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OVERVIEW OF POLYCYSTIC OVARY SYNDROME

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ABSTRACT

The PCOS is anendocrine disorder characterized by elevated androgen level. The main defects in PCOS is ovarian function, insulin secretion and action. It manifests heavy bleeding, acne, weight gain, hirsutism and darkening of skin. The hormone involved in PCOS is FSH and LH and they are glycoprotein polypeptide hormone. FSH is responsible for androgen production and LH is responsible for progesterone production. Obesity plays are major role in PCOS and which results in metabolic disturbances. The factors involved in PCOS are genetic factors, environmental factors and endocrine factors. The drug used in treatment for PCOS is metformin, clomiphene and spironolactone.

Key words: follicle stimulating hormone, luteinizing hormone, hyperandrogenism, hyperinsulinemia

INTRODUCTION

Polycystic ovary syndrome (PCOS) is referred as hyper-androgenic and common endocrine disorder in women reproductive age **[1]**. The complex condition is characterized by elevated androgen levels. In India about 10% of women are affected by PCOS **[2]**. Basically, a woman with PCOS have overweight or obese this affects the metabolism and reproductive function of the body **[3]**. The manifestation of PCOS affects mostly in women of child bearing age (from 18-30) because the ovaries aredeveloping into numerous small collection follicles and failed to regulatory release **[4]**. PCOS increase the risk of various fields like dermatologic, oncologic, metabolic, reproductive and psychological aberrations **[5]**.

PATHOPHYSIOLOGY OF PCOS:

PCOSis a phenotype reflection which involves neuroendocrine, metabolic and ovarian dysfunction **[6]**. Approximately 60-80% of patients have the main key feature in PCOS are excess androgen andhirsutism. The elevated androgen concentration suppress sex hormone binding globulin (SHBG) concentrations contributing to higher free testosterone concentrations **[7]**. Hyperinsulinemia resulted in increased androgen level by suppressing the hepatic sex hormone binding globulin. The primary defects of PCOS is hypothalamic pituitary axis, ovarian function and insulin secretion and action.

Excessive androgen production resulting in the genetic defects (cryptic-21-hydroxylase functions) and then suppressed by LH by gonadotropin releasing hormone (GnRH) super agonist. The biochemical features of PCOS is hyperinsulinemia and it may leadto hyperandrogenmia and hyperandrogenism and bothacts in a different mechanism i.e., it influences the caandrogen synthesis, as well as increasing the circulating pool of bio-available androgen **[8]**.

MECHANISM OF ACTION:

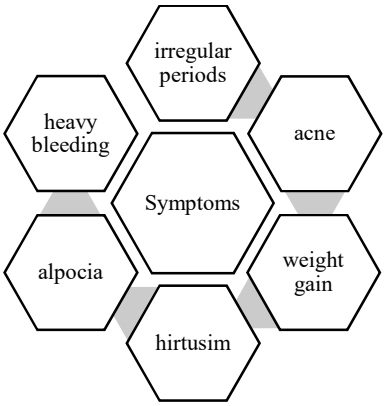
The mechanism of menstrual cycle are involved in two phase's follicular phase and luteal phase. The total duration of the phases is 28 days. In that the follicular phases- 0 to 14 days and luteal phases- 14 to 28 days **[9]**. Upon GnRH stimulation the Follicle stimulating hormone (FSH) and Luteinizing hormone (LH) are produced. In follicular phase, the estrogen is generated. The primordial follicle are converted into primary follicle and induce the secondary follicle in the presence of FSH receptors and then increase the amount of follicle begot by lowering the amount of LH the androgen. Then the androgenis converted into estrogen. When high amount of estrogen is formed they act as negative feedback, and results in production of Luteinizing hormone. By this luteal phases is started and leads to ovulation during this process the ovary releases the follicle and corpus luteum which produce progesterone **[10]**. In PCOS, high level of LH secretion contribute to high level of androgen and low level FSH and it may leads to poor egg development, inability to ovulate and also lead to deficiencies of progesterone production and most often leads to absence of menstrual cycle period.

CHARACTERISTIC OF PCOS:

- PCOS may present with amenorrhea, infertility, hyperandrogenmia with the signs of metabolic disturbances.
- Anovulation (irregular periods)
- Overweight **[11]**
- Insulin resistance **[12]**

- Inflammation – which may directly affect the ovarian dysfunction. Pro-inflammatory markers are responsible for the PCOS or early developed obesity **[13]**.

SYMPTOMS: [14]



COMPLICATIONS:

Complications of PCOS may include:

- Infertility
- Gestational diabetes or pregnancy – induced high blood pressure
- Miscarriage or premature birth
- Non- alcoholic steatohepatitis - a severe liver inflammation caused by fat accumulation in the liver
- Metabolic syndrome

HORMONE FACTORS:

The hormone is involved in PCOS is follicle stimulating hormone (FSH) and luteinizing hormone (LH) which is responsible for reproduction as testis in male and ovarian in female .

Follicle stimulating hormone:

FSH glycoprotein polypeptide hormone and it is situated in the anterior pituitary. FSH is released by stimulation of GnRH secretion from the hypothalamic pituitary hormone **[15]**, which it synthesized and secreted by the gonadotropin cells from the anterior pituitary gland and they regulate the development, growth, pubertal maturation and reproductive process of the body.

Functions:

- In both males and females – stimulation of primordial germ cells.
- In male- FSH induced sertoli cells to secrete androgen-binding proteins
- In females- FSH initiates follicular growth, specifically affecting granulosa cells

Effects in females:

Steriodogenesis

- FSH stimulates various functions ,such as;

i. Stimulated progesterone secretion by the granulosa of intermediate-stage follicle
ii. Stimulates granulosa cells of small follicles
iii. Increases progesterone, androstenedione and estradiol

production by theca cells form small follicles.

- FSH involve in the development of oocytes and yolk deposition
- It also increases the production of growth factors inside the ovary **[16]**

Normal value:

The value is differing from age and sex. Usually the value is low in childhood and high in adult.

Table 1

	Before Puberty	During Puberty	Adult
Male	**0 to 5.0 mIU/mL**	**0.3 to 10.0 mIU/mL**	**1.5 to 12.4 mIU/mL**

Table 2

	Before Puberty	During Puberty	After Menopause
Female	**0 to 4.0 mIU/mL**	**0.3 to 10.0 mIU/mL**	**25.8 to 134.8 mIU/mL**

Luteinizing Hormone:

LH is a hormone produced by gonadotropic cells from the anterior pituitary gland **[17]**. LH is synthesized from the androstenedione by the ovarian theca cells for ovulation and involved in the formation of corpus luteum **[18]**. The action is differing in both sexes, in male it stimulates the testosterone in the testis. In females, it release the progesterone by the stimulation of ovaries.

Function:

In males, LH is used for production for testosterone by acting against testicular leydig cells. In female LH is responsible for releasing progesterone after ovulation from the corpus luteum **[19]**. The ovarian follicle is made up of three cells called theca cells, granulosa cells and oocyte. Theca cells contains LH receptors- LH binds and stimulate to produce estrogen **[20]**.

Effect in female:

In female, LH responsible for maturation of ovary **[21]**. It acts on the theca cells for production and formation of androgen during folliculogenesis. Androgens are converted into estradiol by transferring theca cells to granulosa cells **[22]**.Then LH acts as steroid release from the ovaries and release progesterone by the corpus luteum.

Normal value:

Men: 1.24 – 7.8 IU/L

Female:

Follicular phase	Mid-cycle peak	Luteal phase	During menopause
1.68- 15 IU/L	**21.9 - 56.6 IU/L**	**0.61-16.3 IU/L**	**14.2 – 52.3 IU/L**

Disease state:

When high level of FSH and LH occur following syndrome occur:

- Premature ovarian failure (POF):
  It is defined as ovarian which does not perform normal process thus results in unable to produce estrogen hormone and release egg. It also called hypergonadotropic ovarian failure **[23]**.

Causes:

i. Latrogenic effects
ii. Infections (e.g. herpes zoster)
iii. Chromosome defects

1. Turner syndrome – It neurogenic disorder and loss of sex chromosome **[24]**

2. Fragile X syndrome- inherited intellectual disability which linked neurologic and psychotic disorder **[25]**.

i. Monogenic defects
ii. Syndromic defects
  1.Congenital disorders of glycosylation
  2.Galactosemia
iii. Isolated defects
  1Follicle stimulating hormone receptor (FSH) mutations
  2.Luteinizing hormone receptor mutations (LHR)
iv. Idiopathic

Diagnosis:

The diagnosis method of POF is emotional health, hormone replacement therapy, maintaining bone health and family planning **[26]**.

- Premature ovarian aging (POA)
  - POA is occuring when low number of ovariesare produced in younger age thus results in female infertility. The main risk factors of POA is genetic, autoimmune disorder and modified factors like chemotherapy, radiotherapy and pelvic synergy **[27]**.
- Gonadal dysgenesis- impaired function of gonads **[28]**
- Klinefelter syndrome -it congenital chromosomes in which extra X chromosome in male cause infertility, hypogonadism **[29]**.
- Swyer syndrome- absence of sex glands **[30]**.
- Testicular failure
- Lupus

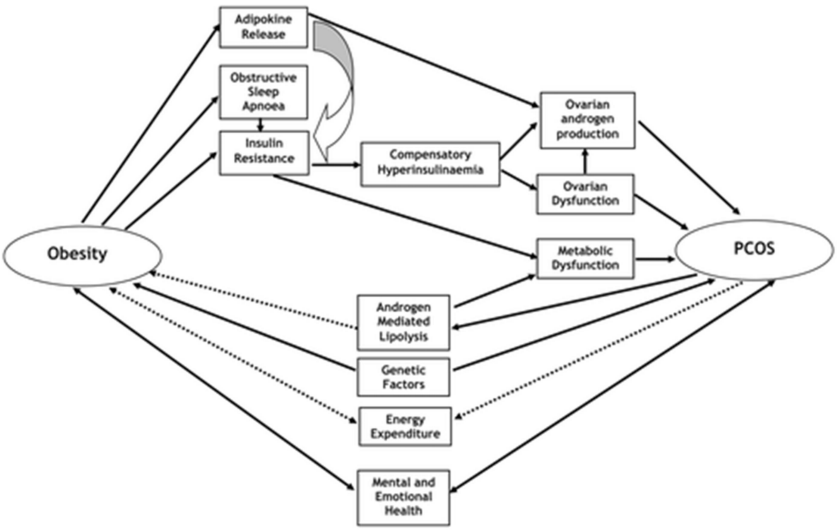
When low amount of FSH and LH is present, the following syndrome are seen such as,

- Polycystic ovary syndrome
- Kallmann syndrome- genetic disorder delay or absence of puberty and delay or absence of smell
- Hypothalamic suppression
- Hypopituitarism
- Hyperprolactinemia
- Gonadotropin deficiency

ROLE OF PCOS:

Role of obesity in PCOS

Obesity with PCOS causes hyperandrogenism, hirsutism, insulin resistance, and infertility and pregnancy complications and associated with genes **[31]**. It is the major key component for metabolic syndrome and associated with level of insulin which subsequently increasedin ovarian androgen production. The excessive adipose tissue is responsible for ovulatory dysfunction and menstrual abnormalities **[32]**. Obesity and insulin resistance increase the risk of type 2 diabetes and cardiovascular disease **[33]**. The upper body obese mainly causes the excessive production of androgen and results in decrease insulin sensitivity and increase the risk of cardiovascular disease **[34]**. About 38-88% of obese women has PCOS **[35]**.



Role of insulin in PCOS:

About 50 – 70% women with PCOS have insulin resistance **[36]**. Hyperinsulinemia and insulin resistance play major role in PCOS. It elevated the GNRH and LH pulse secretion continuous elevation resulting in ovarian steroid hormone particularly androgen **[37]**. Sex hormone binding globulin (SNBG) is associated with the insulin resistance. SNBG is has stronge affinity towards sex steroid. The research shows that, women with insulin resistance shouldhave low sex hormone binding globulin concentrations thus results in PCOS **[38]**. Insulin acts on steroidgenesis by activating LH by inducing secondary messenger's cAMP in which it turns to activate PI3K and produce excessive androgen **[39]**.

Metformin reduces insulin resistance in women withPCOS and its improve the spontaneous ovulation **[40]**.

Role of cholesterol in PCOS:

Dyslipidemia play major role in PCOS about 70% womenare diagnosed with dyslipidemia **[41]**. The Decrease in HDL - C

and increase in triglycerides and LDL level can lead to PCOS **[42-43]**. Abnormal lipid profile is common pattern in women with PCOS **[44]**. The women with PCOS and Dyslipidemia are more prone to cardiovascular disease **[45]**.

Role of diabetes in PCOS:

In the Prevalenceof PCOS, 6-8% of women are developing the risk of diabetes mellitus **[46]**. Gestational diabetes mellitus (GDM) are more common in women with PCOS, the main risk are obesity and also family history and age **[47]**.

Phenotype:

The phenotype limits of a PCOS is 1) identified by the specific phenotype and 2) determine the long term morbidity **[48]**. The different PCOS phenotype have varying degree of adiposity and may differ in metabolic and reproductive profile **[49]**. Division of phenotype can be help to understand the pathophysiology of PCOS and to predict the adverse metabolic and cardiovascular disease. In these studies, the PCOS phenotype can classified into the four types.

Phenotype A (HA+OD+PCO)

Phenotype B (HA+OD)

Phenotype C (HA+PCO)

Phenotype D (OD+PCO)

Hyperandrogenism (HA), ovulatory dysfunction (OD), polycystic ovaries (PCO).

In phenotype A most common phenotype among B and C. Phenotype D is least common one **[50]**

FACTORS INFLUENCING PCOS:

The influencing factors ofPCOS are genetic factors, environmental factors and endocrine factors.

Genetic factors:

Family members who have PCOS also have higher risk for developing the same metabolic abnormalities. There are wide variety of genes and mechanism involved in PCOS. Several studies shows that, PCOS gene affect the hormone level and insulin resistance. Monozygotic twins are more prone PCOS than the dizygotic twins **[51]**. The genes are involved in PCOS is CYP11a, CYP21, CYP17 and CYP19. Each gene have own responsible activity; For example: CYP11a is involved in conversion of cholesterol to Progesterone, CYP21is responsible for synthesis of steroid hormones, CYP17 is involved in conversion pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone and CYP19 – aromatase p450 formation of estrogen **[52]**.

Two possible approaches are used to identify a genetic locus

1. Association studies – where a predisposing allele is expected to be found more frequently in the affecting population than the normal individual.

2. Linkage studies- investigated to determine if particular genomic landmark are distributed independently or in linkage with phenotype **[53]**.

Environmental factors:

Environmental factors take an important role in genetic variants and they are involved in etiology, prevalence and

modulation of the PCOS phenotype including environmental toxins, diet and nutrients, socioeconomic status and geography. Environmental toxins in which it includes the chemical pollutants such as tobacco smoke, lead, pesticide and mercury are harmful for endocrine disrupting chemical and reproductive health **[54]**. In women the high stress level **[55]**, Lack of physical activity and exercise which lead to PCOS **[56]**. Lifestyle and dietary fibers are most prominent to PCOS. The excess weight loss, moderate diet with carbohydrate, fats and high content of fiber lead alteration in menstrual regulations **[57]**.

Endocrine factors:

Endocrine disrupting compounds are chemical agents affecting synthesis, transport, metabolism are attacking through hormone receptors like endocrine receptors and thyroid receptors **[58]**.

DIAGNOSIS OF PCOS:

The Rotterdam consensus include the diagnostic criteria National institute of Health (NH) proposed set any two from the three must present to diagnosis PCOS: hyperandrogenism, ovulatory dysfunction and polycystic ovaries. In adolescents, the diagnosisis based on the hyperandrogenism in the presence oligomenorrhea. In pre-menopause and menopausal stage it is diagnosed based on the post medical history **[59]**.

TREATMENT OF PCOS:

The first line drug for PCOS is metformin and clomiphene and their combination is most effective than alone. Metformin inhibit the ovarian gluconeogenesis which reduce androgen production. Clomiphene is a non-steroidal ovulation induction. The second line drug for PCOS is spironolactone which inhibit that androgen production.

CONCLUSION

PCOS is endocrine disorder mainly affects adolescent's women due to hormonal balance, improper life style, poor nutrition intake and it may cause infertility, metabolic syndrome, sleep apnea, endometrial cancer and depression.

It is very common is one family who has PCOS, which may be reversed by only proper medication, good nutrition and lifestyle change. Public awareness of PCOS is very important, it may help them to understand the symptoms like irregular periods and pelvic pain are important for the diagnosis and later it might be easier to prevent.

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