutism, acne, alopecia (balding), decreased breast size, increased muscle mass, enlargement of clitoris.

**Hirsutism:** Hirsutism is presence of terminal and unwanted hair on the face, chest, back in a masculine pattern.

**Acne:** Acne consists of comedo (an open or closed skin pore/hair follicle clogged with oil, dead skin cells and bacteria). Excess androgens aggregate this process by increasing sebum production by pilosebaceous units.

**Alopecia:** It is defined as progressive thinning of hair or hair loss. Androgenic alopecia is mainly due to seborrhoea and dandruff.

**Table 3: Clinical manifestations as per different organ systems.**<sup>[13]</sup>

Organ system	Symptoms
Reproductive	Amenorrhoea Polymenorrhoea Oligomenorrhoea Immature ovulation Multiple cysts Infertility
Hair and skin	Hirsutism Acne Alopecia Acanthosis nigricans
Mental and emotional health	Mood swings Anxiety Depression
Sleep	Sleep apnea

### COMPLICATIONS

#### Insulin resistance

Insulin resistance develops most commonly in PCOS women which may lead to dyslipidemia. IR increases VLDL secretion thereby decreasing its elimination and also chylomicrons elimination which may further leads to production of triglycerides. IR also leads to clearance of HDL-C constituent which is apolipoprotein-a, and leads to decreased levels of HDL-C. Postbinding decrease in the phosphorylation of tyrosine residues and increased serine phosphorylation of the insulin receptor cause resistance to metabolic actions of insulin. Increase in serine phosphorylation decreases the response of insulin receptor to its substrate and increases the P450C17 activity, which is an important enzyme involved in the adrenal and ovarian steroidal synthesis.<sup>[14]</sup>

#### Obesity

Obesity is the important feature of the PCOS. PCOS women have excess of androgens which may lead to high visceral and subcutaneous fat. Androgens involves in the dysregulation of appetite. There is decreased production of gastrointestinal satiety peptide cholecystokinin and

also dysregulation in secretion of ghrelin, which is a appetite regulating hormone in PCOS women. Their levels are increased in PCOS women, so obesity is more frequently seen.<sup>[14, 15]</sup>

#### Cardiovascular diseases

Patients with PCOS have high levels of biomarkers such as C-Reactive protein and Lipoprotein A.<sup>[10]</sup> The risk of CVD in PCOS is hyperinsulinemia. One mechanism of insulin resistance is direct atherogenic action which results in early onset of cardiovascular dysfunction. The other risk factors for CVD in PCOS is impaired glucose tolerance and DM.<sup>[14, 16]</sup>

PCOS women have elevated concentration of plasminogen activator inhibitor or fibrinogen that results in impaired fibrinolysis.

#### Cancer

Women with PCOS has high risk of developing endometrial cancer. Prolonged anovulation triggers unopposed estrogen secretion which increases risk of endometrial carcinoma. Other risk factors associated with endometrial cancer includes nulliparity, infertility, obesity and DM. More than 3 months of interval between menstruation is associated with endometrial hyperplasia. Studies link the use of drugs such as clomiphene citrate increases the risk of developing ovarian cancer, multiple ovulation, early menarche, late menopause and nulliparous increases the risk of ovarian cancer.<sup>[10, 16]</sup>

#### Infertility

Infertility is 10 times more common in PCOS women compared to healthy controls. As PCOS is the common cause of ovulatory disorder the risk of infertility increases due to associated endocrine and gynaecological abnormalities that affects the ovarian function.<sup>[10]</sup> Endometrial abnormalities affect the implantation in PCOS women.<sup>[17]</sup>

**Gestational complications:-** The risk of gestational complications such as miscarriage, gestational DM and preeclampsia increases in women with PCOS. Several factors such as infertility treatment, IR, multiple pregnancies, obesity, metabolic dysfunction, inflammation and placental alterations results in increased incidence of gestational complications in PCOS women. The risk of developing miscarriage, preeclampsia, gestational DM is 30-50 %, 10-15 % and 20- 30 % respectively.<sup>[10, 18]</sup>

#### Psychological disorders

Women with PCOS have more chance of developing psychological disorders. They may have anxiety, depression, binge-eating, disorder, bipolar disorder, psychosexual dysfunction. Depression is more commonly seen in teenage girls because of difficulty in managing the over weight. Because of the infertility, miscarriage, sub fertility problems adult women also disturb psychologically. Psychiatric disorders also

develop due to insufficient sleep which is seen in the PCOS women.<sup>[10]</sup>

### DIAGNOSIS

As PCOS is a syndrome of ovarian dysfunction the diagnosis of PCOS is difficult. This cannot be diagnosed by a single symptom or blood test. Diagnosis of PCOS can be done by careful history, physical examination, laboratory finding and by following criteria

- Rotterdam Criteria for Diagnosis of PCOS: PCOS is diagnosed if 2 out of 3 criteria is included

1. Oligo and/or anovulation
2. Biochemical and/or clinical signs of hyperandrogenism

-Biochemical: Total T greater than 70 ng/dl, Androstenedione greater than 245 ng/dl, DHEA-S greater than 248 ug/dl

-Clinical : Acne, hirsutism, acanthosis nigrans

3. Polycystic Ovaries:

- Greater than or equal 12 follicles(2-9 mm diameter) in each ovary or ovarian volume greater than 10cc.<sup>[5]</sup>

- National institute of health(NIH) criteria : Includes all of the following

1. Oligo- anovulation
2. Clinical and/or biochemical signs of hyperandrogenism (hirsutism, acne, alopecia).<sup>[5]</sup>

- Androgen Excess and PCOS society criteria : PCOS is diagnosed if all of the following criteria is included

1. Clinical and/or biochemical hyperandrogenism
2. Presence of polycystic ovaries or oligo- anovulation.<sup>[5]</sup>

Physical examination

Includes body weight, menstrual cycle abnormalities, unwanted hair growth, skin.

Pelvic examination:

Check for any swellings or growths in the pelvic region.

Blood tests:

To assess hormones, blood sugar levels, lipid levels, thyroid tests.

Ultrasonography:

Performed to scan for cysts and enlarged ovaries.

Evaluation of clinical features of PCOS can be done by following scales.

**Table 4: Evaluation of hirsutism is done by using Ferrimen-Gallwey scoring system.<sup>[2]</sup>**

S.No	Score	Result
1	0	Absence of terminal hair
2	4	Extensive hair growth
3	8	Hirsutism
4	9	Moderate hirsutism
5	Greater than 15	Severe hirsutism

**Table 5: Evaluation of Acne can be done by Global Acne Grading Scale(GAGS).<sup>[19]</sup>**

S.No	Global score	Severity
1	0	No active acne lesions
2	1-18	Mild active acne lesions
3	19-30	Moderate
4	31-38	Severe
5	Greater than 39	Very severe

Assessment scales of Alopecia include:

- Modified Norwood – Hamilton classification
- Sinclair scale for female pattern AGA.<sup>[20]</sup>

### GOALS OF TREATMENT

1. To control hyperandrogenic features including hirsutism, acne.
2. To treat dysmenorrhoea for endometrial protection.
3. To prevent complications.

### MANAGEMENT

Both non-pharmacological and pharmacological treatment plays a crucial role in management of PCOS.

#### Pharmacological management

Treatment should be based on the patient's clinical presentation.

#### Menstrual irregularity

Endometrium proliferation in women with menstrual irregularity can be reduced by cyclic progestin or combined oral contraceptives. Combined oral contraceptives in low doses are beneficial in the treatment of menstrual irregularity (less than 50 mcg of estrogen and progestin).

They act by reducing LH, testosterone levels and by increasing SHBG by suppressing hypothalamo-pituitary ovarian axis. Oral contraceptives are considered as the first line treatment in the treatment of PCOS. Treatment should be continued for 6 months. Insulin sensitizing drugs are also used in the treatment of excess androgens. Drugs include metformin and thiazolidinediones are mostly preferred. Metformin improves glucose tolerance and decreases androgen levels. It acts by delaying hepatic glucose production which increases insulin sensitivity. Metformin in combination with low dose spironolactone is beneficial than alone. Spironolactone alone is not appropriate for treatment. It is an aldosterone antagonist which acts by binding to androgen receptor.<sup>[2,21]</sup>

#### Hyperandrogenism

Management of hirsutism:

Mechanical methods of hair removal

Other methods for removal of hair include electrolysis, photo epilation devices like laser and intense pulsed light. Other temporary methods like depilation, epilation, bleaching are also effective in removal of hair. Topical agents involved are eflornithine, which is an ornithine decarboxylase inhibitor also reduces facial hair

growth. But there are less frequently used because of the side effects like skin rashes and irritation.

#### Management of Acne:

Management needs careful selection of anti acne agents based on individual patient needs. First line medications include hormonal contraceptives and can be used in conjunction with standard topical acne therapy. Second line drugs include anti androgens.

#### Management of Alopecia:

COCs and androgen blockers are recommended as first line therapy.<sup>[2, 21]</sup>

#### Anovulation

Weight loss is the first line treatment in obese women. First line medications include clomiphene citrate and aromatase inhibitors. It is a selective estrogen receptor modulator. It exerts anti estrogenic effect at hypothalamus by inducing change in GnRH pulse frequency leading to increased levels of FSH from pituitary gland. Aromatase inhibitors block the conversion of testosterone to estradiol and androstenedione to estrone. Second line therapy includes ovulation induction with gonadotropins and LOD.<sup>[22]</sup>

**Table 6: Drug Therapy of PCOS.**<sup>[2,5,10,21,22]</sup>

Sno	Clinical presentation	Drugs	Dose	Side effects
1	Menstrual irregularity	Combined Oral contraceptives estrogen+ progestin drospirenone desogestrel Insulin sensitizers Metformin  pioglitazone Metformin +spironolactone Spironolactone	50 mcg 3 mg 0.15mcg  500 mg  30-45 mg 500+100 mg  100 mg	Weight loss, metallic taste, lactic acidosis Weight gain, fluid retention Weight loss  Polyuria, Abdominalpain,dryness ofmouth
2	Hyperandrogenism Hirsutism  Acne  Alopecia	Combined Oral contraceptives Ethinyl estradiol  Drospirenone  desogestrel  CPA Anti androgens Spiranolactone Flutamide Finasteride  Topical agents Benzoyl peroxide Retinoids (Isotretinoin) Antibiotics Combined Oral contraceptives Drospirenone+EE  Desogestrel + EE  CPA + EE  Combined Oral contraceptives Drospirenone+EE	35 mcg  3 mg  150 mcg  2 mg  25-200 mg 250 mg 5 mg     3 mg + 30 mcg  150 mcg +30 mcg  2 mg + 35 mcg	Gynaecomastia, head ache Nausea, vomiting, verigo, altered LFT Bloating, Weight gain, nausea, headache, rise in B.P Breast tenderness  Teratogenicity(feminization of male infant)    Diarrhoea, nausea, fever  Loss of appetite, weight change  Breast tenderness, head ache

		Desogestrel + EE	3 mg + 30 mcg	Diarrhoea, nausea, fever
		CPA + EE	150 mcg +30 mcg	Loss of appetite, weight change
		Anti androgens	2 mg + 35 mcg	Breast tenderness, head ache
		Spiroinolactoe	25-200 mg	Polyuria ,abdominal pain
Anovulation		Clomiphene citrate	50 mg	Ovarian enlargement, ovarian hyperstimulation syndrome, multiple pregnancies, GI distension, bloating.
		Aromatase inhibitors Letrozole	2.5- 7.5 mg	Osteoporosis dyspepsia, anorexia Hot flashes,
		Anastrazole		vaginal bleeding, drowsiness

### Nonpharmacological management

Non pharmacological treatment have a great impact on the PCOS patient. Effective approaches to nutrition and exercise improves endocrine and reproductive function and minimizes CVS risk associated with PCOS.

Moderate weight loss (greater than 5%) have shown beneficial effects on well being, insulin sensitivity and CVS risk presentation by improving glucose tolerance, reproductive function.

Weight loss is the first line treatment for obese patients. Weight loss occurs when the energy intake is less than energy expenditure.

Stress reduction is other major lifestyle modifications which improves the physical and mental status of an individual.

### Diet

- Fiber rich foods such as broccoli, brown rice, berries, lentils. Fiber rich foods combat insulin resistance by slowing digestion and reducing glucose impact on the blood.
- Consume lean protein sources like tofu, fish, chicken and anti inflammatory foods like cabbage, kale, almonds, olive oil, tomatoes, fish high in omega 3 fatty acids (salmon, sardines).
- Foods that should be avoided include foods high in refined carbohydrates like muffins and white bread, sugary snacks, drinks, processed foods and red meat.
- Pasta, noodles should be restricted as they are high in carbohydrate and low in fibres.
- Alcohol intake, red meat, foods containing hydrogenated oils, gluten grains, white flour, white sugar, caffeine may aggravate the symptoms.

### Recommended calorie intake

- Consumption of unsaturated fatty acids have shown to improve insulin sensitivity. Long chain

polyunsaturated fatty acids (PUFA'S) also have beneficial effects on endocrine and metabolic parameters.

- Follow mediterranean diet.
- Foods with high glycemic index delivers carbohydrates rapidly result in glycemic overload associated with DM. consumption of foods containing low glycemic index is beneficial.
- Individual should encourage intake of macronutrients includes 40 % carbohydrates, 30 % proteins, 30 % or less of fats with exercise.
- Studies confirmed less frequent huge or large eating patterns are associated with fat buildup hence frequent small meals is preferable or desirable.
- Avoid trans fat as they have been linked to anovulation and infertility outcomes in PCOS women.
- Low calorie rich diet with energy restriction of 500-600 kcal/day with reduced carbohydrates intake are recommended to obese women with PCOS.
- According to American heart association guidelines, dietary fiber intake should be 25-30 g/day, MUFA diet should be 24g/day.<sup>[23,24]</sup>

### Lifestyle changes

- Diet and calorie restriction works better when suitable exercise programme is maintained.
- 60-75 minutes of moderate to high intensity physical activity promotes weight loss and show positive impact on the disease.
- Performing 30 minutes aerobic sessions/week for 12 weeks is the standard exercise pattern. Prolonged or vigorous exercise may enhance weight loss.
- Types of exercises include aerobic exercise, endurance exercise, resistance training, exercises to increase flexibility
- PCOS women are advised to perform 90 minutes of aerobic exercise/week at moderate intensity of 60-70



% to improve reproductive and cardiometabolic outcomes.

- Behavioural counseling and meditation session are advantageous for stress management and weight loss. Behavioural counseling includes regular personnel or group sessions of motivational support.<sup>[25, 26]</sup>

### ROLE OF PHARMACIST

Pharmacist can make significant impact on PCOS patients by providing information about disease, lifestyle modifications and medications. Pharmacist plays a vital role in optimizing therapeutic outcomes by counseling patients about appropriate use of medications prescribed, potential adverse effects of medicines and emphasize on importance of medication adherence. Pharmacist should provide additional information about strategies to prevent long term consequences of PCOS. Pharmacist should advice patients to check their blood glucose, lipid profile, BP and weight.<sup>[27]</sup>

### ABBREVIATIONS

PCOS - Polycystic Ovary Syndrome  
 T2 DM - Diabetes Mellitus  
 CVS – Cardiovascular System  
 IGF – Insulin like growth factor  
 TNF – Tumor necrosis factor  
 IL – Interleukin  
 FBN-3 – Fibrillin 3  
 LHR - Lutenizing hormone receptor  
 AGE'S - Advanced glycated end products  
 BPA – Bisphenol-A  
 GnRH – Gonadotropin releasing hormone  
 FSH – Follicle stimulating hormone  
 LH – Luteinizing hormone  
 EGF – Extra ovarian growth factor  
 IGF – Intra ovarian growth factor  
 NGF – Nerve growth factor  
 TGF-Beta –Transforming growth factor beta  
 AMH – Anti Mullerian Hormone  
 VEGF – Vascular Endothelial Growth Factor  
 Fas L – Fas Ligand  
 ACTH – Adrenocorticotrophic hormone  
 HPG – Hypothalamic- pituitary- gondal  
 CNS –Central Nervous system  
 HHOA – Hypothalamus-Hypophysis-ovary Axis  
 SHBG - Sex Hormone Binding Globulin  
 PAI – Plasminogen Activator Inhibiter  
 HTN – Hypertension  
 IR – Insulin Resistance  
 VLDL – Very Low Density Lipoprotein  
 HDL-C – High Density Lipoprotein-Cholesterol  
 CVD – Cardiovascular Disease  
 DHEA-S –Dehydroapiandrosterone – sulphate  
 COC – Combined Oral Contraceptives  
 LOD – Laproscopic Ovarian Drilling  
 CPA – Cyproterone Acetate  
 LFT – Liver Function Test  
 EE – Ethinyl Estradiol  
 PUFA'S – Poly Unsaturated Fatty Acids

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