Chapter

Pathophysiology of Polycystic Ovarian Syndrome

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Abstract

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy that affects 8–20% of the reproductive age females and adolescent girls every year worldwide and approximately 5 million cases reported in the USA annually. It is more prevalent in urban areas as compared to the rural areas because of the difference in the lifestyles of rural and urban ladies. Rarely PCOS is passed on by heredity in some cases. It mostly occurs due to a lack of awareness. Its symptoms become mild to severe like initially hirsutism, acne which further leads to irregular periods and infertility. The pathogenesis of PCOS is not known because it is a complex multi-genetic disorder. Ovary and adrenal steroid genesis, the action of steroid hormone, action and regulation of gonadotropin, action, and secretion of insulin, obesity, and regulation of energy in PCOS involve genes. Its main clinical manifestations are insulin resistance and increased level of androgen. Metformin is used to sensitize the insulin because the risk of glucose intolerance also gets elevated with insulin resistance, type-2 diabetes, and lipid abnormalities. Likely, the outcome of different, deeply interrelated genetic abnormalities that influence each other and perpetuate the syndrome may be represented by PCOS.

Keywords: polycystic ovarian syndrome, insulin resistance, genetics of PCOS, metformin, gonadotropin

1. Introduction

Polycystic ovarian syndrome (PCOS), also known as hyperandrogenic anovulation (HA) or Stein-Leventhal Syndrome, is the most common endocrine disorder which affects reproductive age women [1, 2]. PCOS is a complex psychological, metabolic, and reproductive condition that is characterized by either hyperandrogenism or abnormal gonadotropin secretion and sometimes associated with insulin resistance [3, 4]. It refers to a disorder with a combination of reproductive [5], environmental and metabolic characteristics [6]. It also causes endometrial abnormalities such as fertility implication and cancer implication [7, 8]. It is most commonly found in the reproductive age group female [9, 10] but it can also affect males due to hormonal imbalances. The appearance of polycystic ovary under the transvaginal pelvic ultrasound look are like small cyst. These cysts are eggs or follicles rimming the ovaries, which starts increasing in size and then stops at a tiny follicle size of around 2–10 nm.

They described infertile women with shinny ovaries, which is having multiple cysts in the size of approx. 2–10 mm. According to many pieces of research, PCOS may affect 8–15% women of reproductive age but 35% premenopausal mothers and 40% of sisters were affected by this problem as compared to general rates [11–13]. These ranges of incidence may vary according to the diagnostic criterion of the PCOS. In the case of PCOS, there are multiple cysts present in the woman's ovaries which are not released on its actual time so as a result immature follicle keeps growing, and leads to the formation of multiple cysts. There are reports which say 65–95% of all the women have PCOS also have insulin resistance which might be due to perturbed receptor tyrosine kinase, or other protein of insulin signaling cascade, modified adipokine signaling, and its secretion when compared to normal women [14, 15]. Increased level of insulin induces the rise in male sex hormone androgens, like testosterone which plays an important role in the pathogenesis [16, 17]. The exact pathogenesis of PCOS is still not very clear [18, 19]. There are several clinical significances like hirsutism, infertility, irregular periods, alopecia and many more symptoms begin shortly after puberty [20] and they develop during late terms and into early adulthood [3]. There is no particular treatment done to cure this problem but it can be managed by controlling sugar level and regulating the menstrual cycle by taking forming drug i.e. first insulin-sensitizing drug and it can also be treated by gonadotropin as first step treatment agents in ovulation. Low level of progesterone leads to cause overstimulation of immune system that produces the more estrogen and it will further lead to the production of autoantibodies i.e. anti-thyroid, anti spermatic, antinuclear, anti-ovarian, etc. there is a study in which we come to know that there are many proteins involved in PCOS [21]. The cumulative effect of modified protein, which are the product of mutated genes, along with various other factors like genetic inheritance and environment leads to complications in the case of PCOS [11]. Many genes participated in etiology of this syndrome but this is not fully investigated yet but the study shows that abnormality of genes in case of PCOS mostly affects the pathways of signal transduction which controls the steroidogenesis (formation of steroids) [12], insulin action [22] and secretion, gonadotropin action and regulation [23, 24], steroid hormones action and many more [25, 26].

2. Symptoms

There are many symptoms which are contributed to PCOS such as hirsutism, acne, alopecia, acanthosis, seborrhea, infertility, insomnia, and irregular periods (**Figure 1**) [27, 28].

Hirsutism: It is excessive growth of hair on a woman's face and body. In this case, there is a condition of unwanted hair growth in women mainly on the face, chest, and back, just as males [29].

Acne: It is a chronic skin condition that causes the spots and pimples. It mainly occurs when oil and dead skin cells clog the hair follicles which leads to the formation of whiteheads, blackheads, pimples, cysts, etc. They mainly occur on the face, shoulders, back, neck, chest, upper arms. It may also occur due to the different peripheral sensitivity of the androgen receptors [30].

Alopecia: It is the condition in which there is sudden hair loss which leads to baldness and in this condition, there is also thinning of hair.

Acanthosis: It is skin condition when there are dark velvety patches in the body folds and body creases like underarms and neck. The affected skin can become thicken and blackened.

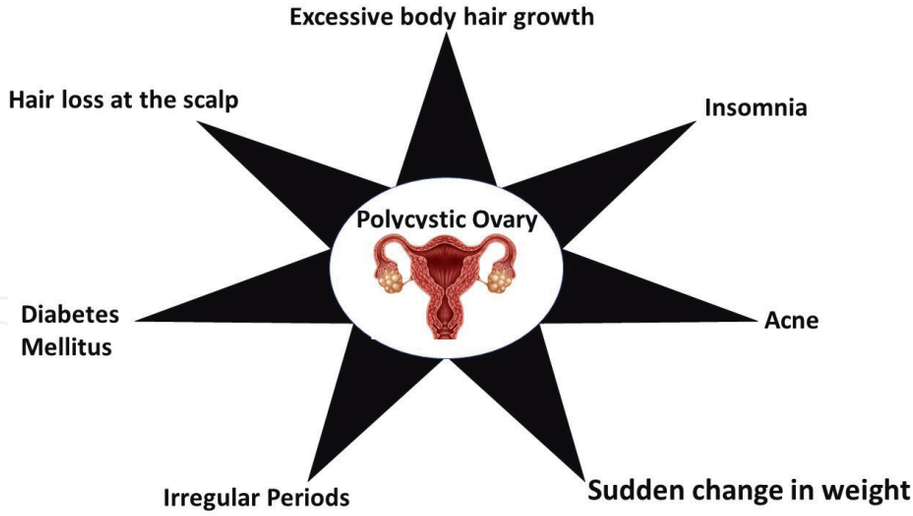

Figure 1.
Common symptoms of polycystic ovary syndrome (PCOS).

Seborrhea: It is a condition when there are patches and red skin mainly on the scalp. There may be yellow plaques on the scalp. It is also a chronic inflammatory disease.

Striae: This is also known as stretch marks. They appear as reddened streaks on the skin it is mainly due to rapid change in body weight or in case of pregnancy also.

Acrochordons: They also knew as skin tags. This is the common skin growth, which sticks out. They are small soft common benign.

Infertility: It is an inability to conceive after a long period with unprotected sex.

Insomnia or sleeping disorder: Women with PCOS reports for the poor sleep or insomnia. There are a number of factor which leads to poor sleep but the PCOS is associated with the sleep disorder called sleep apnea. In the case of sleep apnea person, stops breathing for some duration during sleep.

Irregular periods: It is a problem with menstrual cycles. It is a condition when there are delayed, missed, or more bleeding patterns [31]. It further leads to the problem in the reproductive system. With PCOS, there is a correlation to a low level of androgen with advancing age in women [32].

3. Causes

Exact etiology remains unknown but some of them are written below [33–35].

a. *High level of insulin:* Insulin is a polypeptide hormone, which is synthesized and released by pancreatic beta cells and its main function is to reduce the blood glucose sugar level in the body, which indicates that PCOS has metabolic and reproductive morbidity [36]. If there is no insulin production then there is a high level of sugar in the body. It will act as a driving force for hyperandrogenism [37]. There is insulin resistance also occurring in which insulin is produced by the pancreas but our body not able to use that insulin [38]. A high level of insulin induces the ovaries to produce more androgens such as testosterone which will prevent ovulation [39, 40]. In PCOS pregnancies, unable to prevent excess testosterone [41]. There are two possibilities in the case of hyperinsulinemia i.e. increased hyperandrogenemia [42, 43] and decreased the circulating level of sex hormone-binding globulin [44]. Peripheral insulin resistance is also related to uterine and ovarian problems [45].

b. *Bad dietary choices:* Eating junk food cause PCOS because junk food contains excess fat, simple carbohydrates, and sugar which leads to a high risk of obesity [46], Diabetes, cardiovascular disease, which further leads to PCOS.

c. *Weak immune system:* It is the common cause of menstrual irregularities because a low level of progesterone in PCOS causes overstimulation of the immune system that produces more estrogen which leads to producing autoantibodies.

d. *Obesity:* Obesity is the major cause of PCOS because when we eat more junk food, which causes obesity and an obese person more prone to get diabetes which ultimately leads to PCOS [47]. Insulin resistance and high level of insulin in the blood, which further stimulate ovarian androgen production are associated with obesity [47, 48]. Similarly, the prevalence of dyslipidemia also rises with increasing obesity [49, 50]. Obesity also causes a high risk for several cancers like breast cancer, endometrial cancers, etc. [8, 51–53].

e. *Inflammation and oxidative stress:* Inflammation is considered as one of the key features of endothelial dysfunction and atherosclerosis. A lady with PCOS is prone to have a high level of visceral adiposity in all categories of BMI. This high level of visceral adipocytes is linked with insulin resistance, a rise in blood glucose, and lipid levels [54]. These adipocytes affect endocrine as well as exocrine. Inflammation and oxidative stress are very closely interrelated. The inflammatory process generates reactive oxygen species and oxidative stress process and products induce and aggravates inflammation. There are literature reports available that say the lipid peroxidation level increased in the case of PCOS and this rise is having a positive correlation with the BMI, insulin level, and blood pressure [55]. Women having PCOS also have a decreased number of antioxidants, glutathione, as well as haptoglobin. In these cases, the susceptibility towards the oxidative stress-induced DNA damage also increases. Oxidative stress also involved in many abnormalities od the reproductive system as well such as infertility, endometriosis, anovulation, and defects in the quality of oocyte [54, 55].

f. *The genetic tendency for PCOS:* There are many genes, which are responsible to cause PCOS. It may be occurred among the population and within the families. The critical genetic variations in PCOS across different ethnicities and their associated effects such as hyperandrogenism in women [56], insulin resistance [3, 17, 22, 56–58], miscarriage, recurrent pregnancy loss, endometrial receptivity [59]. Women suffering from PCOS are more prone to different types of cancers [8, 53, 60, 61].

4. The difference in normal ovary and PCOS ovary

In normal case ovaries, fallopian tubes, uterus, vagina are the main reproductive organs of females and they are having a lifetime supply of ovum and these ova are stored in sac-like fluid-filled structures called follicles. The sex hormones, which are helpful to act on the function of the ovaries, are produced by the pituitary gland located just below the hypothalamus at the base of the brain. So pituitary gland secretes follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the bloodstream. Through blood, these hormones reach the ovary where they start to get maturing the immature ovum and increases the size of follicles [62]. As the eggs get

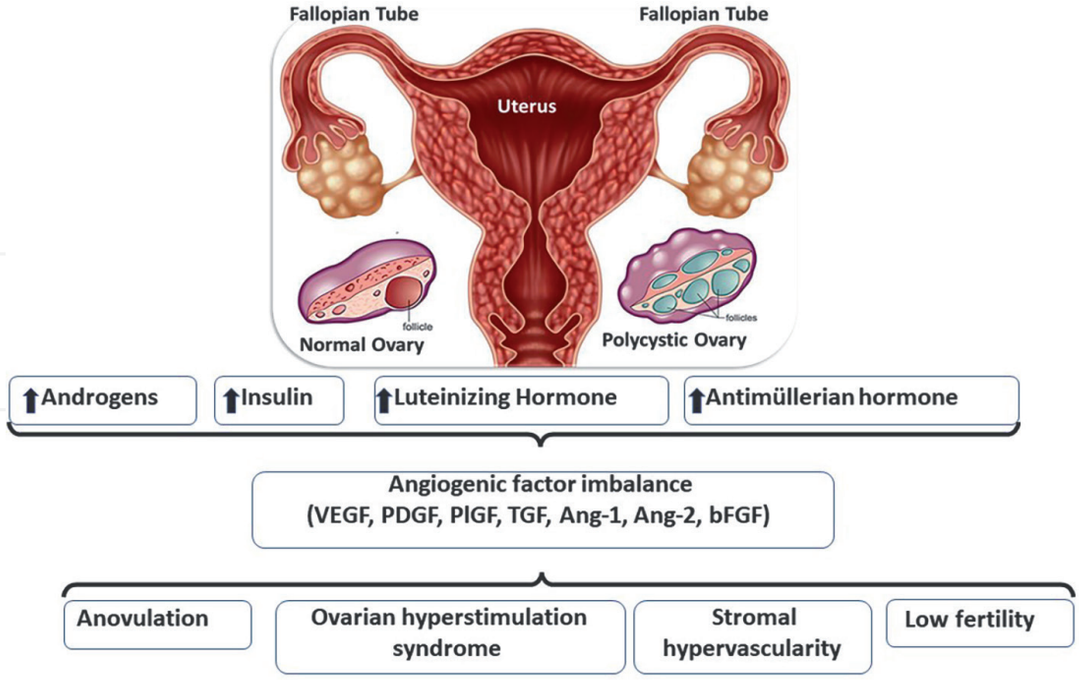

Figure 2.
Pathophysiology of polycystic ovary syndrome.

matured the follicles start releasing estrogen, a female sex hormone. As soon as the estrogen level crosses threshold concentration, the pituitary gland senses the LH flow to ovaries and results in the rapturing of the mature follicles and releases its ovum/egg. This process is known as ovulation. The free ovum then passes through the fallopian tube where the fertilization process occurs and the remaining immature follicle gets dissolved. If ovum does not get fertilized then the egg and line of the uterus are shared to doing the next menstrual cycle. But in the case of PCOS, the Pituitary gland secretes a higher amount of LH due to biochemical destruction which disturbs the menstrual cycle. Then there are no mature follicles present so no ovulation occurs and it will lead to infertility. Some follicles do not dissolve, they remain there as such and formed as fluid-filled sac-like structures which are known as CYSTS (**Figure 2**). Increased level of insulin and LH will produce testosterone [62, 63] which causes hirsutism, acne, prevent ovulation which further leads to infertility [64].

5. Genetics of PCOS

PCOS is a complex genetic disease with several susceptibility genes. It has powerful genetic and environmental components [65]. Many pieces of research show that identical twins are more prone to get PCOS than fraternal twins or non-twin siblings. Women having a 50% chance to get PCOS if their mother or sibling also has this disease. Research also shows that the male siblings of women with PCOS are more susceptible to get insulin resistance than the male sibling of unaffected women. Genes that are linked with PCOS are responsible for the production and metabolism of sex hormones or linked with an impaired function of insulin. Genes involved in PCOS are

a. *DENND1A* gene which is linked to PCOS risk and this gene is responsible in the import of molecules into the cell which is responsible for the recycling of hormone receptors from the cell's surface and leads to PCOS,

b. *THADA* gene is linked with type-2 diabetes mellitus [66] and some other cancers and the production of this gene in the pancreas by releasing some hormones which regulate the blood sugar levels in the body,

c. *SHBG* gene is sex hormone-binding globulin is a biomarker of PCOS and if there are low levels of SHBG then more hormones free for biological action in the body and then they promotes the symptoms of PCOS,

d. *FBN3* gene is placed on 19 chromosomes within the gene and it is linked with PCOS and insulin resistance women who are already having PCOS and if there is the lower level of FBN3 in PCOS affected women then they lead to abnormally increase level of TGF-beta activity which causes many metabolic disorders like hypertension, hyperlipidemia [67, 68], inflammation and cardiovascular diseases (CVD).

e. *LHCGR* is luteinizing hormone/chorionic gonadotropin receptor are the genes which control the development of sex organs and hormones in males but in the case of females, they are responsible for ovulation.

f. *INSR* gene is an insulin receptor gene that encodes the receptor for the hormone insulin etc. [57]. These receptors are extracellular receptors present on the plasma membrane having three different regions like extracellular, transmembrane, and intracellular. Extracellular parts of the receptor receive insulin while the intracellular portion is tyrosine kinase in nature and gets phosphorylated which finally amplifies the signal inside the cells for various physiological roles.

5.1 Genes which are responsible for Ovary and adrenal steroidogenesis

a. *CYP11A:* The initial step of steroidogenesis is the conversion of cholesterol into progesterone which is catalyzed by P450. Then the gene CYP11A which is located at 15q24 encodes P450. The association in the level of serum testosterone has been shown by this gene [69, 70]. The CYP11A alleles also show the association with 5'UTR.

b. *CYP17A1:* This CYP17A1 gene help to convert pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone and also help to invert dehydroepiandrosterone and Δ4-Androstenedione which is created by an enzyme i.e. P450c17. Activities of this enzyme like 17,20-lyase and 17-hydroxylase. P450c17 is encoded by CYP17A, and this gene is located at 10q27.3. It was proclaimed that the women having PCOS has increased activity and expression in ovary theca cells.

c. *CYP19:* The gene CYP19 helps to converts the androgen into estrogen. This enzyme is made up of cytochrome P450 aromatase and NADPH cytochrome P450 reductase. P450 aromatase is encoded by gene i.e. CYP19 which is located at 15p 21.1. Deficiency of aromatase enzyme mostly occur in those people whose is having high androgen level and this aromatase activity is decreased in follicles because as compared to normal follicles PCOS follicles having estradiol which lowers the aromatase stimulation bioactivity and the excess level of androgens leads to improper development of follicles [66].

d. *HSD17B1 & HSD17B2:* The group of alcohol oxidoreductase includes these genes, which is used to catalase the dehydrogenation of 17-hydroxysteroids in the steroidogenesis process. There is an interconversion of androstenedione and testosterone, DHEA and androstenediol and estrone, and estradiol. The level of expression of mRNA synthesizing and inactivating enzyme has been reported high in women without the PCOS endometrial treatment [71].

e. *HSD3B1 & HSD3B2:* The placenta and peripheral tissues show Type I 3β-HSDiso-enzyme but the adrenal gland, ovary, and testis show type II 3β-HSDiso-enzyme. The deficiency of HSD3B in hyperandrogenic women is related to the insulin-resistant PCOS.

f. *StAR:* StAR is a Steroidogenic Acute Regulatory protein. The cholesterol within the mitochondria is transported by such kind of transport protein. But in some patients, defect of steroidogenesis causes PCOS, due to which level of the ovary and adrenal androgen production rises. The transport protein i.e. StAR initiates the process of steroidogenesis [72].

6. Role of hormones in the PCOS

6.1 Steroid hormone actions

PCOS is one of the most common endocrine disorders in females of reproductive age group with multiple manifestations. The reproductive physiology of female is highly affected by her body weight and the metabolic status of her body. PCOS is mainly linked with obesity with the deposition of fats in abdominal regions in almost 51% of women having PCOS. As it is associated with insulin resistance and hence results in hyperlipidemia, cardiovascular disorders, and also cancer of the endometrium. There are some important components of lipid metabolic pathways which play a significant role in the PCOS occurrence.

a. *Androgen receptor:* PCOS is most commonly characterized by more secretion of androgen. This will increase the level of androgen production by the ovaries i.e. hyperandrogenism which is the second most common characteristic in PCOS. 17–83% of women are in occurrence to PCOS [73].

b. *Serum Sex hormone-binding Globulin (SHBG):* SHBG, a glycoprotein, influences the bioavailability of lipid-soluble steroid hormones. The serum SHBG level has been reported in patients with hyperandrogenism and PCOS. It results in hyperinsulinemia [43, 45], which will lead to lower the level of SHBG. And it will also suppress the SHBG synthesis in the liver [74].

6.2 Gonadotropin action and regulation

Kisspeptin is a protein that is coded by the KISS1 gene. Initially, this protein was discovered as its role in the tumor suppression mainly for melanoma and breast cancers. Kisspeptins have recently emerged as essential upstream regulators of GnRH neurons with many roles in reproduction such as puberty onset [75, 76], brain sex differentiation [77], gonadotropin secretion [78], ovulation and metabolic regulation of fertility [79].

i. *Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH):* PCOS is characterized by an inappropriate gonadotropin secretion. One of the common reasons for PCOS is an elevated level of LH. High LH secretion and low FSH secretion has been seen in females affected with PCOS. The ratio used to indicate abnormal gonadotropin secretion is normally 2–3/1. The decreased level of FSH which stimulates the growth of follicles in ovaries is a characteristic feature of PCOS. They are having mature eggs. The absence of FSH for a longer period will be responsible for immature follicles and eggs will not be released. Thus, this would result in infertility. Thus, small cysts will be produced in ovaries due to immature follicles [80, 81].

ii. *Inhibin βA and Inhibin βB:* Insulin resistance is highly associated with PCOS. FSH secretion is regulated by a heterodimer, Inhibin. The release of inhibin suppresses the increase in FSH concentration. It has got two variants Inhibin A and Inhibin B which are secreted by gonads, pituitary gland, placenta, etc. During the follicular phase, Inhibin B is more important than Inhibin A. The level of inhibin is higher in a woman with PCOS than the normal ones.

iii. *MADH4:* Mothers against decapentaplegic homolog 4 are a protein involved in signaling in mammals. The protein belongs to the SAMD family. SAMD4 has two functional domains MH1 and MH2 consist of a tridimensional structure (Regions M and H represent MAD homology). This resembles a similarity between SAMD4 in mammals and Drosophila protein.

6.3 Insulin action and secretion

Many women having PCOS have shown glucose-induced hyperinsulinemia, insulin resistant, independent body mass index. The insulin-dependent glucose level decreases by 35–40% in the case of PCOS affected women when compared to normal women. More than 2% of women with PCOS moves from normal to type 2 diabetes mellitus and almost 16% of women move from impaired glucose tolerance to type 2 diabetes mellitus. The incidence of PCOS with obesity is very complex. Although PCOS occurs both in obese and lean women some recent studies and meta-analysis reveal that obesity more frequently occurs in women with PCOS. And it is a well-known fact that obesity leads to insulin resistance and finally to diabetes mellitus type 2. To fulfill the body's requirement, the pancreas produces a high amount of insulin and a condition of hyperinsulinemia occurs. This condition mainly affects fibroblasts and adipocytes. One of the main effects of this hyperinsulinemia is the autophosphorylation of tyrosine in the insulin receptor decreases whereas the autophosphorylation of serine increases in both types of cells. In the fibroblast, the insulin-dependent glucose uptake, translocation of GLUT4 to the plasma membrane, and insulin-dependent glycogen synthesis decrease whereas in the case of adipocytes also glycogen synthesis decreases. Insulin influences the function of LH on to the ovary which increases the production of androgens. Insulin also inhibits sex hormone-binding globulin (SHBG) production by hepatocytes increases the free androgen fraction in blood circulation. An increase in adipocyte tissue also increases the severity of insulin resistance. Hence, it exacerbates the metabolic and endocrine derangements of PCOS (**Figure 3**).

i. *Insulin and IGF-I:* Growth of ovary is stimulated by insulin and IGF-I. The action of gonadotropins on ovary steroid synthesis is increased by them.

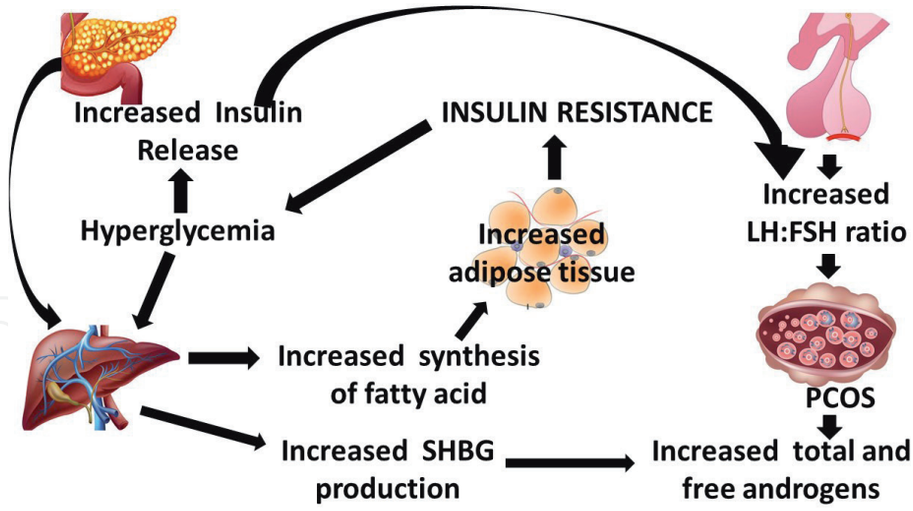

Figure 3.
Role of insulin in polycystic ovary syndrome.

The concentration of IGF-I and androgens is augmented by Insulin. It does this by regulating the synthesis of IGFBP-1 and SHBG in the liver. One of the common symptoms of PCOS is resistance to insulin. The important reasons resulting in PCOS is increased in insulin level and IGFBP-1 activity.

ii. *Insulin VNTR gene, IGF-II, insulin receptor substrate, and insulin receptor gene:* The insulin gene consists of a changing number of tandem repeats present at the 5'regulatory region. The main reason for the regulation of the translational rate of insulin is Polymorphism of the VNTR gene. It is also responsible for the regulation of gene encoding IGF-II. Class-I alleles are made up of a length of 40 tandem repeats and Class-II alleles are made up of 80 tandem repeats. Insulin resistance caused by PCOS may directly affect the pancreatic beta-cell. Insulin resistance in some PCOS phenotypes is affected by VNTR polymorphism. SNP at the tyrosine domain of the insulin receptor is greatly found to be associated with PCOS.

iii. *Peroxisome proliferator-activated receptor gamma (PPAR-γ):* It is a nuclear transcription factor that is involved in the regulation of glucose, lipid metabolism, and ovary steroidogenesis. Proline and Alanine in exon B are the most extensive findings on polymorphism in PPARγ. C1431T in exon6 is another polymorphism studied in the PPARγ gene. This variation is associated with PCOS. Insulin resistance path physiology is influenced by the PPARγ gene in women affected with PCOS.

6.4 Obesity and energy regulation

i. *Leptin and leptin receptor:* Leptin plays a major role in the pathological process of PCOS. Leptin and the free leptin index levels are higher in PCOS affected obese females than in thin PCOS females. In the case of PCOS, there is a high level of free leptin index but the low level in leptin receptors. And these both factors in PCOS, dependent on Body Mass Index (BMI).

ii. *Pro-opiomelanocortin (POMC):* It is a 16 K fragment that is used for the identification of factors that are responsible for excessive adrenal androgen levels.

iii. *UCP2 + 3:* Androgen synthesis of granulosa cells of affected PCOS patients is controlled by UCP2 which is an uncoupling protein. Treatment with the T3 hormone increases the expression of ovary UCP2. It may also change the pregnenolone synthesis which further results in P450 sec expression. This will further affect testosterone production.

7. Diagnosis

Diagnosis is the main purpose to detect or to identify the disease by seeing their symptoms, or by performing many tests. Like in the case of PCOS doctors may see the sign and symptoms and may also do to test for PCOS [82].

Appearance: Diagnosis of PCOS occurs by seeing the appearance of ovaries like in case of PCOS there are polycystic ovaries due to having more than 12 follicles present in it which cause enlargement of the ovary.

Medical history: To diagnose PCOS doctors may check a patient's medical history like is there any person already having the same problem in the patient family.

Symptoms: The doctor may check all the signs and symptoms of that disease, for example, hirsutism, acne, alopecia, acanthosis, seborrhea, striae, acrochordons, infertility, fatigue, pelvic pain, mood changes, sleeping problems, irregular periods. The person with PCOS is more prone to mental health problems like depression, anxiety because it is a chronic disease with increase male hormone i.e. testosterone causing problems and this hormone during pregnancy having reported increasing the risk of neurodevelopmental disorders. They may also have hypertension, high cholesterol, heart attack, sleep problem, diabetes, and breast cancer.

The Rotterdam criteria for the diagnosis of PCOS: A group of scientific experts, in 2003, elaborated the diagnostic criteria to include the ultrasound images of polycystic ovaries as another diagnostic marker and if two out of three diagnostic criteria will were met and the same endocrinopathies were excluded (**Figure 4**). This is known as

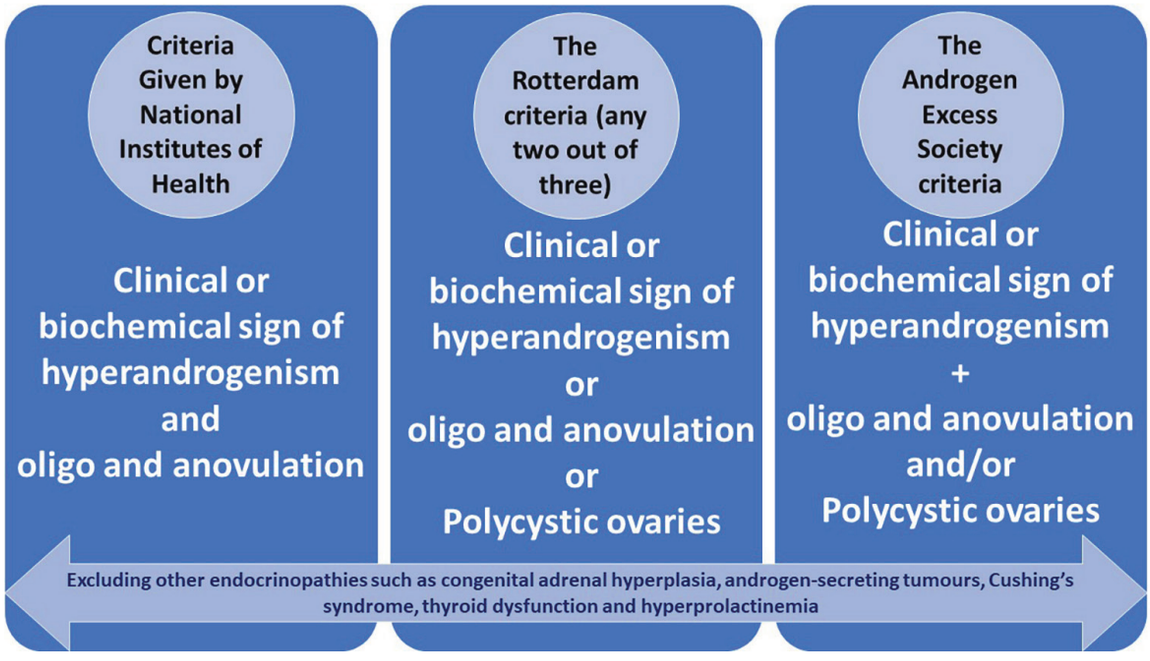

Figure 4.
The Rotterdam criteria for polycystic ovary syndrome.

Rotterdam criteria [83]. Slowly and steadily these criterions were accepted by various societies and commitees like European Society for Human Reproduction and Embryology (ESHRE), and the American Society for Reproductive Medicine (ASRM). Although this criteria is controversial and the Androgen Excess Society (AES) come up with a new set of diagnostic criteria in 2006 which are still the most commonly adopted criteria by different guidelines [84]. These guidelines are accepted and used by a wide group of obstetricians and gynecologists as well as other specialists.

Blood test: There are many tests done to check or to access the PCOS:

i. *Hormonal blood test:* These tests are used to check the level of hormone in our body. The most important hormonal test to check whether women may have hyperandrogenism is tested for androgens like testosterone and free androgen index. There are many other tests performed to detect the hormonal level, which may affect mensuration and ovulation. These tests include LH, FSH, Estrogen, sex hormone-binding globulin, dehydroepiandrosterone sulfate, androstenedione, thyroid-stimulating hormone, prolactin, hormones related adrenal function test example: 17-hydroxyprogesterone.

ii. *Another blood test:* As in PCOS; insulin resistance and weight are the main causes; therefore, the risk of cardiovascular disease and diabetes is necessary to be assessed. There are many tests perform to check these conditions. These tests include:

- Cholesterol
- Blood pressure
- Diabetes
- Glucose tolerance test etc.

Ultrasound: It is a type of imaging that is used to look at organs and structures inside the body. To identify any cyst, which is present in ovaries, and to check the size of ovaries whether they are enlarged or small, ultrasound of uterus, ovaries, and pelvis is suggested. Transvaginal ultrasound is a painless test with no radiations, it is performed on sexually active women otherwise abdominal scan can be done to check where is the ovaries are viewed from the outside through the stomach walls. In this type of ultrasound, a pen-shaped probe with an ultrasound sensor on the tip of the probe is used. This is helpful to see the clearer picture than an abdominal ultrasound.

8. Treatment

Unfortunately, PCOS cannot be cured, it can only manage by controlling the symptoms by doing exercise or by taking a healthy diet. It can be managed best to regulate their menstrual cycle and lower blood glucose level [65]. High fiber food like broccoli, cauliflower, sprouts, green and red pepper, olive oil, almonds, spinach, walnuts, fruits, etc. may help to reduce the impact of sugar in the body. Women with PCOS are majorly suffering from infertility so fertility drugs are given to aid anovulation [85]. Women with PCOS having hirsutism and acne problems are recommended to complete the

course of anti-androgen and do exercise for 45 minutes daily. Metformin is prescribed to lower the insulin level and it also aids in the regulation of the menstrual cycle and improves ovulation and pregnancy rates [86]. Metformin which is used for the treatment of diabetes for a long time is only a remaining member of the biguanide family. It will also help by improving the sensitivity of peripheral tissue against insulin [87]. It also inhibits hepatic gluconeogenesis [88, 89]. It also helps to reduce fatty acid oxidation. The dose of metformin is 500 to 2500 per day, an increase of dose may lead to worsening of side effects. Spironolactone is a steroid that acts as an antiandrogen, is chemically related to mineralocorticoid aldosterone. It blocks the synthesis of androgen to a particular extent [89, 90]. So, it is being used for the treatment of anovulation [91] and hyperandrogenism mainly for hirsutism [91, 92]. This drug in PCOS is limited [93], it has a good impact if used in a limited amount [94, 95]. One of the major factors for PCOS is the reduction of antioxidants and a rise in oxidative stress. Diabetes mellitus also leads to oxidative stress due to hyperglycemia. The supplementation with antioxidants has shown a positive result in the severity of diabetes alone and also improved insulin sensitivity in the case of PCOS. The intake of antioxidant or antioxidant containing food can be a good strategy to manage PCOS [96].

9. Significance of metformin in PCOS management

Metformin is a biguanide having the action for the reduction of glucose levels by increasing its utilization and also lowers down the androgen levels [97, 98]. The first insulin-sensitizing drug [99, 100] used to check the role of insulin resistance in PCOS is Metformin [101]. But according to research, Metformin alone is not a first-line treatment for the management of PCOS [102, 103]. Normal dosage for Metformin is 500–2500 mg/day [104]. According to research, a particular period of metformin dose of 1500 mg/day leads to a huge decline in the levels of circulating androgens and BMI [33]. It will help to regulate and improve the menstrual and help in reduction in circulating androgens levels and it will also help in reduction in body weight [105]. Thiazolidinediones are also used in the management of PCOS [106, 107]. Because it may improve the menstrual cycle and also help to reduce the androgen levels but with the help of this, there is no change in body weight. Metformin affects ovarian steroidogenesis [108]. The addition of metformin to IVF will increase the pregnancy outcome and also help to decrease the risk of ovarian hyperstimulation syndrome. It improves the oocyte quality in PCOS patients undergoing IVF [109]. Metformin also used to reduce the BMI because taking metformin with a low-calorie diet will reduce the fat. Metformin reduces the hyperandrogenism by effecting on ovaries and adrenal gland [110], which further leads to, suppresses their androgen levels and reduce the LH and increase the sex hormone-binding globulin.

Metformin i.e. Fortamet, Glucophage, etc. by taking Spironolactone will lower the level of sex hormone but it can cause birth defects. So, do not take it during pregnancy or if any plan to get pregnant [111]. Orlistat stops the body from digesting some fat in your food so improve your cholesterol level that's why it may take to get weight loss. In the case of fertility, Clomiphene encourages steps in the process that triggers ovulation [86, 107]. Hypothalamus secretes a gonadotropin-releasing hormone [32], which binds its receptor on secretory cells of the adenohypophysis [112]. As a result of GnRH, gonadotroph produces LH and FSH, which help to regulate development growth menstruation and reproduction of the body [113].

10. Infertility treatment

To start treatment in a stepwise fashion from least aggressive to more aggressive treatment, the use of clomiphene citrate and IVF protocol [32, 82].

Step one: Clomiphene treatment: The main indication is irregular or absent ovulation. PCOS patient is an excellent candidate for the use of clomiphene but almost 50% of the patient experiences the failure of clomiphene. Clomiphene citrate is the effective method of inducing ovulation and improving fertility and its adverse effects are multiple pregnancies and ovarian cyst. This resistance and failure in ovulation induction with clomiphene citrate are also thought to be related to chronic low-grade inflammation [114].

Step second: Gonadotropin treatment: Gonadotropins are the natural next step for ovulation induction. One characteristic of ovulation induction in PCOS patients is the slow response and the risk for ovarian hyperstimulation syndrome and cyst formation. The most used current step up is characterized by a low starting dose, which is maintained for a longer period then increased only of the small amount per week. This protocol is associated with a low incidence of severe OHSS and multiple pregnancies.

Step third: IVF: The goal of induction of ovulation is the development of one or few ovulatory follicles and the goal of stimulation in In vitro fertilization (IVF) cycles is to obtain multiple follicles but without in occurring in ovarian hyperstimulation syndrome [112, 113].

11. Conclusion

The polycystic ovarian syndrome is a common endocrinopathy, which is characterized by hyperandrogenism, insulin resistance, and abnormal gonadotropin secretions. PCOS disturbs both reproductive and metabolic functions. Their symptom varies from mild to severe like hirsutism, acne, alopecia, striae, irregular periods, and ultimately leads to infertility. PCOS is a complex multi genetic disorder so its pathogenesis is unknown. Stein and Leventhal discover it in 1935. They described infertile women with shinny ovaries, which is having multiple cysts in the size of pigeon eggs. High insulin resistance, bad dietary choices, weakened the immune system and many more are main factors that promote the PCOS. It cannot be diagnosed only based on symptoms, so blood tests are done to measure hormonal levels, ultrasound also is done to check the reproductive organs, and personal and family history is also useful for diagnosis purposes. Some hormonal levels are measured when considered to PCOS i.e. LH, FSH, DHEAS, Prolactin, testosterone, Progesterone, Androstenedione. Many proteins are involved in PCOS. It is a familial condition so genes play a major role in PCOS. Genes who are linked with PCOS are responsible for the production and metabolism of sex hormones or linked with an impaired insulin function. Genes involved in PCOS are DENND1A, SHBG, THADA, FBN3, LHCGR, and INSR, etc. Oral contraceptives are used to reduce the androgen and LH levels with improvement in hirsutism, acne, body weight, and also help to regulate the menstrual cycle. Metformin is the most effective insulin-sensitizing drug. Treatment for infertility includes clomiphene, laparoscopic ovarian drilling, and gonadotropins.

Authors' contributions

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