Review Article

Diagnosis and Treatment of Polycystic Ovary Syndrome (PCOS) - A Comparative Review

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is defined as polycystic ovary syndrome is a hormonal disorder that occurs in women of reproductive age. There are 4 possible phenotypes for a patient with PCOS. These phenotypes are ruled out based on 3 criteria. They are hyperandrogenism, anovulation and polycystic ovarian morphology. The key goal of the therapy in PCOS is the management of symptoms. Treatment options should be based on the patient's choice for contraception and pregnancy. Treatment focuses primarily on the treatment of infertility, regulating menstrual irregularities, reducing the symptoms of hyperandrogenism or treatment of obesity. Treatment primarily includes oral contraceptives, clomiphene citrate, cyproterone acetate, metformin, Flutamide, spironolactone, Finasteride, ketoconazole, steroids. Oral contraceptives are considered the first line of therapy in the treatment of PCOS. Risks include venous thromboembolism. Commonly preferred oral contraceptives include Clomiphene citrate, Cyproterone acetate, Drospirenone, Ethinylestradiol, norethindrone. Metformin has insulin-lowering effects by improving insulin sensitivity and, in turn, can decrease circulating androgen levels. it may also help reduce hirsutism although this may take several months and Metformin may not be as effective as other treatments for hirsutism. As the diagnosis and treatment are still unclear, every day newer therapeutic options have to be explored. Long term use of OCP should be monitored and follow up should be done. The patient should be counselled regarding PCOS and its complication which might occur in future. Early intervention can minimize complications and the patient can achieve a healthy lifestyle.

Keywords: Anovulation, Hirsutism, Hyperandrogenism, Oral contraceptives, Poly cystic ovary syndrome.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is defined as Polycystic ovary syndrome is a hormonal disorder that occurs in women of reproductive age[1]. This also affects girls in their adolescence. In 1721, an Italian medical scientist, Vallisneri described a married, infertile woman having ovaries of size as pigeon eggs and the ovaries were shiny with a white surface[2,3]. Later, in 1844, Chereau and Rokitansky described enlarged, polycystic ovaries encapsulated in a smooth capsule[3,4,5]. In 1935, Stein and Leventhal proposed a correlation of amenorrhea with polycystic ovaries and they have observed that there was a thickened ovarian capsule in those women[3,5,6]. Their study involved 7 women with common features i.e. disturbances in menstrual cycles, hirsutism and enlarged ovaries with multiple cysts. Following ovarian wedge resection, menstrual cycles were returned in all of the 7 patients and 2 of them became pregnant[3,5,7]. As this was the first successful study towards PCOS, this syndrome was named after the 2 physicians as "Stein-Leventhal syndrome".

Menstrual cycle and PCOS

The menstrual cycle refers to the maturation and release of an egg from the ovary. A typical cycle takes approximately 24-35 days. The menstrual cycle is ruled through hormone stages in the body which enhances and fall in a month-to-month pattern that continues throughout reproductive life. While the cycle is strolling easily the pituitary gland inside the base of the brain produces a hormone called follicle-stimulating hormone to prepare an egg for release FSH stimulates a fluid like a sac surrounding the egg to grow into a follicle about 2cm extensive. About 2 weeks before the period, while the egg is prepared, the pituitary gland produces the luteinizing hormone. This activates follicles to release one egg into the fallopian tube referred to as ovulation.

While that is occurring, ovaries secrete different hormones consisting of estrogen and progesterone to thicken the liner of the uterus and put together if for being pregnant. ovaries additionally produce a small number of androgens together with testosterone which is transformed into estrogen if the egg meets the sperm in the fallopian tube idea may additionally occur, the fertilized egg is swept via the tube closer to the uterus and implanted into the lining of the uterus if fertilization does not arise the levels of

estrogen and progesterone drop once more and the liner of endometrium comes away that is referred to as period.

PCOS

In a menstrual cycle, follicles develop and form eggs one of that's launched throughout ovulation. As soon as this manner is completed the follicles are supposed to break down and disappear. In PCOS, these follicles stop growing at about midway to adulthood and ovulation does no longer continue. These follicles end up as cysts which is commonly much less than 1cm and are organized across the ovary simply below the surface. On an ultrasound, the diagnosis of PCOS is shown if there are more than 12 follicles visible on one ovary. This cyst leads to a hormonal imbalance of an increased amount of testosterone. This can bring acne, facial body hair and irregular periods[8].

Irregular cycles and ovulatory dysfunction

Regular ovulatory cycle onset is likewise related to age at menarche. In individuals who start menses before 12 years, among 12 - thirteen years, and after 13 years of age, 50% of cycles are ovulatory through 12 months, three years, and 4.5 years, respectively. At age 15, greater than 50% of girls who are oligomenorrheic continue to be so at age 18. Overall, irregular cycles (> 35 or < 21 days) that hold for greater than years submit-menarche are probable to have oligo-anovulation, based totally on popular population information, with consideration wanted for an age of menarche. With growing gynecologic age, fewer girls revel in cycles exceeding 45 days[9].

Risk Factors

1) Family history of diabetes mellitus

2) Genetic influence: greater risk seen in monozygotic twins when compared to dizygotic twins.

3) History of weight gain

4) In epilepsy patients while using valproic acid most of the females suffer from irregular menses. To suppress this, an alternative drug is prescribed that is lamotrigine which reduces insulin and testosterone levels.

5) Number of factors that increases the risk of PCOS in children i.e., high birth weight in girls born to overweight women, low birth weight and congenital virilization.

Some factors that appear later in childhood are Premature pubarche, obesity syndrome, acanthosis nigricans, atypical central precocious puberty and metabolic syndrome[10].

Clinical Presentation

Ovarian hyperandrogenism is primarily due to defects in the intrinsic steroid synthesis of ovarian theca cells. Extra-ovarian components, like significant degrees of LH and insulin and low degrees of FSH, and intraovarian factors, such as the anti Müllerian chemical (AMH) and inhibin, may upgrade the hyperandrogenism state. Additionally, significant degrees of androgens are perceived as one of the potential reasons for PCOS insulin resistance[11].

Polycystic ovarian syndrome is characterized by clinical or biochemical hyperandrogenism, oligo-anovulation and polycystic morphology. Most common abnormalities involved in polycystic ovarian syndrome[12].

Table 1: Most Common Abnormalities in PCOS[12]

Abnormalities	Frequency
Hirsutism	85-90%
Infertility	73-75%
Abdominal obesity	30-70%
Metabolic syndrome	40%
Arterial hypertension	20%
Type 2 Diabetes mellitus	10%
Disturbed lipid metabolism	Unavailable

PCOS has metabolic implications like insulin resistance, dyslipidemia and type 2 diabetes mellitus. Moreover, ladies with PCOS additionally have a propensity for weight gain which compensate for these side effects. Cardiovascular risk factors like persistent irritation, oxidative pressure and disabled fibrinolysis are expanded and there is proof that cardiovascular infection (CVD) has a higher pervasiveness in these women. Affected ladies are bound to experience the ill effects of moderate to severe symptoms such as low confidence, negative self-perception and psychosexuality compared to healthy women. PCOS also negatively impacts women's ability to optimize a healthy lifestyle[12].

Diagnostic Criteria

PCOS is a diverse condition whose diagnosis depends on the clinical signs and symptoms of the disease. There were different criteria proposed and many changes were made to the existing criteria. In 1990, the first attempt to diagnose PCOS was made by the National Institute of Health (NIH) which included hyperandrogenism, ovarian dysfunction as the two criteria excluding any other conditions that mimic PCOS. 2 criteria must be satisfied for a patient to be diagnosed with PCOS according to these criteria. Later, in 2003, Rotterdam criteria by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) suggested the addition of the appearance of polycystic in the ovaries on the ultrasound. 2 out of 3 criteria must be satisfied[13]. Later, in 2006, Androgen excess and PCOS society suggested that diagnosis can be based on any of the 2 criteria i.e., hyperandrogenism with either ovarian dysfunction or polycystic ovarian morphology[14]. Later on, in 2012, NIH accepted Rotterdam's criteria for PCOS. All the criteria suggested the exclusion of other conditions such as hyperprolactinemia, non-classic congenital adrenal hyperplasia, and Cushing's syndrome which mimics PCOS[8].

There are 4 possible phenotypes for a patient with PCOS[13,15]. These phenotypes are ruled out based on 3

criteria. They are hyperandrogenism, anovulation, polycystic ovarian morphology.

Table 2: 4 possible phenotypes for a patient with PCOS

Phenotype	Type A	Type B	Type C	Type D
Hyperandrogenism	✓	✓	✓	
Anovulation	✓	✓		✓
Polycystic ovarian morphology	✓		✓	✓

Ovulatory dysfunction is assessed by the menstrual history of oligo/anovulation with bleeding intervals outside the normal interval (25-35 days), happening frequently at ≤ 21 days and/ or infrequently at ≥ 35 days[16]. Polycystic ovary morphology as defined by ESHRE/ASRM consensus criteria is as at least one ovary with ≥ 12 follicles of 2–9mm (between day 2-5 of a cycle) or ovarian volume > 10mL in the absence of a cyst or dominant follicle > 10 mm[17]. Clinical hyperandrogenism includes hirsutism, acne, and androgenic/ central alopecia[9].

Generally, the measure of hirsutism is evaluated outwardly utilizing the adjusted Ferriman-Gallwey (mFG) score. Nine spaces of the body (upper lip, jawline furthermore, neck, upper chest, upper midsection, lower mid-region, lower midsection or male shield, upper back, lower back, upper arms, furthermore, thighs) are reviewed each a score of 0 (no noticeable terminal hair) to 4 (terminal hair) what's more, added, with a potential complete score of 36. An absolute mFG score >3 is characterized as unusual body hair, and a score of at least 6 is huge hirsutism[18].

Treatment

The key goal of the therapy in PCOS is the management of symptoms. The therapy can be of two phases i.e. treatment of acute symptoms involving the treatment of menstrual irregularity and androgenic symptoms and the other is the treatment of chronic symptoms mainly focusing on treating infertility[19]. Treatment options should be based on the patient's choice for contraception and pregnancy[20]. Management of PCOS includes weight reduction, diet, exercise, bariatric surgery in obese individuals, ovulation induction, treating menstrual dysfunction and androgen-related symptoms[21]. Treatment focusses primarily on the treatment of infertility, regulating menstrual irregularities, reducing the symptoms of hyperandrogenism or treatment of obesity[22].

Table 3: Symptoms and suggested drugs

Symptoms	drugs
Ovulatory Dysfunction (Menstrual irregularity)	Oral contraceptives, progesterone withdrawal, lifestyle changes which includes maintaining a healthy diet and regular physical exercise, Metformin[19].
	Pregnancy desired: YES → First line: Clomiphene or letrozole; Second line: Metformin NO→ First line: Hormonal contraception, including the levonorgestrel-releasing intrauterine system Second line: Metformin[20].
	Oral contraceptives, Metformin, Troglitazone, rosiglitazone, Aromatase inhibitors (anastrozole and letrozole), Glucocorticoids (prednisone and dexamethasone), Gonadotropins[21].
	Metformin, Hormonal contraceptives, Clomiphene[22].
Insulin Sensitivity	Metformin, Myoinositol[19]. First line: Metformin[20, 22,] Metformin and thiazolidinediones[21]
Anti-androgens Hirsutism:	Hirsutism: Decreasing testosterone production Decreasing testosterone action Oral contraceptives Lifestyle modification/weight loss Metformin Plucking/shaving/electrolysis/laser[19]
	Pregnancy desired: YES → First line: Electrolysis and light- Hirsutism based therapies (effective for mild cases) NO→ First line: Hormonal contraception with or without antiandrogen therapy Second line: Spironolactone monotherapy, electrolysis, light-based therapies, eflornithine (Vaniqa), finasteride (Proscar) Third line: Metformin[20]
	Oral contraceptive pills: Ethinyl estradiol, norethindrone, desogestrel, norgestimate, cyproterone acetate, drospirenone, Eflornithine hydrochloride, direct hair removal through electrolysis or laser[21].
	Eflornithine[22].
Acne	Pregnancy desired: YES→ Topical creams (e.g., antibiotic, Acne benzoyl peroxide) NO→ First line: Hormonal contraception; topical creams, including benzoyl peroxide, tretinoin (Retin-A), adapalene (Differin), or antibiotic cream Second line: Spironolactone[20].
	OCPs and antiandrogens[21]
	Isotretinoin[22]
Alopecia	OCPs and androgen blockers, CPA, finasteride[21, 22]
General anti-androgens	Spironolactone, CPA, Flutamide, CPA+ Ethinyl estradiol[21] GnRH analogues, Ketoconazole, Steroids, Spironolactone, Flutamide[22]
Obesity	Lifestyle modification

Oral Contraceptives

Mechanism of action

Oral contraceptives are considered the first line of therapy in the treatment of PCOS. They act by promoting negative feedback on LH secretion resulting in a reduction of androgen synthesis from the ovary[23]. In general combination, drugs are mostly preferred. The principal mechanism is the prevention of ovulation they inhibit follicular development and prevent ovulation. Progestin negative feedback works at the hypothalamus to lower gonadotropin-releasing hormone which in flip will lower the secretion of follicle-stimulating hormone and decrease the secretion of luteinizing hormone. If the follicle isn't developing then there is an increase in estradiol levels. Progestin negative feedback and absence of estrogen, positive feedback on LH secretion will stop the mid-cycle LH surge with no follicle development will prevent the ovulation. Estrogen has to inhibit follicular development on the anterior pituitary it lowers the FSH secretion its simply not as distinguished as the progesterone impact. Every other mechanism, of motion, is progesterone ability to inhibit sperm from penetrating through the cervix[24].

Impact of OCP on carbohydrates and lipid metabolism, it was noticed that estrogens could decrease glucose tolerance and progestins, particularly more androgenic ones, could induce insulin resistance

With regards to carbohydrate metabolism, the results have incorporated improvement of insulin sensitivity and glucose tolerance. For lipids, we can see elevated levels of triglycerides, particularly with fewer androgenic pills; HDL cholesterol levels might increase with OCPs of low androgenicity furthermore, may decrease with pills of high androgenicity[25].

Benefits

The reasons to choose COCs are sustained by several pharmacological benefits: a decrease in LH pulsatile secretion, a reduction in total and free circulating testosterone, inhibition of 5 α-reductase enzyme activity, an increase in sex-hormone-binding globulin (SHBG) levels, diminishing free testosterone levels, an increase in insulin muscle sensitivity, menses regulation, elimination of the clinical indication of hyperandrogenism, and protection of the endometrium against neoplasms[26].

Risks

Few studies stated the use of oral contraceptives in PCOS. COC like Cyproterone acetate and Ethinyl estradiol has a risk of venous thromboembolism compared to other OCP and non-users of ocp[27].

The contraindications of oral contraceptive use are past or current thromboembolic complications, Cerebro or cardiovascular disorders, obesity (BMI over 30 kg/m2), pregnancy or suspected pregnancy – valvular heart disease, active hepatic disease, mammary or uterine cancer, reproductive tract bleeding of unknown etiology, estrogen-dependent tumors[22].

Commonly preferred oral contraceptives include Clomiphene citrate, Cyproterone acetate, Drospirenone, Ethinylestradiol, norethindrone[19-22]. Cyproterone acetate containing Oral contraceptives have shown greater anti-androgen activity than desogestrel and drospirenone in patients with long term usage than medium/short term usage patients[28]. In PCOS patients, if there are no contraindications to the combined hormonal contraceptives (CHCs), any CHC can be used, however, CHCs containing Ethinyl Estradiol should be preferred[29]. Estrogen–progestin combination therapy remains the predominant treatment for hirsutism and acne in PCOS[30]. The use of oral contraceptives is associated with adverse effects such as venous thromboembolism, stroke, myocardial infarction, (MI), atherosclerosis, breast cancer, cervical cancer, endometrial cancer, and ovarian cancer[31]. Systolic arterial hypertension is regarded as an adverse effect of COCs[32]. In women with PCOS, those who were taking COCs had a twofold increased risk of VTE (characterized by deep vein thrombosis and pulmonary embolism) and those not taking oral contraceptives had a 1.5-fold increased risk[33].

A Randomized cross-study was conducted in 200 participants in that 95 participants has discontinued and 14 participants have lost follow up based on diagnostic criteria they have screened 88 participants they have compared OCP of different types of estrogen and different types of progestins and they have concluded that OCP containing DSG, CPA, DRSP for 3 months does not show any difference in the quality of life compared to levonorgestrel. After 6 months participants treated with CPA has increased the score of QOL when compared with OCP containing levonorgestrel[34].

Metformin

Mechanism of Action

Metformin is the only member of the biguanide family that has been utilized for the treatment of diabetes for quite a while. It is the most generally utilized medication in T2DM. Metformin improves the sensitivity of peripheral tissues to insulin, which decrease the circling insulin levels. Metformin inhibits hepatic gluconeogenesis and it additionally builds the glucose uptake by peripheral tissues and diminishes fatty acid oxidation. Metformin positively affects the endothelium of adipose tissue autonomous of its activity on insulin and glucose levels[35]. Metformin turns on the adenosine monophosphate (AMP)-activated protein kinase pathway (AMPK), each in-vitro and in vivo, resulting in decreased glucose production and increase fatty acid oxidation in hepatocytes, skeletal muscle cells, and mouse ovarian tissue. The mechanism by which metformin turns on the AMPK is no longer clear; but, phosphorylation of threonine in AMPK is important for metformin's action[36].

Insulin stimulates ovarian theca cell androgen production and secretion and suppresses the hepatic production of sex

hormone-binding globulin. The increased intraovarian androgens disrupt folliculogenesis. Hyperinsulinemia may also straightforwardly cause premature follicular atresia and antral follicle arrest. The resulting anovulation prompts unopposed estrogen production and endometrial proliferation in women with PCOS, leading to an increased risk of endometrial hyperplasia.

IR has been shown to take an interest in the regenerative as well as metabolic irregularities related to PCOS. IR is defined as a decreased glucose reaction to a given measure of insulin and for the most part, results from the insulin receptor and post-receptor flagging. IR and secondary hyperinsulinemia influence around 65–70% of women with PCOS. Most of the women who were obese will further exhibit their insulin resistance[37].

Metformin has insulin-lowering effects by improving insulin sensitivity and, in turn, can decrease circulating androgen levels. In addition, it also plays a critical role in the treatment of PCOs, because women with PCOs are at an increased risk of insulin resistance[38]. Indeed, metformin improves insulin-mediated glucose disposal in women with PCOs[39]. Metformin reduces the circulating levels of many markers of atherosclerosis and subclinical chronic inflammation, suggesting that it may be beneficial in reducing the long-term risk of type 2 DM and CVD in women with PCOS, although long-term studies are lacking[36]. Metformin works best in overweight women with PCOS. However, it is less effective in women who are markedly obese. Its effects are enhanced by weight loss. the majority have shown that Metformin can make periods more regular and improve fertility in women with PCOS. The use of Metformin may also make weight loss easier. Finally, it may also help reduce hirsutism (unwanted hair growth) although this may take several months and Metformin may not be as effective as other treatments for hirsutism.

Side Effects

Mainly Nausea, Vomiting and vitamin B12 deficiency are seen, rarely lactic acidosis is observed.

Contraindicated in renal failure and liver diseases.

Treatment for Hirsutism

Excess testosterone production is predominantly ovarian and is resulting from each increased luteinizing hormone stimulating from the pituitary gland and the effect of hyperinsulinemia at the ovary. By reducing gonadotropin production. Overall hirsutism rating is stepped forward by using the usage of 2 or 3 generation oral contraceptives.

The above remedy will suppress testosterone levels. There are several androgens to be had in the market amongst them we can talk approximately spironolactone right here.

Spironolactone is an aldosterone antagonist it also has a testosterone receptor that reduces hirsutism score by 40% and it is effective when used alone

Dose: 50mg twice a day and can be increased up to 100mg twice a day it should be used for at least 6 to 12 months.

Other treatment options for hirsutism i.e., plucking/ shaving/Electrolysis/Laser

Many ladies have already used one or a mixture of these methods to govern hirsutism through time they save you for clinical evaluation. Amongst these methods plucking is typically avoided as its reason folliculitis, scaring in girls. Shaving is possibly to be the most inexpensive and handiest manner to dispose of undesirable hair but won't be perfect for some women

Electrolysis involves electrocoagulation of the hair follicle which can also or may not be permanent and usually does not result in scarring laser remedy of hirsutism includes selective thermal damage to the hair follicle whilst warding off surrounding tissue and therefore works satisfactorily in fair-skinned sufferers with darker unwanted hairs. Laser remedy might also lead to erythema, oedema, blistering and transient hypo or hyperpigmentation[19].

Acne

Acne is most commonly seen in PCOS patients. First-line medications are Hormonal contraceptives, Topical acne therapy Eg: Retinoids, Benzyl peroxide, or antibiotic cream Spironolactone is used as a second-line agent to treat acne[20].

Lifestyle Modification

Healthy lifestyle behaviour (Healthy eating and regular physical activity), is recommended in all PCOS women and those who have excess weight by doing this daily an individual will achieve or maintain a healthy weight and quality of life is improved.

Counselling should be done in all PCOS women because most of the women will experience symptoms like anxiety, depression and eating disorders counselling will improve their disease condition and can attain a healthy lifestyle.

A combination of diet and physical activity will reduce most of the symptoms of PCOS. In diet mostly prefer low glycemic index foods, millets, dry fruits are most commonly preferred whereas for physical activity intense exercise should be done or a minimum one hour of walking should be done in obese individuals.

CONCLUSION

Polycystic ovary syndrome is a common endocrinology disorder mostly affecting women. As the diagnosis and treatment are still unclear, every day newer therapeutic options have to be explored. Supportive treatment must be provided for hyperandrogenism symptoms such as hirsutism and acne, alopecia which are more prevalent in this disease. Long term use of OCP should be monitored and follow up should be done. The patient should be counselled regarding PCOS and its complication which might occur in future. Early intervention can minimize complications and the patient can achieve a healthy lifestyle.

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Authors Contributions

Harshini Kancherla and Gayathri Konduri designed the study and both were managed the literature searches and prepared the manuscript. Ramya Bala Prabha and Ramo Rao did the first part of the manuscript. All the authors read and approved the final manuscript.

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