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Review Article

Updated therapeutic approach in the management of Polycystic Ovary Syndrome (PCOS): A Review

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ABSTRACT: Polycystic ovary syndrome (PCOS) is a heterogeneous clinical entity that is defined as the association of hyperandrogenism with chronic an ovulation in women without specific underlying diseases of the adrenal or pituitary glands. PCOS is also associated with a metabolic disturbance with complex inter relation of obesity, insulin resistance and endocrine abnormalities remains unresolved. However, several studies link obesity, body fat distribution and nutritional habits with the hormonal and metabolic profiles of PCOS. Moreover, intervention studies have suggested that reducing weight and hyper insulinaemia either by diet alone or by a combination of diet with drugs improves hirsutism, fertility, hormonal and metabolic profiles of PCOS. In fact, the evaluation of nutritional factors in PCOS is helpful for the screening of metabolic abnormalities and the management of women with PCOS. A point of particular interest in the management of PCOS is that the choice of contraception remains difficult in these high cardiovascular risk women. The lack of prospective studies to evaluate long-term metabolic and cardiovascular tolerance necessitates care and the assessment of other hormonal possibilities

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INTRODUCTION

Polycystic ovary disorder (PCOS) is the most widely recognized endocrine issue in reproductive aged women, with the prevalence in the range of 5% and 15%, depending upon the diagnostic criteria applied [1-2]. PCOS as a disorder of oligo-amenorrhea, polycystic ovaries, anovulatory infertility, clinical and biochemical indications of hyperandrogenism, overweight or obesity, and insulin resistance [3].

PCOS is likewise connected with pancreatic β -cell brokenness, and variations from the norm that present a considerably expanded hazard for metabolic disorder and type 2 diabetes mellitus (T2DM). These reproductive and metabolic abnormalities from the norm are heritable, and female first-degree relatives are in danger for metabolic disorder and T2DM [4]. The primary causes related with it are:

- Insulin Resistance
- Elevated Androgens
- Reproductive problems including infertility and menstrual dysfunction [5]

Consequently, a woman to have PCOS if 2 out of 3 criteria is accomplished:

- Hyperandrogenism biochemical or clinical without non classical adrenal hyperplasia,
- Most ordinarily hirsutism, skin inflammation, crown design hair loss,
- Ovulatory dysfunction and morphological polycystic ovaries [6].

PCOS and infertility is clearly visible, in light of the fact that PCOS has a place with the most regular causative components of an ovulation and the last itself is in charge of about 40% of female sterility. The diagnosis of the PCOS requires the finding of "pearl line" in ultrasonography, event of early follicular stage (2-5 day of menstrual cycle), biochemical abnormalities including: abnormal state of luteinizing hormone (LH) (>10 IU/l), LH/FSH (follicle stimulating hormone) proportion > 2 , testosterone level above 2.5 mmol/l, androstendione > 10 mmol/l and free androgen list > 4 . The rejection of other endocrine infections, for example, congenital adrenal hyperplasia, hormone-producing adrenal or ovary tumors, cushing disorder or illness, prolactinoma and disorders of the thyroid organ is additionally essential [7].

There are three arrangements of criteria for conclusion of PCOS:

1. The 1990 National Institutes of Health agreement criteria,
2. The 2003 Rotterdam criteria, and
3. The 2006 Androgen Excess Society criteria.

The etiology of PCOS is unclear and conclusive clinical examinations are restricted by moral and strategic requirements. Because of the expanding pervasiveness of PCOS in India, there is a requirement for early finding and treatment that can mitigate the indications and counteract wellbeing related problems [8]. Many synthetic medications accessible for the powerful

treatment and the board, anyway their various reactions and surprising expense impact has driven an approach to look for plant-based remedies for the treatment of PCOS. So, there is dependably an inclination for the women to pursue alternative treatment for the management of PCOS [9].

The National Institutes of Health criteria incorporate patients with an ovulatory menses and clinical or biochemical proof of hyperandrogenism, with or without polycystic ovaries on ultrasonography (figure 1), in whom different conclusions (e.g., late-beginning congenital adrenal hyperplasia and thyroid infection) have been avoided. The Androgen Excess and PCOS Society guidelines likewise incorporate those patients who experience typical menses yet have biochemical or clinical hyperandrogenism and furthermore polycystic ovaries on ultrasonography [10].

Over the most recent five years, they had the chance to oversee 41 adolescent young girls with PCOS. There is a wide range of clinical articulations of PCOS in the pubertal period. Moreover, to the exemplary postmenarchal structure, PCOS may show after untimely adrenarche, adolescence or before menarche. A few investigations have shown an expanded danger of PCOS in teenagers from influenced families. Early insulin obstruction as well as hyperinsulinemia, especially in corpulent pubertal girls should flag the clinician's consideration. From their experience, long term sequelae of PCOS now present a test for pediatric endocrinologists to make an early analysis (in the puberty period) and to treat these young people both symptomatically and prophylactically [11-12].

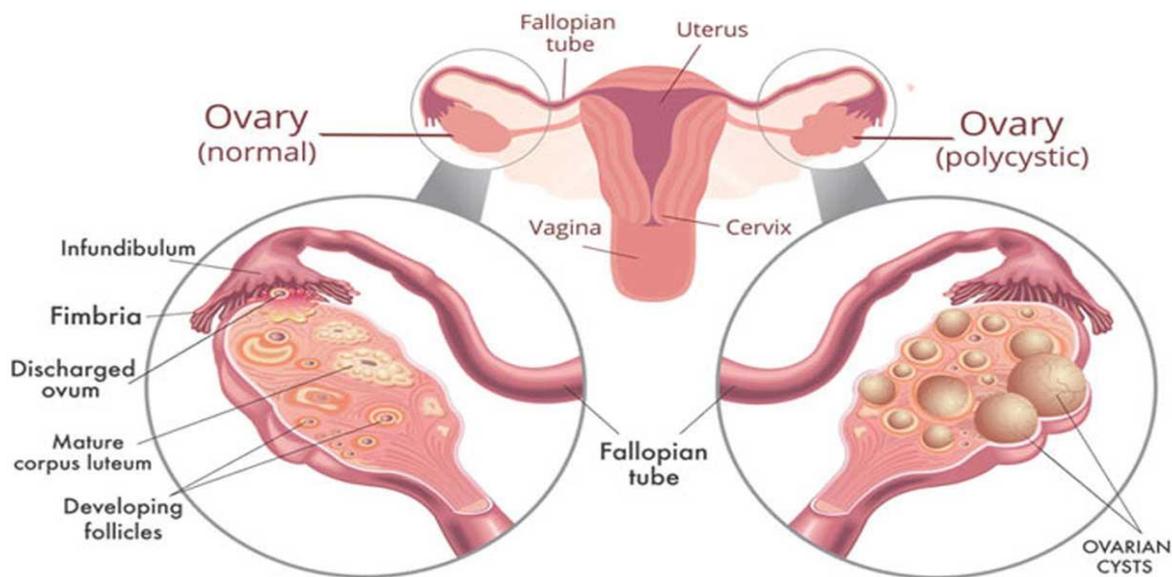


Figure 1: Development of PCOS

Signs and Symptoms

It includes irregular or no menstrual periods, heavy periods, put on weight and facial hair, skin break out, pelvic pain, trouble getting pregnant, and patches of thick, darker, smooth skin. Related with potential complications incorporates type-II diabetes, obesity, obstructive sleep apnea, coronary illness, mood disorders and acanthosis nigricans, immune system thyroiditis,

endometrial malignancy and breast cancer. Cysts might be detectable by ultrasound. Different conditions that produce comparative side effects incorporate adrenal hyperplasia, hypothyroidism and hyperprolactinemia. 5-10% of women of childbearing age are influenced by PCOS with $<50\%$ of women analyzed. PCOS is in charge of 70% of infertility issues in women who experience issues ovulating [13].

Pathophysiology of PCOS

The pathophysiological conditions result from the endocrine, metabolic and cardiovascular instruments. However, how much every mechanism adds to creating PCOS is as yet unknown. The endocrine part explicitly manages the unusual steroid union from ovaries and adrenals bringing about high androgen levels. An unseemly gonadotropin emission is related with the PCOS women displaying great type of PCOS, for example hyperandrogenaemia, polycystic ovaries, interminable anovulation, hirsutism and corpulence (figure 2).

Despite what might be expected, the non-classic structure is a progressively unpretentious condition typically found among lean ladies who show a portion of the above highlights related with PCOS. Despite the fact that androgens are obligate substrates for estrogen amalgamation, an overabundance of androgens appear to meddle with the procedure of follicular development. Contrasted and the follicular period of the typical menstrual cycle, ladies with PCOS show an excessively high luteinizing hormone (LH) emission with generally consistent low follicle invigorating hormone (FSH) discharge. The example of steroid secretion in polycystic ovary recommends a summed-up dysregulation of ovarian androgen discharge, which is additionally enlarged by insulin. PCOS is, in this way, portrayed by a metabolic issue in which hyperinsulinaemia and peripheral insulin resistance (IR) are central features.

The trademark unsettling influences of insulin emission and activity are considerably more noticeable in PCOS ladies with amenorrhoea or anovulatory menses than in similarly hyperandrogenic ladies with regular cycles [14]. Insulin and FSH synergistically affect estrogen generation in granulosa cells from an ovulatory PCOS, which isn't found in most of ovulatory patients. Insulin additionally appears to create a greater increase in androgen generation by theca cells separated from PCOS ladies than controls. Another normal clinical element of PCOS is corpulence. Roughly half of PCOS women are overweight or obese. The historical backdrop of the weight gain as often as possible goes before the beginning of oligomenorrhoea and hyperandrogenism, recommending a pathogenetic job of corpulence in the consequent improvement of the disorder [15].

Endothelial dysfunction has been seen in PCOS women. Chronic inflammatory markers, for example, TNF- α and Interleukin-6 (IL-6), advance IR and hyperandrogenism and along these lines have been involved in PCOS pathophysiology [16]. Women with PCOS additionally show lower high-thickness lipoprotein (HDL) levels, higher triglyceride and higher low-thickness lipoprotein (LDL) levels than age-and weight-coordinated control women, which is in charge of the expanded occurrence of hypertension, coronary illness and thrombosis. There is likewise an expanded commonness of endometrial hyperplasia and carcinoma in ladies with the PCOS [17-18].

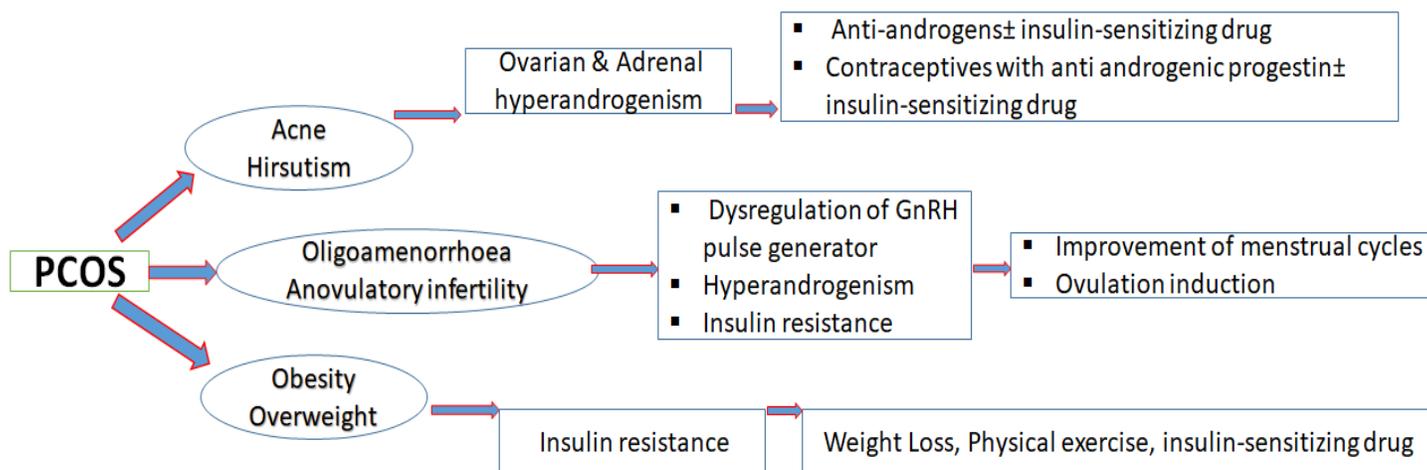


Figure 2: Pathophysiology of PCOS and the major health implications

Therapeutic Management

Treatment should concentrate on both the short-and long term reproductive, metabolic and mental features. It is critical to deliver mental factors at first to advance self-viability, status to change and manageability of way of life mediations just as to improve quality of life (QoL). Screening, appraisal and treatment of dejection and uneasiness are indispensable, and acknowledgment of different parts of passionate prosperity, including poor self-perception, sexual dysfunction, disorder eating and dietary issues — all increasingly basic among women with PCOS [19]. It should concentrate on help and training, and needs to unequivocally underline solid way of life, with focused therapeutic treatment as required.

Given the putative etiological job of IR and obesity in PCOS, prevention of weight increase is significant over the life expectancy.

Moreover, among the individuals who are as of now overweight, multidisciplinary way of life intercession went for improving IR and aiding weight the board is perceived as first line treatment for most women who are overweight [20]. Pharmacologic treatment for PCOS incorporates three choices: cyclic utilization of progestins to instigate withdrawal bleeding; utilization of estrogen-containing contraceptives (pills, transdermal fix, or vaginal ring) to diminish ovarian androgen creation and increment steroid hormone restricting globulin; and utilization of metformin to lower circulating insulin levels and decrease ovarian steroid hormone generation [21].

Oral Contraceptives and Progestational Agents

For many years, the main stay of oral contraceptives has been always effective in normalizing menstrual cycle. Oral contraceptive contains estrogen and progestin decrease androgen production and regulate estrogen for PCOS treatment and had a mechanism underlying the positive impact which comprises: a reduction LH secretion, inhibition of ovarian and adrenal androgen production [22]. The consequences of administration of these contraceptives is most in cases hirsutism, acne and irregular menses [23]. Oral contraceptives are considered as the first line treatment in women with PCOS.

Presently availability of newer formulations are generally safer than those of the past years. Progestational agents (synthetic analogs called Progestins) have many important functions, including regulation of the menstrual cycle, treatment of dysfunctional uterine bleeding, prevention of endometrial cancer and hyperplastic precursor lesions. Although recently their administration in PCOS is coming under great scrutiny, because of worsening in potential effect on insulin sensitivity [24].

Taking progestin for 10 to 14 days every one to two months can regulate menstrual cycle and protect against endometrial cancer. Progestin therapy doesn't improve androgen levels and won't prevent pregnancy.

Adolescents and perimenopausal women may require progestational agents for the treatment of dysfunctional uterine bleeding resulting from anovulatory cycles. These agents may also be used in women at risk for endometrial hyperplasia because of chronic unopposed estrogen stimulation. Progestin-only contraceptives can be used in women with contraindications to estrogen; however, efficacy requires rigorous compliance.

New progestins for use in combination oral contraceptive pills were specifically developed to reduce androgenic symptoms. It is unclear whether these progestins increase the risk of venous thromboembolic disease. Progestin-only emergency contraception offers a regimen that is more effective than combination oral contraceptive pills, with fewer reported side effects [25].

Oral Anti-Estrogen

It is used as a first line therapy to induce ovulation. It falls in the category of antiestrogens. This drug is a selective estrogen modulator receptor. The administration of clomiphene results in state of pseudo hypo-estrogenism which changes the frequency of GnRH pulses and results in elevation of LH secretion. The initial dose of clomiphene is the most often 50 mg per day administered orally for 5 subsequent days, usually starting from day 2-3 or day 3-5 from the beginning of the menstrual cycle.

According to some researcher, if the patients resistant to standard doses, then clomiphene therapy should be prolonged to 8 days or a standard drug dose should be increased to 150 mg or even 200 mg per day. The therapy results in an increased endogenous secretion of FSH, induction of follicle growth and appearance of ovulation in about 75-80% patients [26].

GnRH Analogs

GnRH agonists are the most commonly used group of drugs for the medical therapy of endometriosis. Prolonged administration of GnRH agonists suppresses gonadotropin secretion and secondarily suppresses endogenous ovarian steroidogenesis. The GnRH agonists bind to receptors for a prolonged time and induce protracted periods of downward regulation. GnRH agonists (e.g., Goserelin, Triptorelin, Buserelin and Leuprolide) are decapeptides, with similar structure to native GnRH and a great affinity to the GnRH receptors. The administration of GnRH agonists has been increased the probability of a single follicle development and to diminish the risk of multiple gravity or ovarian hyperstimulation syndrome [27].

In condition of permanent high level of GnRH, the synthesis and secretion of FSH and LH are impaired. This effect, known as "receptor desensitization" is clinically similar to hypothalamic amenorrhea, where pulsatory administration of GnRH agonists is very effective. In some of the studies, implementation of this scheme was associated with a high rate of ovulation (even up to 90%) and pregnancy (40%) so far, only one study has been conducted to compare the effectiveness of GnRH analogs and FSH. Its results showed the higher frequency of ovulation in the latter but similar pregnancy rates in both treatment groups.

Some authors prefer a combination of GnRH analogs with oral contraceptive drug, which stimulate SHBG synthesis and, therefore, cause additional effects, like lowering free androgen fraction or normalization of hypoestrogenism induced by GnRH analogs. Because of the risk of complications from the osseous system and high costs of therapy, the combined treatment with GnRH analogs and oral contraceptives should be limited only to severe forms of PCOS. GnRH analogs are sometimes applied as the initiation for human menopausal gonadotropin (HMG) therapy in the "short protocol" (14 days) [28].

Anti-Androgens

In the therapy of hyperandrogenism there are two main strategies: reduction of serum free androgens; and inhibition of androgen action in target tissues. Many women with PCOS having typical symptoms of hirsutism, acne do not have effective benefit from administering oral contraceptives therefore they may take advantages of anti-androgen treatment which is applied in combination therapy with oral contraceptives in adolescent girl patients with PCOS during puberty. The largest experience regarding drugs acting at the androgen receptor level is with cyproterone acetate and spironolactone. These compounds are not pure antiandrogens, because they interact with other steroid receptors and frequently cause mild but troublesome side effects.

Experience with flutamide is shorter. It is considered a pure antiandrogen and is consequently often preferred in experimental studies. Although flutamide is usually well tolerated, it carries the risk of rare but occasionally severe liver toxicity. The advantages of this combination is there is a hyperadditive synergism between these drugs and minimization of the risk of irregular menses [29-30].

Aromatase Inhibitors

Selective aromatase inhibitors such as anastrozole and letrozole are promising new ovulation-inducing agents. Letrozole inhibits estrogen production in the hypothalamus–pituitary axis, which implies an increase in gonadotropin-releasing hormone (GnRH) and FSH. It is believed that there exists a relative decrease in aromatase in women with PCOS, which reduces the production of follicles responsible for efficacious ovulation. To use this relative deficit, aromatase inhibitors were considered in order to provoke ovulation, because their selective action of blocking the peripheral passage of androgens to estrogens reduces the quantity of estrogens, thereby producing positive feedback in the pituitary, increasing FSH, and optimizing ovulation. The advantage of letrozole is that it avoids peripheral antiestrogenic effects on the endometrium while stimulating monofollicular growth.

Letrozole at 2.5–5 mg is administered for 5 days and may be accompanied by FSH (at the normal doses for PCOS patients) and human chorionic gonadotropin (HCG; 10,000 IU) when the follicle diameter reaches 18 mm in order to program the ovulation. However, in a prospective randomized trial comparing letrozole with clomiphene, pregnancy rates were similar [31].

Insulin-Sensitizing Agents

The particular anti-diabetes medications called metformin and pioglitazone may also be suggested for women with PCOS. These two medications are FDA-approved for diabetes treatment but may also improve ovulation and help make menstrual periods more regular, but this process can take four to six months. These insulin-sensitizing medications can help the body respond more readily to insulin, and better control glucose levels. Both metformin and pioglitazone can reduce the insulin resistance and high insulin levels that commonly occur with PCOS, and in turn, can reduce high androgen levels. As a result, also, while these medications can work well for some women, these medications don't help every woman.

While taking metformin or pioglitazone, the American College of Obstetricians and Gynecologists warns doctors that women who start insulin-sensitizing agents should consider using birth control pills if they are sexually active but don't want to become pregnant. The reason: Women who take these medications may start ovulating again. By reducing the high levels of androgens, these medications can also help take care of acne, excess hair growth, hair loss at the scalp, may promote easier weight loss, reduce high cholesterol levels, and may even reduce the risk for heart disease, too [32].

Life Style Modification In PCOS

It is well documented that modest weight reduction (5–14%) by means of energy limitation improves CVD hazard factors, hormonal profile, conceptive capacity in overweight women with PCOS [33]. Improvements incorporate decreases in stomach fat, blood glucose, blood lipids and IR. Enhancements in menstrual cyclicity, ovulation and fertility [34]. decreases in testosterone levels and free androgen record (FAI) and increments in sex-hormone restricting globulin (SHBG).

Studies have likewise appeared confidence, depression, HRQOL and anxiety in obese infertile women incorporating those with PCOS following way of life alteration or potentially energy restriction [35].

CONCLUSION

In the therapeutic management of patients with PCOS, the primary concern is to managing healthy lifestyle to optimize health and wellbeing so as to prevent obesity and manage excess weight when necessary. The PCOS treatment must be individualized and the decision of the medication for each situation should be based on the age of the patient, severity of symptom, need of treatment and comorbidities. In the light of recent studies not only traditional drugs (oral contraceptives, anti-estrogens, anti- androgens) but also newer treatment alternatives (anti-diabetes, GnRH agonists, aromatase inhibitors, dietary treatment,) alone or in combination are effective in some group of patients. The last one appears to be even the drug of choice.

Key factors related with PCOS were obesity, lack of physical activity, improper diet and stress. Women having conditions like PCOS, many menstrual cycles are anovulatory due to increase in the BMI. This reduction in weight can be done by increasing physical activities and regular treatment.

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