

# **Polycystic ovary syndrome: Pathogenesis and Treatments**

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## **Abstract**

In current scenario, the number of patients suffering from disease like polycystic ovary syndrome are increasing tremendously due to several reasons such hormonal imbalance, environmental factors, life style disorder, due to genetic reasons and many more. It was also observed that continuous use of first line therapy against these cases leads to overcome this horrible situation. Here, in the present work, we have discussed about polycystic ovary syndrome along with its pathogenesis, diagnostics methods, available treatments and their associated effects. This review will help the readers to understand the different approaches to tackle this problem.

**Keywords:** Polycystic ovary syndrome, Insulin Resistance, Metformin

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**Introduction**

Due to life style disorders, now days the cases of hormonal imbalance diseases have been increases. One of example such disorder or disease is Polycystic ovary syndrome (PCOS), which is a mostly widespread endocrine disease mainly occurs during women`s childbearing years that disturb the female reproductive organ or may be responsible for infertility [1]. Apart from these symptoms, it may also stop their periods, causes acne, stimulates unwanted body and facial hair growth and at last also may cause diabetes and high in blood pressure [2]. It was also observed that PCOS patients have higher possibility for emotional distress and depression. There are so many factors behind occurrence of PCOS such as high levels of androgens, hyperprolactinemia, excessive exposer of toxic chemicals, thyroid dysfunction and lifestyle faults [3].

**Pathogenesis of Polycystic ovary syndrome (PCOS)**

The pathogenesis of PCOS is not exactly well known. There are numerous mechanisms like hormonal imbalance, insulin resistance, and genetic inheritance play an important role in its pathogenesis [4]. In this condition, polycystic ovaries are enlarged with a smooth, thick, avascular capsule and resist the release of the egg and ovulation. It is associated with increased level, unusual production and metabolism of androgens and estrogen, testosterone, androstenedione, and dehydroepiandrosterone sulphate (DHEA-S) in the body [5-6].

It is mainly related with increased androgen level and its synthesis occurs in ovaries and adrenal gland with the help of cytochrome P450 enzymes. Usually In theca cells, cholesterol is converted to androstenedione by luteinizing hormone (LH) [7-8]. The obtained androstenedione diffuse from theca cell to granulosa cell where it converts into estrone by aromatase and this process catalyse by follicle stimulating hormone. Similarly, in granulosa cell converts intotestosterone top dihydrotestosterone and estrone to estradiol by 5 $\alpha$  reductase and 17 $\beta$ hydroxysteroid dehydrogenase. This steps leads to increased level of androgen [9-10]. We can summarize this that raised levels of androgenic hormones and irregular or absent ovulation may occurs due to stimulatory effect of secreted luteinizing hormone (LH) from the

anterior pituitary gland on the ovarian theca cells [11]. Apart from this, the another reports suggested that reduced level of follicle stimulating hormone (FSH) minimizes the aromatization of the androgen hormones to estrogen which leads to low level of available estrogen and absence of ovulation [12-13].

Another important thing was observed that is strong correlation between PCOS and resistance to insulin the body. It has been suggested that the high levels of insulin alter the effect of gonadotropins and the function of the ovaries, leading to PCOS. The presence of excess insulin leads to more production of testosterone in ovaries, followed by delay in the follicles development, which leads to inhibition of ovulation and PCOS [14-15].

This condition is more severe in case of overweight or obese women because of the resistance to insulin due to excessive fat. It was also suggested that raised level of adiponectin hormone also plays a role in the pathogenesis of the condition. In the next section, we will discuss about its available diagnosis methods and treatments [1, 5-7].

### **Diagnosis Methods and Treatments**

No single test is available to diagnose PCOS. To confirm the presence PCOS (by observing Irregularities/absence of periods, hirsutism, acne, thinning of scalp hair and many more) and exclude other causes of symptoms, physical examination and number of different tests, as given below, have to perform.

- **Physical exam.** It is important to measure patient`s body mass index (BMI), blood pressure, and waist size along with observation of their facial skin for extra hair as well as for discoloration and acne. Sometimes, it is also advisable to note down hair loss or diameter of enlarged thyroid gland.
- **Pelvic exam.** It is a vital parameter to observe signs of enlarged or swollen ovaries and extra male hormones (for example, an enlarged clitoris). It will provide information about growth of any masses or cysts in the ovary.
- **Pelvic ultrasound (sonogram).** This test uses sound waves to examine patient`s ovaries for cysts and check the endometrium (lining of the uterus or womb).

- **Blood tests.** To investigate the raised level of androgen hormone levels, sometimes called male hormones, it is an important test. It is also advisable to observe cholesterol levels and blood glucose level [16-18].
- **An ultrasound.** For evaluating the conditions of the ovaries as well as thickness of the lining of uterus, transvaginal ultrasounds have to be carried out transducer. The transducer produces sound waves that are changed into images on a computer screen

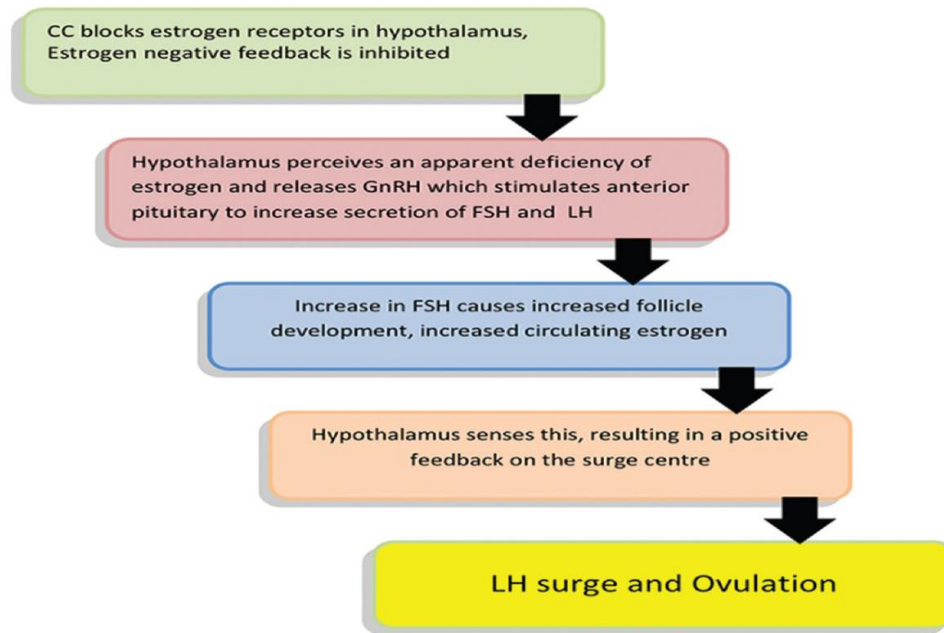
Its treatment included for various symptoms like, infertility, hirsutism, acne or obesity. Some of the treatment also influence involves lifestyle changes or medication to prevent diabetes. Proper exercise and diet should have to followed, which further helps in weight loss, hyperandrogenism, and decreases the fasting insulinemia and better ovulation. Obese female are advised to follow health life style, yoga to avoid high risk of complicated pregnancy, caesarean delivery, congenital anomalies, gestational diabetes mellitus and increased perinatal mortality [19-20]. Few Medicines are also available for the treatment of PCOS. The structures of these drugs are shown in below table 1. Here, we will also discuss about their mechanism of action along with other effects associated with them.

**Clomiphene Citrate:** It is first-line treatment therapy, acts as an estrogen agonist or antagonist via stimulating ovulation (the release of an egg from the ovary). It is a non-steroidal fertility drug, mainly metabolises in liver and excreted through faeces [21].

**Mechanism of action:** In normal menstrual cycles, decreased level of estrogen causes deregulation of release of gonadotropins during the early follicular phase due to negative feedback in the hypothalamus and pituitary gland. Oral administration of clomiphene citrate (CC) blocks the negative feedback mechanism and gradually raises the gonadotropins, as shown in figure 1.

The important thing for PCOS treatment is dosing frequency of clomiphene citrate. Initially it is given for five days at a dose of 50 mg per day. If successful results are not obtained then maximum dose, which is around 120-200 mg is prescribed daily for another five days. In case of failure of ovulation is observed then that patient is considered as resistant to this treatment.

There are many other effects associated with this therapy such as mood swings, virtual disturbance, breast tenderness, pelvis discomfort and nausea. Sometimes the rare effect, which is known as ovarian hyper stimulation syndrome (OHSS) is occurs due to taking high amount of fertility drugs and stimulates the egg growth [18-21].



**Fig 1 :** Mechanism of Clomiphene citrate [22]

**Letrozole:** Another first line drug treatment for inducing ovulation. This drug helps to stimulate the ovaries and blocks the aromatase enzyme, which is responsible for the formation estrogen. Letrozole shows better results than clomiphene citrate for the treatment of infertility in PCOS patient. But overuse of this drug leads to heat in your face or chest, hirsutism, joint/bone/muscle pain, fatigue, infrequent sweating or night sweats, vomiting and diarrhoea [20-22].

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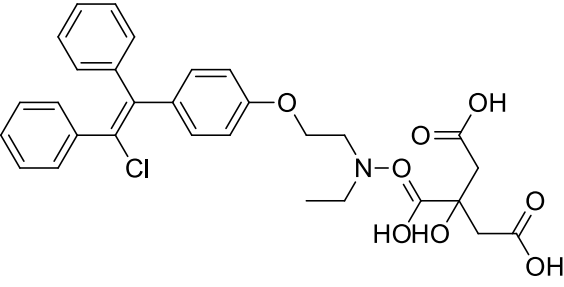
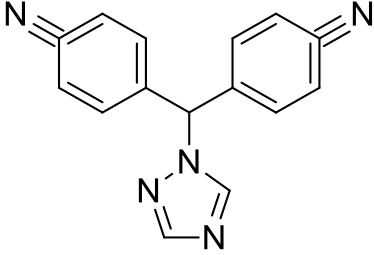
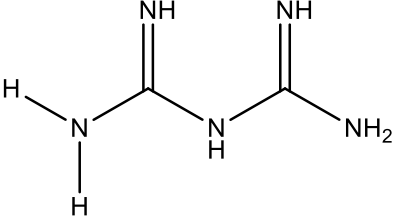
**Fig 8:** Mechanism of Letrozole

**Metformin:** It is not used as first line drug for PCOS because clomiphene and Letrozole were effective in ovulation. So it is used in combination. It helps in lowering the insulin level from bloodstream, improved tissue-specific insulin sensitivity, and decrease the androgen synthesis from ovary. It is used in type 2 diabetes mellitus and recovers insulin resistance and also help in decreasing the insulin level from bloodstream. Some reports suggests that It helps to improved pregnancy and child birth rates by  $P < 0.0001$  and  $P = 0.020$ , respectively with decreased possibility of cancelled cycles. Sometimes it may also produces other associated effects such as gastroenterological consisting of swelling, stomach distress, vomiting and diarrhoea [20, 22-23].

**Gonadotropins:** These are second-line treatment, first time used in year 1961. It contains FSH, LH or a combination of the two and human chorionic gonadotropins (Hcg), also known as fertility used for activation of ovulation process. Many of these are derivatives of urinary products but now days they have been manufactured via recombinant technology with producing similar ovulation and pregnancy rates. Recombinant techniques developed gonadotropins are administered by subcutaneously route and are more patient friendly; however, they are expensive when compared to those derived from urinary products which are given intramuscularly. Gonadotropins can be used for clomiphene resistance and clomiphene failure. These are available in different branded forms such as Gonal-F, Follistim, Ovidrel, Menopur, and Luveris. They are given by injection only. Apart from this, these are little bit expensive along with significant risks such as multiple pregnancy and ovarian hyper stimulation. Intensive monitoring with multiple ultrasound examinations over several days is required to monitor follicular growth [19-22].

**Table 1:** Drugs used for treatment of PCOS

Name of the Drug	Structure of the compound	Marketed name and manufacturer
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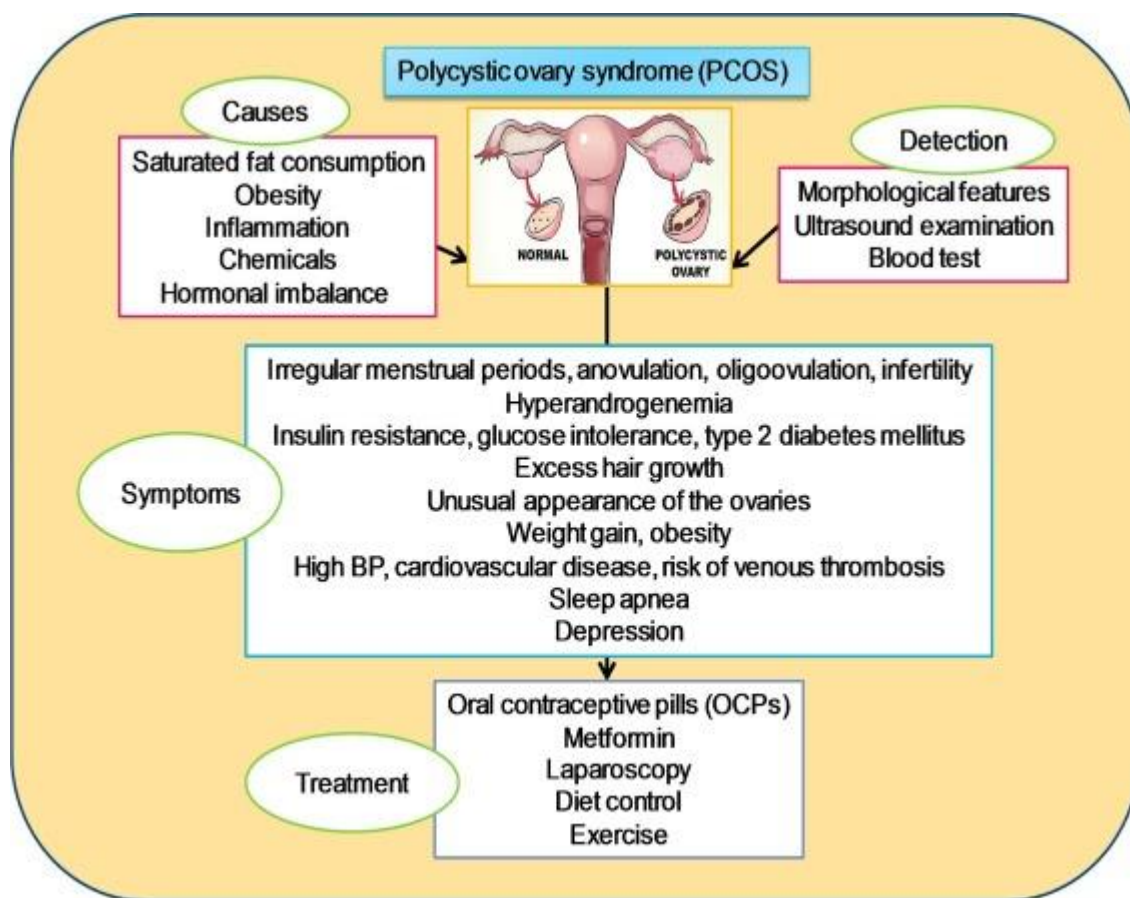
<p>Clomiphene citrate</p>	 <p>The image shows the chemical structure of Clomiphene citrate. It consists of a central carbon atom bonded to two phenyl rings, a chlorine atom, and a piperazine ring. The piperazine ring is further substituted with a propyl chain that is part of a citric acid moiety.</p>	<p>Clomid(SanofiAvent isUS), <u>Serophene</u>(, Milophene</p>
<p>Letrozole</p>	 <p>The image shows the chemical structure of Letrozole, which is a triazole ring substituted with two 4-cyano-phenyl groups.</p>	<p>Femera( discovered by Novartis and manufacture by Teva pharmaceutical industry,Dr.reddy's lab, sun pharama, etc.)</p>
<p>Metformin</p>	 <p>The image shows the chemical structure of Metformin, which is a 1,3,5-triazin-2,4,6-triamine derivative.</p>	<p>Glucophage(Bristol-MyersSquibbU.S), Glumetza(Salix Pharmaceuticals US), Fortamet(Mylan US)</p>

Other than these drugs and hormones, many types of other medicaments such as oral contraceptives, progestin therapy, hormonal birth control, and hormone intrauterine device (IUD) are also available methods to prevent PCOS. In next section, we will discuss about few of them in brief.

**Oral contraceptives:** These are the present in combination form for example estrogen and progestin pills, which helps in reducing androgen level and controls estrogen. It is suggested that optimum hormonal level will reduces the chances of endometrial cancer, excess bleeding, hirsutism and acne. Other examples available in the market are FDA-approved

Ethinylestradiol/norgestimate (ortho-tri-cyclen) combination, mainly used against acne vulgaris in females [18-20].

**Progestin therapy:** This therapy involves treatment for almost 10 to 14 days for 1-2 months for regulating menstrual cycle and also to prevent endometrial cancer. It causes thickening in the lining of the uterus and only useful in condition where women don't want to conceive [19-21].



**Fig 3:** Overall about PCOS

**CONCLUSION:** PCOS is a hormonal syndrome mainly occurs among female of reproductive age. Almost 70% of female actually are not aware with PCOS and its symptoms, so, they remain undiagnosed. It was observed that female suffering with PCOS if not get treatment on time; it will lead to type-2 diabetes and cardiovascular disease. The present work will help to understand its diagnostics methods and treatments.



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