ejpmr, 2023,10(7), 88-100

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

AN OVERVIEW ON POLYCYSTIC OVARY SYNDROME

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Article Received on 11/05/2023 **Article Revised on 01/06/2023** **Article Accepted on 21/06/2023**

ABSTRACT

Polycystic Ovary Syndrome is the most prevalent endocrine metabolic disorder affecting 6-10% of reproductive aged women worldwide. Women with Polycystic Ovary Syndrome (PCOS) seek health care for 3 major reasons: infertility, menstrual irregularity, and androgen excess. The infertility is associated with anovulation. The condition of menstrual irregularity is generally chronic and such a condition may arise either from the beginning of the menarche or anytime during the reproductive period. Symptoms like amenorrhea and irregular bleeding are the common characteristic feature of anovulation. Androgen excess may be manifested by varying degrees of hirsutism. Patients may also report acne. The rapid development of virilizing signs, such as deepening of the voice, increased muscle mass, and temporal balding, would prompt a person to search for a tumour and would distract her away from a diagnosis of PCOS. Typically the treatments for PCOS are aimed at alleviating the symptoms such as ovulation induction for infertility, oral contraceptives or a progestin for menstrual irregularity, and oral contraceptives or spironolactone for hirsutism. On the basis of recent epidemiologic data which expresses about the increased cardiovascular risk among women with PCOS, such treatment might be complemented by a long-term approach that addresses the underlying pathophysiology of insulin resistance. In the following work we have practiced in hospital for a period of one week to understand the syndrome PCOS and we have collected the possible necessary data for our survey.

KEYWORDS: Polycystic Ovary Syndrome, Puberty, Menstrual cycle, Infertility, Phenotypes, Diagnosis, Treatment and Management.

INTRODUCTION

Ovarian dysfunction associated with infrequent or absent menses in obese infertile women was first reported in the 1930s by Stein and Leventhal, for whom the syndrome was originally named. Once thought to be relatively rare, it now appears that this clinical entity is one of the most common endocrinologic disorders among women in the reproductive years.

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting 5% to 10% of women of reproductive age, and is a frequent source of chronic anovulation. The disorder is characterized by varying degrees of menstrual irregularity, signs of hyperandrogenism (acne, excess body hair [hirsutism], male-pattern hair loss), and infertility, and is often associated with hyperinsulinemia or insulin resistance. Whether this condition is a primary ovarian defect or a result of hypothalamic-pituitary dysfunction is still being debated.

According to the World Health Organization (WHO) estimation revealed over 116 million women (3.4%) are affected by PCOS worldwide. The typical woman with PCOS has hyperinsulinemia and many of the signs of the metabolic syndrome It has been shown that the cause of hyperinsulinemia is insulin resistance. The frequency and degree of hyperinsulinemia in women with PCOS is often amplified by the presence of obesity. In addition to its clinical manifestations, long-term health problems including cardiovascular disease and type 2 diabetes have been linked to PCOS. Classic lipid abnormalities include elevated triglyceride levels, low HDL levels, and elevated LDL levels. Hypertension is also common in women with PCOS. There is also concern that women with PCOS who are anovulatory do not produce progesterone. This, in turn, may subject the endometrium to an unopposed oestrogen environment, which is a significant risk factor for the development of endometrial cancer.

The underlying etiology of the disorder is unknown, although most women have altered gonadotropin levels.

This is manifested by increased release of LH in relation to FSH release, with a resultant increase in production of androstenedione and testosterone by the theca cells of the ovary. Androstenedione, in turn, is converted to estrone within adipocytes. Although estrone is a weak oestrogen, it causes suppression of pituitary FSH release and stimulation of LH release. Although the presence of some FSH allows for new follicular development, full maturation is not attained, and ovulation does not occur. The elevated LH level results in increased androgen production, which in turn prevents normal follicular development and contributes to a vicious cycle of anovulation and multiple cyst formation. Increased androgen levels also lead to the development of acne and hirsutism.

There is increasing evidence that the disorder may begin before adolescence and that many of the manifestations of PCOS begin to make their appearance at that time. Because many of the symptoms common to PCOS, such as excess hair, acne, and obesity, can be detrimental to a teenage girl's health and self-esteem, early detection and treatment of PCOS in adolescents are essential.

The diagnosis of PCOS can be suspected from the clinical presentation. Although there is no consensus as to which tests should be used, laboratory evaluation to exclude hyperprolactinemia, late-onset adrenal hyperplasia, and androgen-secreting tumors of the ovary and adrenal gland is commonly done. Because of the high risk of insulin resistance, a fasting blood glucose, 2-hour oral glucose tolerance test, and insulin levels are done to evaluate for hyperinsulinemia. Confirmation with ultrasonography or laparoscopic visualization of the ovaries is often done, but not required.

The condition usually is treated by the administration of the hypothalamic-pituitary-stimulating drug clomiphene citrate to induce ovulation. This drug is used carefully because it can induce extreme enlargement of the ovaries. If fertility is not desired, combined oral contraceptives can induce regular menses, prevent the development of endometrial hyperplasia caused by unopposed oestrogen improve hirsutism and acne. When medication is ineffective, laser surgery to puncture the multiple follicles can be helpful. Bilateral wedge resection seldom is performed today. The preferred and most effective treatment for PCOS is lifestyle modification. Weight loss may be beneficial in restoring normal ovulation when obesity is present. The addition of spironolactone, a mineralocorticoid antagonist that inhibits the production of androgens by the adrenal gland, may be beneficial to women with severe hirsutism

The overall goal of treatment should be directed toward symptom relief, prevention of potential malignant endometrial sequelae, and reduction in risk for development of diabetes and cardiovascular disease.[1,2,3]

Puberty

Puberty is the process of physical changes through which a child's body matures into an adult body which is capable of sexual reproduction. It is initiated by hormonal signals from the brain to the gonads i.e; the ovaries in a female and the testes in a male. In response to the signals, the gonads produce hormones that stimulate libido and the growth, function, and transformation of the brain, bones, muscle, blood, skin, hair, breasts and sex organs. Physical growth i.e; height and weight accelerates in the first half of the puberty and is completed when an adult body has been developed. Before puberty, the external sex organs, known as primary sexual characteristics, distinguish males and females. Puberty leads to sexual dimorphism through the development of the secondary sex characteristics, which further distinguish the sexes.

On average, girls begin puberty at ages 10–11 and complete puberty at ages 15–17 whereas boys generally begin puberty at ages 11–12 and complete puberty at ages 16–17. The major landmark of puberty for females is menarche, the onset of menstruation, which occurs on average between ages 12 and 13. For males, first ejaculation, spermarche, occurs on average at age 13.[4]

Menstrual Cycle

Menarche, the onset of menstruation, usually occurs between the ages 12 and 13 years of age, with a range of 10 to 16 years. Menarche is normally preceded by a period of maturation that may span 2 years. During this interval, an orderly sequence of events occurs, which includes breast development, growth of pubic and axillary hair, and a spurt in somatic linear growth. Generally, the cycle interval ranges from 15 to 45 days, with the average being 28 days. Duration of flow varies with a range of 2 to 8 days, with the average being 4 to 6 days. Menstrual blood does not clot. The amount lost each cycle ranges from 60 to 80ml.[5]

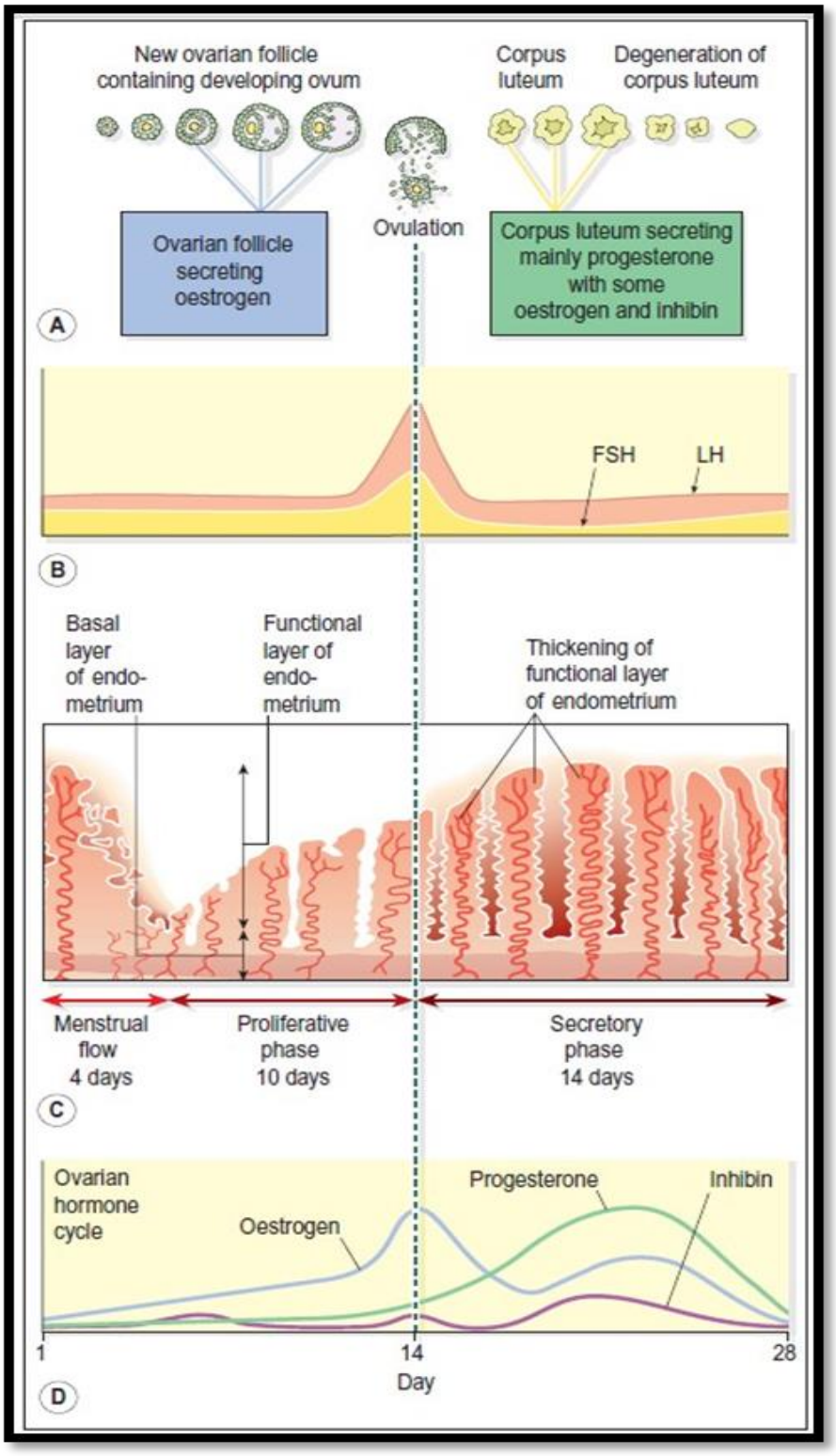

Figure 1: Summary of one female reproductive cycle.[6]

A. Ovarian cycle; maturation of follicle and development of corpus luteum. **B.** Anterior pituitary cycle; LH and FSH levels. **C.** Uterine cycle; menstrual, proliferative and secretory phases. **D.** Ovarian hormone cycle; oestrogen, progesterone and inhibin levels.

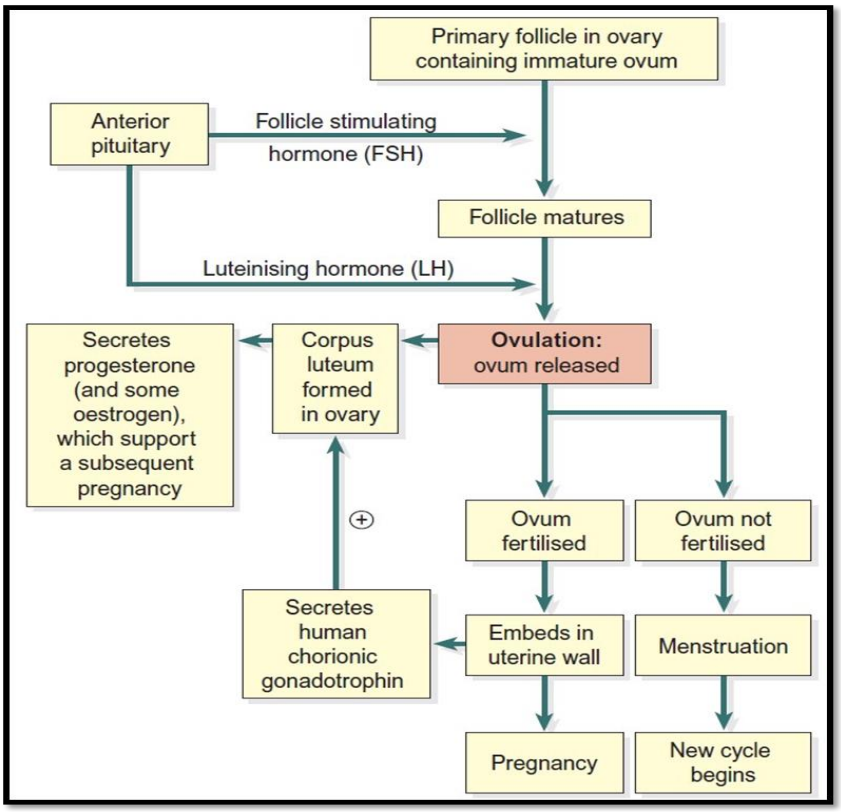

Figure 2: Summary of the stages of development of the ovum and the associated hormones.[7]

Hormones Involved In Menstrual Cycle

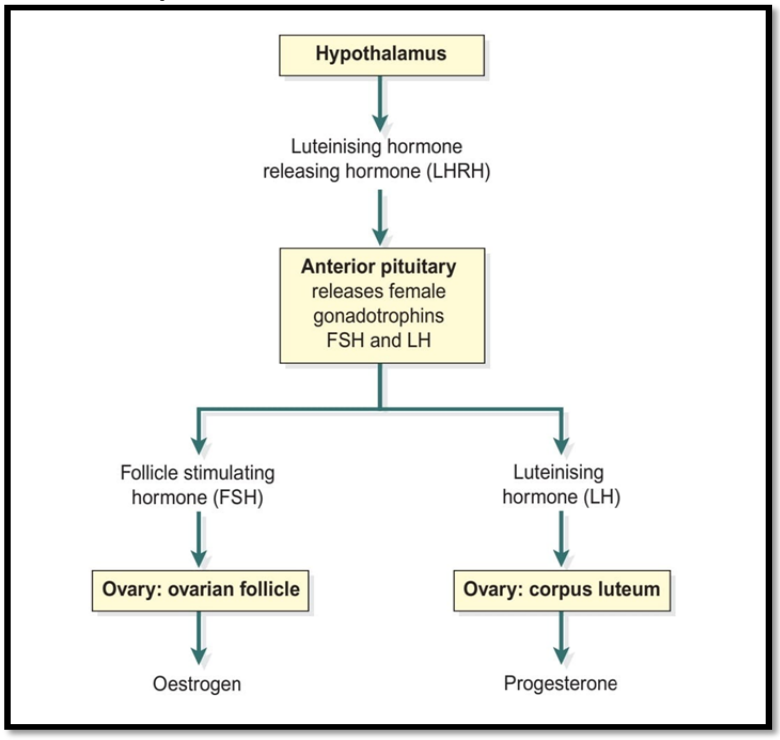

Figure 3: Hormones involved in menstrual cycle.[8]

Since this is a series of events, occurring regularly in females every 26 to 30 days throughout the child bearing period between menarche and menopause, the cycle consists of a series of changes taking place concurrently in the ovaries and uterine lining, stimulated by changes in blood concentrations of hormones. Hormones secreted during the cycle are regulated by negative feedback mechanisms. The hypothalamus secretes luteinising hormone releasing hormone (LHRH), which stimulates the anterior pituitary to secrete.

- Follicle Stimulating Hormone (FSH), which promotes the maturation of ovarian follicles and the secretion of oestrogen, leading to ovulation. FSH is therefore predominantly active in the first half of the cycle. Its secretion is suppressed once ovulation has taken place, to prevent other follicles maturing during the current cycle.
- Luteinising Hormone (LH), which triggers ovulation, stimulates the development of the corpus luteum and the secretion of progesterone.

The hypothalamus responds to changes in the blood levels of oestrogen and progesterone. It is stimulated by high levels of oestrogen alone (as happens in the first half of the cycle) but suppressed by oestrogen and progesterone together (as happens in the second half of the cycle).

The average length of the cycle is about 28 days. By convention the days of the cycle are numbered from the beginning of the menstrual phase, which usually lasts about 4 days. This is followed by the proliferative phase (approximately 10 days), then by the secretory phase (about 14 days) [8]

The Reproductive or Menstrual Cycle

The reproductive cycle involves changes in ovaries as well as in uterus which are known as ovarian cycle and uterine cycle respectively.

Ovarian Cycle

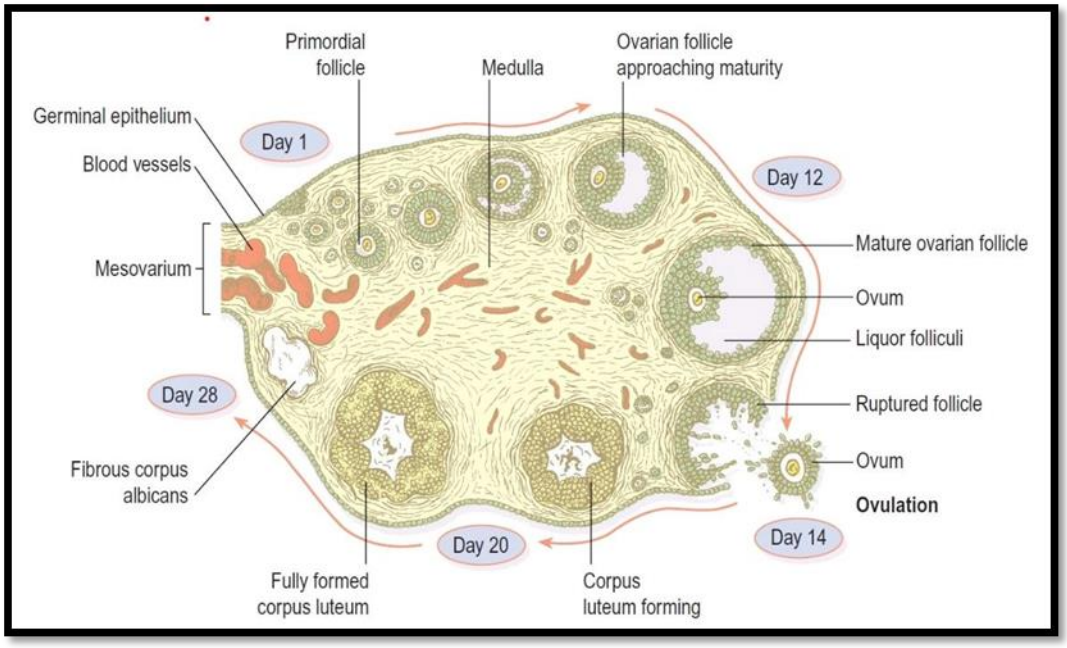

Figure 4: A section of an ovary showing the stages of development of one ovarian follicle.[9]

The ovarian cycle consists of two phases

1. Follicular phase
2. Luteal phase

1. Follicular Phase

The follicular phase also known as the pre-ovulatory phase occurs 14 days before ovulation starting from day 1 to day 14**.** [4] Now initially in the beginning of the menstrual cycle there is an increase in Gonadotropin releasing hormone secreted by the hypothalamus and this increase in gonadotropin releasing hormone causes a steady increase in FSH and LH. But actually we can see an increase and then a slow dropping level of FSH and we have a steady level of LH, during the initial stage of follicular phase. The cycle begins with the first day of menstrual flow, or sloughing of the endometrium. FSH induces the growth of several primordial follicles in the ovaries. Generally only one continues to grow and becomes the graafian follicle and the others degenerate. The follicle consists of an ovum and its two surrounding cell layers. The inner layer of granulosa cells synthesizes progesterone, which is secreted into follicular fluid during the first half of the menstrual cycle and serves as a precursor for oestrogen synthesis by the Surrounding layer of theca interna cells. oestrogen is synthesized in the luteinized cells of the theca interna. The pathway of oestrogen biosynthesis proceeds from progesterone and pregnenolone via 17-hydroxylated derivatives to androstenedione testosterone, and estradiol. A high content of aromatizing enzyme in these cells facilitates the conversion of androgens to oestrogens. In the follicle the primary oocyte begins to mature. At the same time the growing follicle secretes increasing amounts of oestrogen into the system. Rising oestrogen levels cause luteinizing hormone releasing hormone to be released by a positive feedback system.[10,11]

Ovulation Phase

As the menstrual cycle proceeds towards the end of the follicular phase, the LH triggers ovulation. The ovulation

of the follicles will release the female egg or the oocyte. After ovulation, the LH and Gonadotropin releasing hormone levels will drop down. The FSH had a small spike as a side effect of the surge of LH release.[10,11]

Ovulation divides the proliferative and secretory phase of the menstrual cycle, and usually occur 14 days before the onset of the next menstrual cycle.[12]

2. Luteal Phase

The Luteal Phase also known as the Post-ovulatory Phase occurs 14 days after ovulation starting from day 14 to day 28.[4] After the follicle ovulates, the follicles will turn into a corpus luteum which is basically a dead follicle.

The corpus luteum secretes three hormones which are Oestrogen, Inhibin and Progesterone.[1] The hormone inhibin which was not present until ovulation, it begins to increase after ovulation, while Progesterone levels were low before ovulation and hence after ovulation, there is a rise in Progesterone levels. Hence from 14th to 21st day of the menstrual cycle, there is an increase in progesterone and inhibin while oestrogen levels are dropped which has a negative feedback at the Anterior Pituitary Gland and it will inhibit the secretions of GnRH.[4] But the main effect of Progesterone is that, it will stimulate endometrial growth. The endometrial lining is the lining of the uterus which will shed each month or it is where the fertilized egg implants. [10],[11]

Uterine Cycle

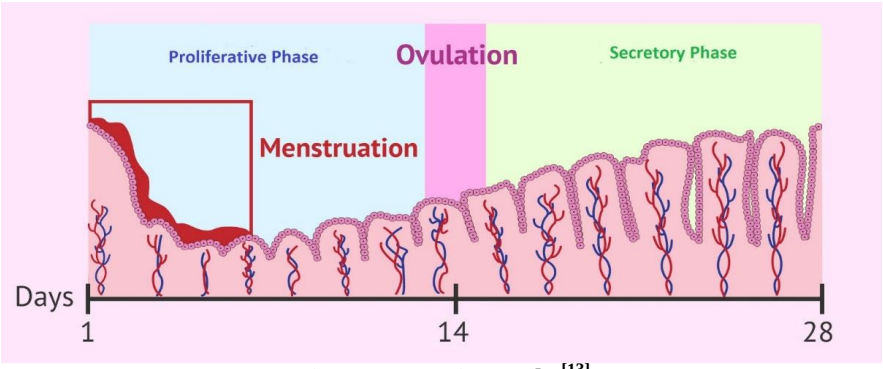

Figure 5: Uterine cycle.[13]

The uterine cycle consists of mainly two phases

1. Proliferative phase
2. Secretory phase

Proliferative phase

Immediately after menstruation, the endometrium is thin and in a resting state. This stage lasts about 5 days. At this stage an ovarian follicle, stimulated by FSH, is growing towards maturity and is producing oestrogen, which stimulates proliferation of the functional layer of the endometrium in preparation for the reception of a fertilised ovum. The endometrium thickens, becoming very vascular and rich in mucus-secreting glands. Rising levels of oestrogen are responsible for triggering a surge of LH approximately mid-cycle. This LH surge triggers ovulation, marking the end of the proliferative phase.[6]

Secretory phase

After ovulation, under the influence of increasing levels of progesterone and continuing oestrogen from corpus luteum, the endometrium becomes thick and velvet-like. There is greater and more elaborate convolution of glands and infolding of the glandular epithelium, giving a "saw tooth" appearance. The nuclei of the cells move downward, and the surface of the epithelium acquires a frayed appearance. The stroma becomes edematous. Heavy infiltration with leukocytes occurs, and the blood vessels become more and more tightly coiled and dilated. The length of the secretory phase among all women is constant at 14 + or – 2 days.[14]

Menstrual phase

The corpus luteum functions until about the 23rd or 24th day of a 28-day cycle and then begins to regress. The resulting sharp drop in progesterone and oestrogen removes the stimulation to the endometrium. Ischemic changes occur in the arterioles and the menstrual flow occurs.

If the egg is not fertilized corpus luteum in the ovary will degenerate hence allowing a new set of levels of follicles to mature. As the corpus luteum degenerates the levels of all the hormones produced by corpus luteum [oestrogen, progesterone, inhibin] decreases that is when corpus luteum degenerates the level of progesterone is decreased. And also due to the decrease of progesterone and oestrogen, there is a lack of maintenance of endometrium or endometrial lining by these low levels of hormones. And therefore the endometrium will shed and this is know as the period and after that endometrial lining sheds and due to low levels of progesterone, it inhibits GnRH which will again allow a new menstrual cycle to occur.[11]

Infertility

Infertility is the inability of a couple to achieve pregnancy over an average period of one year (in a

woman under 35 years of age) or 6 months (in a woman above 35 years of age) despite adequate, regular (3-4 times per week), unprotected sexual intercourse. Infertility may also be referred to as the inability to carry a pregnancy to the delivery of a live baby. Infertility can be due to the woman, the man, or both; primary or secondary.[15]

Types of infertility include:

- **Primary:** A woman who was never pregnant and who can't conceive after one year of not using birth control.
- **Secondary:** Secondary infertility occurs when a woman can't get pregnant again after having at least one successful pregnancy. [16]

Causes of Female Infertility

According to the Center of Disease Control (CDC, 2013), the causes of female infertility can be divided into three broad categories.

1. Defective Ovulation

Defective ovulation occurs because of the following causes:

a) Endocrine disorders,
b) Physical disorders,
c) Ovarian disorders.

2. Defective Transport

3. Uterine or cervical causes

4. Other causes of infertility in females include:

a) Body weight
b) Emotional stress and lifestyle
c) Advanced ages (over 35)
d) Hormonal disorders
e) Cancer
f) Sexually transmitted diseases [15],[17],[18]

Diagnosis

These tests can also help diagnose female fertility problem:

- Pelvic exam
- Blood test
- Transvaginal ultrasound
- Hysteroscopy
- Saline sonohysterogram (SIS)
- Hysterosalpingogram (HSG)
- Laparoscopy [16]

Prevention of infertility

1. Maintaining a healthy lifestyle
2. Preventing or treating existing diseases, especially STDs
3. Having safer sex strategies
4. Not delaying Parenthood.[15]

Pathophysiology of Pcos

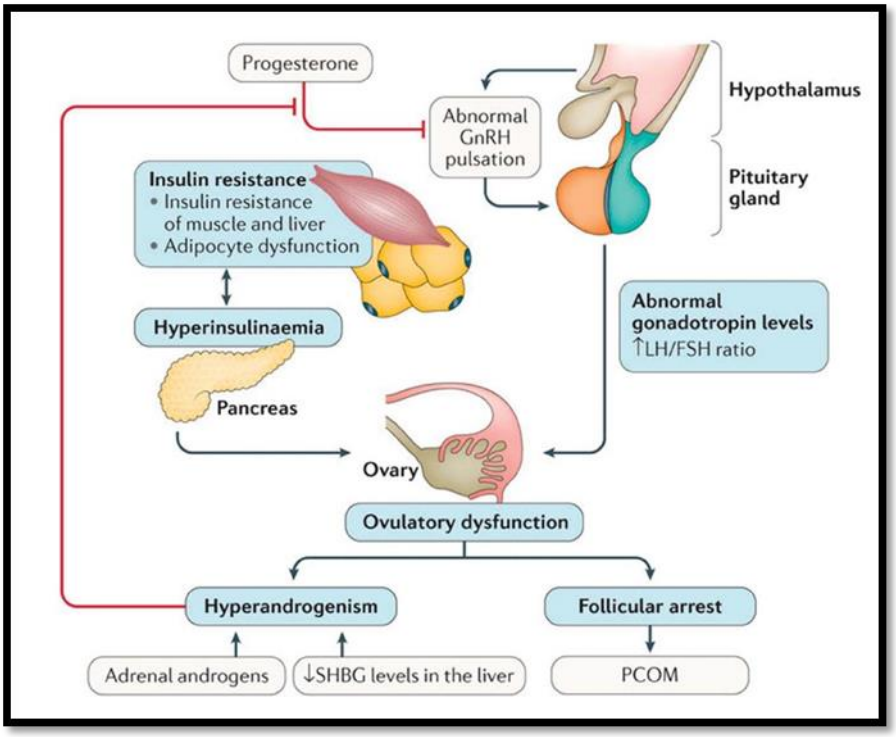

Figure 7: Overall Pathophysiology of PCOS.[19]

The fundamental pathophysiologic defect of Polycystic Ovary Syndrome remains unknown and is a source of controversy and ongoing study. There is a growing consensus, however, that the key features include insulin resistance, androgen excess, and abnormal gonadotropin dynamics.

PCOS is most commonly characterised by two factors, they are

1. Peristaltic anovulation, (in which egg does not release from ovary during menstrual cycle)
2. Excess secretion of androgenic hormone (testosterone).[20]

There are a number of generalities about the pathophysiology of PCOS that can be addressed, focusing on major defects observed and their interactions. The pulsatile release of GnRH from the hypothalamus is often disturbed in PCOS, leading to LH hypersecretion by the pituitary gland, which induces ovulary dysfunction and hyperandrogenism. This perturbed secretion of LH seems to arise early in puberty and is related to disturbed inhibition of GnRH secretion by progesterone. Although serum FSH levels are generally normal, follicles seem to be more resistant to FSH in women with PCOS than in control women. This effect might be the result of increased levels of intraovarian Anti-Mullerian Hormone (AMH). Notably, genetic and epigenetic variants contribute considerably to susceptibly for most of these alterations. Environmental factors contribute somewhat less, most by exacerbating insulin resistance and dysregulated gonadotropin secretion.[19]

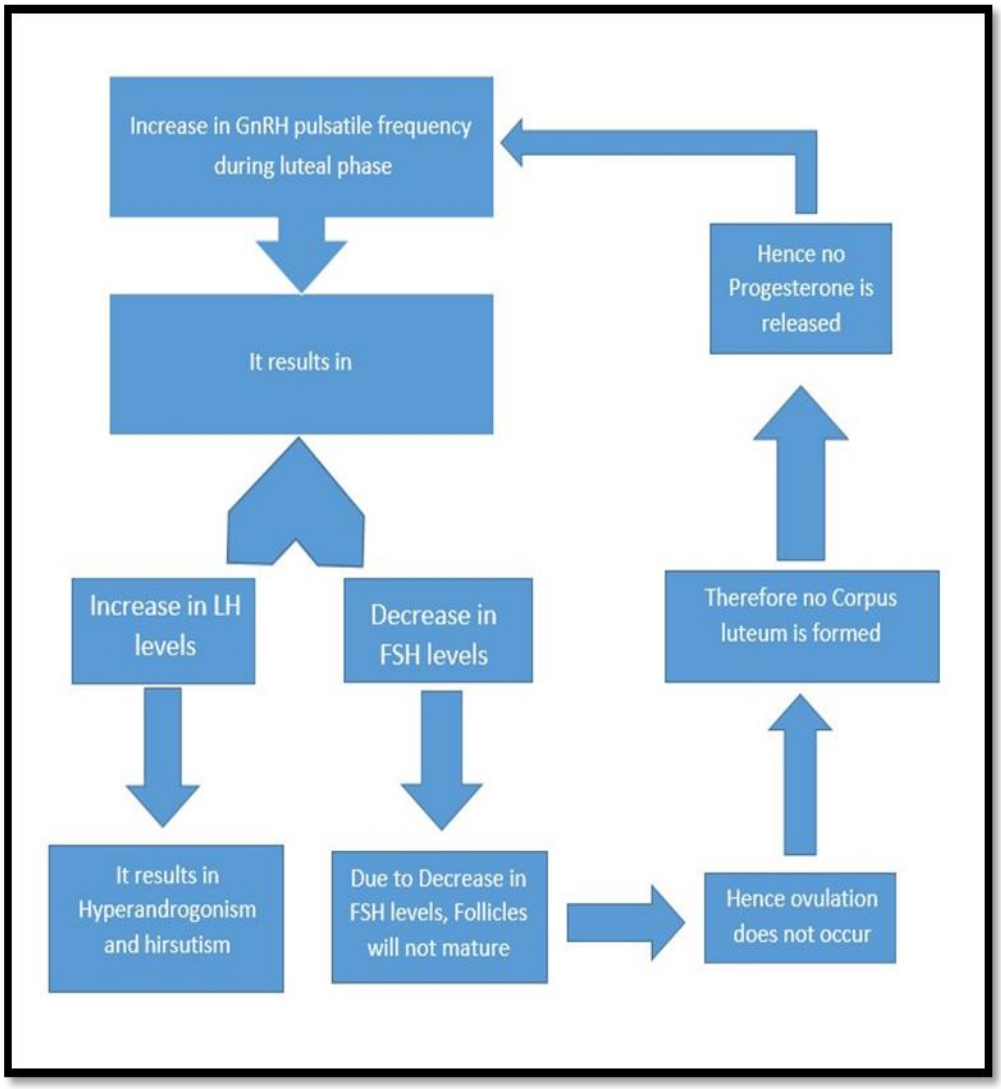

Figure 8: Pathophysiology of PCOS involving hormones acting on ovaries.[21]

There is also evidence of adrenocortical steroidogenic dysfunction in PCOS with approximately one third of women with PCOS demonstrating excess dehydroepiandrosterone sulfate, an androgen metabolite or prohormone that is secreted almost exclusively by the adrenal cortex. However, the role of adrenal androgens in the development and maintenance of PCOS is still unclear. The aforementioned insulin resistance and compensatory hyperinsulinemia play a critical role in the pathophysiology of PCOS. Excess insulin, acting synergistically with LH, stimulates androgen production by ovarian theca cells and, along with androgen excess, suppresses the hepatic production of sex hormone-binding globulin. Both of these factors favour the development of hyperandrogenism.[19]

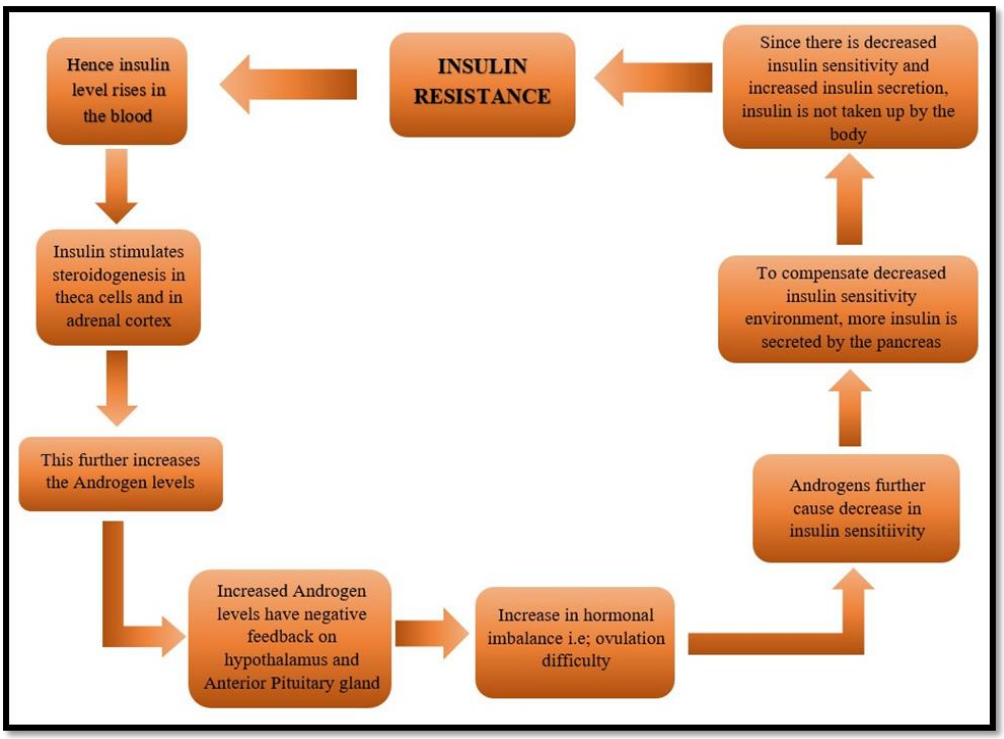

Figure 9: Pathophysiology of PCOS involving Insulin Resistance.[21]

Phenotypes of Pcos

Globally, the prevalence of PCOS is estimated to be between 5.5% and 12.6% in women in the age group of 17–45 years. In India, the prevalence estimates are between 8.2% and 22.5% depending on the diagnostic criteria used. Majorly PCOS has been categorized into 4 phenotypes using the diagnostic criteria

- Phenotype - A [Hyper Androgenism (HA) , Ovulatory Dysfunction (OD), Polycystic Ovarian Morphology (PCOM)]
- Phenotype - B [Hyper Androgenism (HA) and Ovulatory Dysfunction (OD)]
- Phenotype - C [Hyper Androgenism (HA) and Polycystic Ovarian Morphology (PCOM)]
- Phenotype - D [Ovulatory Dysfunction (OD) and Polycystic Ovarian Morphology (PCOM)]

Patients with PCOS presenting to clinics or more or base and more hyper-androgenic with more severe phenotype and higher metabolic risk compared with women with PCOS in unselected or background population in subjects identified in clinical population where is phenotype C is more common in unselected population.[22]

Diagnosis of Pcos

Polycystic Ovary Syndrome is difficult to diagnose due to the intrinsic characteristics of the syndrome: the heterogeneity of the symptoms; their variability in different age ranges. PCOS is difficult or impossible to diagnose in adolescent and menopausal women because the puberty mimics the signs and symptoms of Polycystic Ovary Syndrome. Menarche is also the appearance of multiple small antral follicles, and it is very easy to confuse. In menopausal women, the recall of menses is highly inaccurate and also on the basis of biochemical hyperandrogenemia.

PCOS is marked by oligomenorrhea or amenorrhea, infertility and the presence of cystic ovaries, which is initially identified on laparotomy and confirmed by biopsy. Transabdominal 2-D ultrasound (TAUS) has largely been superseded by (TV) scanning because of greater resolution and in many cases patient preference. The transabdominal scan offers a panoramic view of the pelvic cavity, and it may be useful if any associated uterine or ovarian developmental abnormalities are present. Transvaginal scan has greater resolution and gives a more accurate view of the internal structure of ovaries especially in obese women. The ultrasonographic examination allows evaluating both external and internal ovary aspects. One of the most immediate common symptoms of PCOS is the excess of androgens (hyperandrogenism) which is diagnosed by laboratory investigations, that is, by looking for increased serum levels of androgens, or through clinical examination.

PCOS has undergone many iterations of diagnostic criterias, out of which there are three important diagnostic criteria namely

a) NICHD/NIH Criteria (1990)
b) ESHRE/ASRM Rotterdam Criteria (2003)
c) AES Criteria (2006).[23]

Table 2: Diagnostic Tools For Polycystic Ovary Syndrome.

NICHD/NIH Criteria (1990)	ESHRE/ASRM Rotterdam Criteria (2003)	Androgen Excess Society (AES) Criteria (2006)
• Hyperandrogenism • Oligo-ovulation/anovulation • Exclusion of other related disorders	• Hyperandrogenism • Oligo-ovulation/anovulation • Polycystic ovaries	• Hyperandrogenism • Oligo-ovulation/anovulation • Polycystic ovaries • Exclusion of other related disorders

Three tools can be used to diagnose PCOS. In 1990, the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) hosted a panel of experts who developed the first known criteria for PCOS. Over the next decade, it was discovered that ovarian morphology was a key component in the diagnosis. The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) sponsored a workshop in Rotterdam. During the workshop, polycystic ovarian morphology on pelvic ultrasound was added to the NICHD/NIH criteria. It was then decided that only two of the three criteria had to be met for a diagnosis of PCOS.

In 2006, the Androgen Excess Society (AES) suggested that the NICHD/NIHS criteria could be used with modifications that included the Rotterdam tool. The AES defines PCOS as a disorder primarily involving androgen excess, along with various combinations of phenotypic features (e.g., hyperandrogenemia, hirsutism, oligo-ovulation/anovulation, and/or polycystic ovaries) that may promote a more accurate diagnosis.

In 2012, the NIH sponsored an evidence-based methodology workshop on polycystic ovary disease. The expert panel concluded that each criterion has its own strengths and weaknesses; however, the use of multiple criteria was considered confusing, impeding progress in understanding PCOS.

If PCOS is suspected, a complete medical history, physical examination, blood tests, and a pelvic ultrasound should be performed. A medical history and physical examination provide the physician with information about unexplained weight gain, menstrual cycle abnormalities, male-pattern hair growth, skin changes, and elevated blood pressure (BP).

Blood is drawn to assess hormone, glucose, and lipid levels, and a pelvic ultrasound is performed to scan for ovarian cysts. During the assessment period, other potential causes associated with reproductive, endocrine, and metabolic dysfunction should be excluded. Physicians should rule out adrenal hyperplasia, Cushing's syndrome, and hyperprolactinemia before a PCOS diagnosis is confirmed.

After PCOS is diagnosed, studies show that more than 50% of patients develop prediabetes or diabetes, and there is an increased risk of myocardial infarction (MI), dyslipidemia, hypertension, anxiety, depression, endometrial cancer, and sleep apnea. Moreover, pregnant women with PCOS should be informed of the increased rates of miscarriage, gestational diabetes, pre-eclampsia, and premature delivery.[24]

Other diagnostic parameters are

- **Ovulation morphology on ultrasound or polycystic ovaries**

The inclusion of ultrasonographic evidence of PCO morphology is controversial.

- **Hyperandrogenism**

Determination of HA in females can be problematic during clinical and biochemical assessment.

- **Menstrual dysfunction with oligo/anovulation**

The absence of menstruation for a period of 45days or more and or 8 or menstrual cycles per year are also important diagnostic signs. Oligomenorrhea is considered as a highly predictive surrogate machee of PCOS. Additional characteristics are excessive hair growth, abnormal bleeding, obesity, hair loss, acne and infertility.

- **Recent diagnostic parameters**

Antimullerian hormone [AMH] levels proposed as a parameter to replace ultra-sonographic assessment. Another diagnostic parameter is an assessment of ovarian stromal volume, measured as a ratio of stromal area to the total area of the ovary (S/A ratio). A physical examination is measuring blood pressure, weight and height should be completed. A routine and general physical examination should also have conducted and note the presence of secondary sex characteristics, along with palpation of thyroid gland for masses or enlargement. Further diagnostic information can be obtained through laboratory measurement of FSH, LH, thyroid-stimulating hormone, prolactin, dehydroepiandrosterone and testosterone levels to detect the exact hormonal imbalance. Total cholesterol and HDL also obtained. The presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter and or increased ovarian volume (10 ml) which is obtained by sonography.

- **Differential diagnosis**

The clinician must consider several possibilities including:

- Exogenous androgens and Thyroid dysfunction
- Androgen secreting tumours
- Acromegaly
- Cushing's syndrome
- Primary ovarian failure

➢ **Diagnostic evaluation and work-up**
- Routine physical examination
- BMI->30 is obese
- BP recording

➢ **Laboratory investigations**
- Demonstration of biochemical hyperandrogenaemia.
- FSH estimations.

➢ **Laparoscopy**
- Many patients with PCOS, particularly those who are having trouble becoming pregnant will have a laparoscopy.
- In laparoscopy operation, the patient receives a short general anaesthetic; a small cut is made in the umbilicus and a telescope is inserted to look at the pelvic contents including the uterus, tubes and ovaries. The ovaries are look like ping-pong balls.

➢ **Hysteroscopy**

In hysteroscopy operation, a fine telescope is used to look inside the cavity of womb. it is used for patients those who have abnormal bleeding.
- **Oestrone**: -Serum androgen concentrations have little attention in diagnosis.
- **Vitamin D: -**Deficiency of vitamin D is common in women with PCOS. Especially in obese ones. Its deficiency also affect fertility in women with PCOS.[23]

Treatment and Management

Polycystic Ovarian Syndrome (PCOS) has been associated with numerous reproductive and metabolic abnormalities. Despite tremendous advances in the management of reproductive dysfunction, understanding of the metabolic implications of PCOS is limited by the lack of uniform diagnostic criteria, the heterogeneity of the condition. Obesity has a role in long term health effects and may further lead to reproductive and metabolic dysfunction and will also negatively affect the response to treatment in women with PCOS. Diabetes, cardiovascular disease and cancer are also at the forefront of any risk assessment or comprehensive treatment strategy for these women. There is no treatment which reverses the hormonal disturbances of PCOS and treats all clinical features, so medical management is targeted at individual symptoms, and only in association with lifestyle changes.[25]

Non-Pharmacological Approaches

A. Education and Counselling

Education and counselling about the condition is very important. The explanation and discussion of PCOS should be culturally sensitive as well as appropriate, comprehensive, and tailored to the individual. This discussion should use an empathetic approach, promote self-care, and highlight peer support groups. Counselling about fertility concerns is important, as adolescents with PCOS are more concerned than theirs peers about future fertility after diagnosis.

B. Lifestyle Interventions

Healthy lifestyle interventions must be incorporated in the management plan of all adolescents with PCOS because a large proportion of these adolescents are overweight /obese or are at risk for gaining excessive weight. Lifestyle interventions comprise multiple components, including healthy diets, physical activity, decreased sedentary behaviours, and behavioural strategies. The interventions should also include the family, as parents' involvement and their readiness to change affect adolescent outcomes, since family therapy in addition to other lifestyle interventions show beneficial effects on adolescent PCOS symptoms.

Nutrition education in addition to exercise training and behavioural therapy for longer duration, frequency, and intensity results in better maintenance of health and weight loss, as well as improvement of menstrual irregularities and androgen levels in adolescents with obesity and PCOS. Exercise interventions can also improve cardiometabolic risk factors in women with PCOS. Prevention of weight gain and effective weight management is important in adolescent PCOS, as obesity exacerbates metabolic and psychological comorbidities of PCOS

Engagement and adherence to lifestyle interventions can be improved by management of psychological factors such as anxiety, body image concerns, and disordered eating, which are common in adolescents. Lifestyle interventions in adolescents with PCOS have shown additional improvements in quality of life.[26]

C. Therapy for hirsutism

Cosmetic removal include temporary such as tweezing, shaving, waxing and depilatories, while electrolytes and laser treatment will remove hair permanently. This treatment should not be started until 6 months after the start of medical therapy. The pharmacological treatment of hirsutism slows the growth of new hair but does not affect established hair. Reduction of testosterone to a normal level can be finished by ovarian suppression with 100-200 mg spironolactone daily.

D. Surgery

Laparoscopic Ovarian Drilling (LOD) which is used in patients who do not respond to clomiphene therapy, it destroys androgen producing tissues. Correcting in hormonal imbalance and restoring ovarian functioning. Treatmentinclude suppression of hyperandrogenism to improve acne and hirsutism.

E. Diet regimen

Diet regimen not only aims at weight management but also prevents long term risk of PCOS such as Type-2 diabetes mellitus, cardiovascular disease etc.

The following products should be avoided

- Alcohol, caffeine, nicotine and their addictive agents
- Soy products-as they impede ovulation
- Milk-protein limits normal testosterone processing causing levels to rise
- Saturated fats-red meat, dairy products as they increase oestrogen production
- High glycemic index such as white rice, potatoes.

The following products should be consuming

- Whole grains-ragi, red rice
- Green leafy vegetables-rich minerals, vitamins and nutrients
- Dry fruits-dates, fig
- Low glycemic whole fruits-apples, pears, grapes, oranges and plums
- Bright coloured vegetables-carrots, capsicum, beets, salad etc
- Carbohydrates and proteins

Pharmacological Approaches

A. Clomiphene citrate

It is used as first-line treatment for ovulation induction in PCOS patients. It is the oestrogen receptor antagonist that interfere with negative feedback of oestrogen signaling pathway resulting in increased availability of FSH. Increased FSH leads to follicular growth. It takes in the first part of menstrual cycle. It is also used to treat infertility.

B. Metformin

Insulin sensitizing agents such as metformin, troglitazone antagonize some hyperandrogenic signs, by reducing total and free testosterone concentration. It increases ovulation and reduces the problem caused by insulin resistance and regulates excessively raised levels of androgens. It restores menstrual cycle, ovulation and fertility. Short term treatment of 3-6 months of metformin in PCOS to improve ovulatory functions and circulating androgen is fall. During pregnancy, it reduces number of pregnancy related problem such as gestational diabetes and gestational hypertension.

C. Flutamide

It proposed as alternative to spironolactone, which act by inhibiting the androgen receptor. It is the non-steroidal pure antiandrogen which inhibit the androgen receptor in a dose dependent manner and not having better efficacy than spironolactone.

D. Glucocorticoids

Prednisone and dexamethasone have been used to induce ovulation. In PCOS patients with high adrenal androgen, low dose dexamethasone (0.25-0.5 mg) at bed time can be used.

E. Gonadotropins

It is used as second line of therapy after resistance to clomiphene citrate. It induces ovulation, maintain and provoke optimum follicle growth with the controlled administration of FSH and its treatment started with low doses.

F. N-acetyl-cysteine (NAC)

It has antioxidant required for the body's production of glutathione which inhibit the oxidative stress and prevention of hyperinsulinaemia.[23]

CONCLUSION

PCOS is a complex disorder involving multiple organ systems which might be caused in women with onset during puberty, the list of factors involved in the pathophysiology continues to expand with occuring evidence indicating that hyperandrogenism being the main factor which affects multiple tissues, hyperandrogenism level elevates which further leads to various hormonal imbalance such oestrogen, follicle stimulating hormone, luteinizing hormone, insulin etc…

Hormonal imbalance leads to various dysfunctions such as infertility, type-2 diabetes, cyst formation in ovary, endometrial cancer, hirsutism, acne, obesity, etc… multiple treatment approaches are required as per the reason for which the patient seeks the treatment for.

There is no complete cure for Polycystic Ovary Syndrome. A healthy life style such as proper sleep, stress free environment, healthy diet, healthy weight can reduce the chances of Polycystic Ovary Syndrome. Lifestyle modification is one of the best way to prevent ourselves from Polycystic Ovary Syndrome.

Epidemiological studies of PCOS shows that phenotype C [Hyper Androgenism (HA) + Polycystic Ovarian Morphology (PCOM)] is most common type of PCOS based on our data collection in the hospital.

More than fifty percentage of PCOS cases are being undiagnosed therefore various well designed awareness programs are required to reduce the prevalence of PCOS.

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