

# Polycystic Ovary Syndrome: An Update on Management Strategies

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## ABSTRACT

In the reproductive years of a female, she often comes up with a common disorder known as polycystic ovary syndrome also called as PCOS. In this disorder the level of androgen, male hormone, increases above the normal level that causes ovulatory dysfunction. Moreover, this disorder also causes severe metabolic anomalies, specifically weight gain and insulin resistance which is a well-known attribute of the pathophysiology of PCOS. PCOS leaves adverse impacts upon the ovarian cycle and fertility of women. This review paper encapsulates possible treatments present for PCOS in females by discussing current and potentially available options.

**Keywords:** Obesity, polycystic ovary syndrome, hirsutism, therapeutic approach.

## INTRODUCTION

Women of reproductive age often face issues regarding their reproductive cycle, one of the most well-known endocrinopathies is PCOS, polycystic ovary syndrome. The criteria set for the diagnosis of PCOS has basic aspects: identification of the specific morphology of polycystic ovaries (PCOM); hyperandrogenism which is characterized by the presence of excessive levels of a total of free testosterone (FT); and chronic anovulation and oligo amenorrhea that leads to ovarian dysfunction (OD). While diagnosing PCOS, it is important to exclude all androgen excess lead disorders, and these criteria fits accordingly based upon different phenotypes. The classification of diagnosis of the disease is usually defined based upon some of the criteria mentioned above, and if all the criteria are added then the phenotype is of classic nature. On the other hand, dysmetabolic attributes like insulin resistance, compensatory hyperinsulinemia, abnormal glucose intolerance condition, mild inflammation, lipid anomalies, and sudden weight gain are all clinically and scientifically proven evidence of the existence of PCOS disorder in classic phenotype patients. Moreover, the increase in body weight, which can often lead to obesity, leaves even more adverse impacts upon the body's natural hormonal balance and metabolic activities which in turn declines the sensitivity of the patient's body towards certain PCOS treatments available and implied worldwide.<sup>1</sup>

In recent years, professionals have extensively observed the dire need to not only improve the diagnosis criteria for PCOS but also its treatment strategies. A report from Expert Panel at NIH, in 2012, has enumerated a list of actions that proved helpful in understanding the identification and management of polycystic ovary syndrome by using specific markers for opting clinical and biological phenotype approach. The report has also advised for expanding the diagnostic technical criteria for the calculation of androgens circulating in the body and to deeply indulge the scientific efforts in finding the causes, predictors, and long-term impacts of PCOS along with patient's body requirements to cure this disorder effectively. In this review, contemporary approaches for the management of polycystic ovary syndrome are discussed. Elaboration of therapeutic approaches is extremely important and helpful for the correct diagnosis and treatment of PCOS.

**Management of Hyperandrogenism in PCOS:** The first key step in management of PCOS in females is the treatment of hyperandrogenism. It aims at adjusting the levels of hormones in the body. The therapeutic approach given for its treatment is as follows:

- **Treatment of Hyperandrogenemia:**

In recent years, the criteria for hyperandrogenemia diagnosis has updated a lot represented both by biochemical (TT blood levels) and clinical status. It has been found that assessment of androgen profile is far more effective in defining PCOS rather than the evaluation of TT alone. As a matter of fact, in 2009, a report of Androgen Excess & PCOS Society (AE-PCOS) has depicted findings, based upon data collected from 18 different studies, that approximately 60% of females suffering from PCOS had TT or FT blood levels above than normal range and hirsutism was found

only in less than a quarter of patients.<sup>2</sup> Therefore, in recent studies, it is made quite clear that even though TT or FT levels do participate in women's androgen pool as important factors, but the measurement of these factors alone does not lead towards accuracy. The fact here is that, a large number of weak or more potent androgens remain undetected which gives unsatisfactory results. Liquid chromatography and tandem mass spectrometry are in trend these days for measuring steroids. Based upon these tests it has been found that androgens levels, do not affect just ovaries alone rather they also impact adrenal glands, adipose tissues, and the skin where rich steroidogenesis is present responsible both for regulation and metabolism of these hormones.<sup>3</sup> Therefore, a combination of TT, free androgen index (FAI), 5 $\alpha$ -dihydrotestosterone (DHT), and  $\Delta$ 4-androstenedione ( $\Delta$ 4-A) are better in predicting hormonal imbalance, and adverse metabolic risks like insulin resistance and glucose intolerance.

Currently, the treatment for hyperandrogenemia and hirsutism (abnormal hair growth like men on chin, chest and back) encapsulates the process of reducing excessive production of androgens through the help of non-hormonal processes. In females, excessive androgen production becomes the reason behind the pathophysiological mechanism of hirsutism. An interesting fact here is, androgens are capable of producing in de novo in the hair follicles, therefore the androgen circulation does not necessarily account for the rise of hirsutism as its production can also be local and site-specific. Several studies have shown that hirsutism is one of the biggest developers of psychological problems. Typical treatment methods, specifically for hirsutism, includes estrogen-progestins, antiandrogens alone or in combination with ethinylestradiol, insulin sensitizer like metformin. Moreover, cosmetic measures are also often taken like epilation or depilatory methods.<sup>4</sup>

When it comes to hyperandrogenemia management the pharmacological approach is effective. For instance, Estrogen-progestin compounds are helpful in improving androgen levels, as well as they are cost-effective and safe to use. Their effectiveness can be understood by the ability of progestin to hamper the levels of luteinizing hormone (LH) which in turn suppresses the ovarian androgen production, and estrogen here increases the sex-hormone-binding globulin (SHBG) which declines the free bioavailability of androgens.<sup>5</sup> Moreover, these EPs also directly affect steroid synthesis by inducing a mediocre decline in adrenal androgens. Progestins are often known as anti-androgenic because they inhibit 5 $\alpha$ -reductase activity and are antagonizing to the properties of androgens. Some of the well-known drugs are drospirenone, cyproterone acetate, clormadinone acetate, dienogest, and third-generation progestins. However, the problem here is that how long the treatment should be continued is unclear, as the reports found holds the study of a maximum 6 to 12 months observation. Previous reports have depicted a success rate of 60 - 100% in reducing hirsutism.<sup>5</sup>

Antiandrogens besides EPs also provide a better option for improving hirsutism and hyperandrogenemia. The common antiandrogens used are 5 $\alpha$ -reductase inhibitors (finasteride) and

androgen receptor blockers (flutamide, spironolactone). Even though these compounds are found effective, but their dosage and use vary from country to country based upon their regulatory agencies. Flutamide, for instance, has been found negatively impacting liver both in adolescent and adult females. Importantly, it has been stated that these side effects can be tackled by administering low doses of this drug, and by this long term efficacy on hirsutism can be achieved. However, these drugs cannot be given to pregnant females due to the danger of feminization of male fetuses.<sup>6</sup> Impact of metformin, an insulin sensitizer, was observed on androgen levels. A systematic review and meta-analysis of controlled but randomized reports on thiazolidinediones, or metformin alone as well as in combination with Estrogen-Progestin or antiandrogens was carried out, it revealed that insulin sensitizers are not 100% effective and they only provide modest effects for hyperandrogenemia and limited impacts upon hirsutism concerning placebo. Therefore, this study leads to question the administration of metformin in these patients.<sup>7</sup> In general, the impacts of the above-mentioned compounds are found to be acceptable, reversible, and mild, with the existence of some exceptions.

**Therapeutic Approach for Ovarian Dysfunction and infertility: Oligo-amenorrhea and Oligo-Anovulation:** Diagnosis and treatment of OD and chronic anovulation differ in adolescents from adults, in the latter, these are cardinal features with PCOS and are easy to define but difficult in the former case.

• **Management of Menstrual Dysfunction in Adolescent Females with PCOS:**

In the recent years, the Pediatric Endocrine Society became successful in defining diagnostic criteria for PCOS in young females. According to them, excessive abnormal uterine bleeding (inappropriate for young age) which remains persistent for one to two years, presence of increased levels of TT that causes hyperandrogenism and hirsutism, and severe inflammatory acne vulgaris are combined attributes for diagnosis of PCOS. It is very difficult to prove anovulation in young age. It is advised to appropriately evaluate changes with time in girls instead of immediately jumping for medicines. Nevertheless, the visible signs in young girls, like excessive weight gain or obesity, severe acne, insulin resistance, and hyperinsulinemia which might be due to androgen's excessive level in blood, must not be ignored. Moreover, it has been found that insulin resistance and obesity can also alter and adversely affect theca and granulosa cell functioning.<sup>8</sup> Due to this dysfunction, excess insulin, weight gain, and hyperandrogenemia also get associated with chronic anovulation and ovarian dysfunction. Therefore, specific attention is needed, which might include both the use of EPs and management of comorbidities like weight control and metabolic alteration (insulin resistance handling). As per the report of Endocrine Society, it is advised to give EPs in late adolescent age, however, despite uncertainty about the duration of therapy, it has been found that long term use of EPs prevents developing of hyperandrogenism in the latter age of adulthood. Obesity has been often found as the leading cause of PCOS, therefore lifestyle management should also be introduced. Researches often link hormonal and metabolic abnormalities as the contributing factor for PCOS. As no evidence based on randomized, double-blind, placebo-control study is present, therefore, adolescents with this issue are treated with contraception EPs as the main therapeutic agent for PCOS. In some cases, metformin was also found helpful in normalizing the menstrual cycle, improvement in hyperandrogenemia and metabolic functions in both non-obese and obese females. In addition, this research has given some evidence that metformin is more effective in adolescents than in adults.<sup>9</sup>

• **Management of Menstrual Dysfunction in Adult Females with PCOS:**

Oligomenorrhea and amenorrhea are two menstrual dysfunctions that can be observed in almost 75 to 86% of adult females with PCOS. In these patients, both the androgen level as well as OD

are usually managed. Anovulatory infertility poses a biggest threat to women with PCOS who wants to conceive. From a clinical perspective, lifestyle intervention must be the priority for obese adult women with PCOS who is also facing insulin resistance. Several uncontrolled studies have depicted that, weight loss provides very promising results at the overall hormonal, and metabolic levels of PCOS. When it comes to pharmacological options, metformin and clomiphene citrate (CC) are in extensive use.<sup>10</sup>

• **Pharmacological Management of Infertility and Oligo-anovulation in Adults with PCOS:**

In the last two decades, many new protocols and techniques have been introduced, like assisted reproductive technologies (ARTs), that aided in increasing the pregnancy rates all across the globe. Due to PCOS, anovulatory infertility is common and therefore, for its treatment many drugs are in common use.

For instance, metformin is used for treating type II diabetes, therefore it is given to women with PCOS to improve insulin resistance and hyperinsulinemia by increasing SHBG synthesis. This in turn reduces circulating androgen level in the blood and free androgen bioavailability. Metformin leaves a combined effect upon theca and granulosa cell functions, thus it improves fertility in women who are hypo- or infertile with PCOS.<sup>11</sup> Metformin leaves an impact upon multiple sites like the liver, skeletal muscles, adipose tissues, endothelium, and ovaries. Moreover, glucose hepatic production is also suppressed by halting gluconeogenesis and increasing insulin mediates glucose uptake in multiple sites of the body. As metformin has found to leave direct impacts upon ovaries, thus, studies have shown that its long term use aids in improving menstrual cycle and ovulation rate in PCOS patients.<sup>12</sup>

Some factors that are required to assist in the maintenance of pregnancy and implantation have also been found supported by metformin, like insulin growth factor binding protein 1 and uterine artery blood flow rate and glycodeilin rate. A meta-analysis encapsulating 13 controlled randomized trials clearly confirmed that in females with PCOS balanced ratio of ovulation was achieved by metformin with an odds ratio of 3.9 in comparison to placebo. In another study it was found that metformin in comparison with placebo improved ovulation rate as OR= 2.1; 13RCTs, and pregnancy rate OR= 3.9; 6 RCTs but not live birth rate OR=1; 1.9RCTs. on the basis of this data, the widespread use of metformin for PCOS patients was favored to improve menses cycle alteration and ovulation.<sup>13</sup>

There is another agent which is in use since last 40 years as first line medical drug for ovulation induction, it is CC a selective estrogen receptor modulator (SERM). CC binds estradiol in the hypothalamus and pituitary to its receptors where it prevents the rise of negative feedback effects of estradiol and endogenous estrogens. As a result of this action, pulsatile gonadotropin-releasing hormone secretion is activated which increases follicle-stimulating hormone and LH secretion rate. With the rise in FH rate, follicular growth is also stimulated along with estradiol with the final mid cycle LH surge appearance and ovulation.<sup>14</sup> 50mg/day to 150mg/day, the CC is gradually increased and is administered on 2-5 day of menstrual cycle. If ovulation does not begin then CC administration is ceased temporarily. Through CC administration, if after 6 ovulatory cycles pregnancy is not attained then CC is considered a failure. Studies have shown its success rate with 65-86% ovulation rate, and 29-51% pregnancy rate after about 6 ovulation cycles.<sup>15</sup>

In the recent years, another range of drugs, that are aromatase inhibitors, have shown challenging status in treating infertility in PCOS females. For some time, this drug is well known for increasing fertility in infertile females suffering from PCOS by blocking the functionality of the hypothalamus and pituitary gland's ovarian functions. A recent randomized, double-blind trial has shown that letrozole, which is an aromatase inhibitor, is better in treating infertility in comparison to CC and has shown better pregnancy outcomes. Its impacts showed greater ratio of live births, and cumulative ovulation rates with no prominent difference

in groups with pregnancy loss and twin pregnancies. Based upon these findings, professionals stated that letrozole might will replace CC shortly.<sup>16</sup> However, some concerns do exist like, whether the efficacy of this drug is similar in overweight to normal weight females; its association with lifestyle intervention; inefficacy on androgens; the presence or absence of letrozole resistance, and the potential risk it poses to the fetus.

**Obesity and PCOS: Treatment Strategies:** Obesity is increasing worldwide like an epidemic. This issue encapsulating each and everyone despite their age and gender. For instance, In the USA, the BMI for young people between the age between 2 to 19 is quite high and the percentage often exceeds 30%. A retrospective study in the same country showed clearly that the risk of developing PCOS drastically increased by 75% in obese patients when they reach their late adolescence. It was found that over weight was one way or another, became the reason by menstrual cycle disturbance and ovulatory disorders as it aids in the rise of androgen levels by triggering their production sites. Longitudinal studies have shown that androgen serum levels might pool up and shows in the late adolescent age where it adds up to develop PCOS and the risks rises particularly with increased body weight. Moreover, neuroendocrine variations, specifically at the hypothalamus-pituitary level, can cause changes in sex hormone ratio like ample substrate aromatization in adipose tissue (fat tissue) which in turn causes estrogenization at the early age and excessive adrenal androgen increase. When the insulin resistance in adipose tissues increases, the level of insulin rises in the body, and it becomes responsible for anomalies as insulin can trigger adrenal steroidogenesis.<sup>17</sup> Collectively, these findings summarized that obesity during adolescence does not only alters insulin levels, but also become the reason of developing PCOS phenotype which become severe in adult women, if condition is not treated.

On the basis of these findings, treatment of metformin for insulin and antiobesity drugs or bariatric surgery for obesity might be the first choice in such patients. Besides, an Australian research has also emphasized upon the need of lifestyle intervention and assessment of emotional health, which must be treated if necessary along with other associated psychological disorders. Because these disorders are often linked with PCOS.

Evidence has been found in favor of metformin for achieving significant weight loss with doses higher than 2000 mg/day. A study was conducted encapsulating long term lifestyle intervention of patients who are obese with POS and were treated with bariatric surgery. Follow up period was of 20.5 ± 12.5 months, females were of average 65 years of age, empowered, obese and with PCOS. Systematic lifestyle intervention was used. At the end of the study, it was found that 16% of these females had persistent severe PCOS phenotype, 47% showed partial improvement with minor recovery in blood androgen levels and ovarian dysfunction, and 38% of these females showed full recovery from PCOS with normal androgen level in the blood, normal menstrual cycle and ovarian functions and hirsutism below score 8. Interestingly, the rate of weight loss was almost alike in 3 different subgroups and BMI changes values were: -4.7 ± 2.8, -5.9 ± 3.2, and -5.5 ± 2.4, respectively. These results should be copied, but nonetheless they provide surety about improvement of PCOS and endocrine disorders by losing weight.<sup>18</sup>

Studies showed much more promising results in which women with PCOS underwent bariatric surgery for weight loss.<sup>19</sup> In fact, a metaanalysis of 13 studies including 2000 patients with PCOS has provided results that confirmed the benefits of weight loss on PCOS in excessively overweight females. Out of these, the most promising research showed that after the period of 1 year and sustained drop in weight BMI decreased from 46.3 to 34, and level of PCOS declined from 46% preoperatively to 7% with 12 months follow up. Interestingly, studies also found that menstrual abnormalities drop down from 56% to 8%, hirsutism declined from 67% to 39%, and infertility decreased from 18.2% to 4.3%. On the basis of these evidences, it was demonstrated that weight loss in comparison to initial weight do significantly impact the PCOS

characteristics adversely along with infertility. These results, can therefore in focusing on weight gain to encourage the improvement in PCOS cases, which can also pave way for finding out more pathophysiological and clinical mechanisms for curing this disease.

## CONCLUSION

Even though obvious differences are found in adolescence and adult women suffering from PCOS, nonetheless multiple therapeutic strategies are almost similar for both of them to correct major biochemical and clinical issues of PCOS. Every physician who is treating her PCOS patient must be able to select the best therapeutic option in association with the clinical and biochemical severity of disease and possible chances of attaining pregnancy. Obesity or excessive weight should be given specific attention. Pharmacological therapy has shown more promising results in cases where the patient is obese and is having PCOS as well. However, for certain PCOS-related issues like hirsutism, pharmacological therapy is not the only option. Epilatory and depilatory therapies including laser are also quite helpful in the latter case. On the contrary, these methods are not for ovarian stimulation with gonadotropins, or for assisted fertilization aid including ARTs. As these issues are complex, professional intervention and dedication with deep study of the patient's condition and availability of options, are imperative before initiating any specific treatment.

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