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Veritable evaluation and inspection of PCOS and its apropos medicaments

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Polycystic Ovary Syndrome (PCOS) is a vastly familial, prevalent yet complicated endocrine disorder seen in 5 to 15% of premenopausal women. An estimated one in five ~ 20% Indian women suffer from PCOS. In India, PCOS is a tabooed disorder; If neglected, the condition can prove fatal. However, the past decade has seen the changing discourse in India. PCOS negatively affects reproduction, general health, sexual health, and quality of life. Genetic predisposition of hormonal and non-hormonal factors influence ovary functioning and are responsible for the onset of the syndrome. Hormonal imbalance, metabolic abnormality, and insulin resistance are characteristic features that significantly increase the risk of anovulatory infertility, type 2 diabetes, and cardiovascular diseases. The underlying cause of the path physiology of PCOS is still under the radar, but the derangement of the hypothalamic-pituitary-ovarian axis could be the sweeping reason for the same. PCOS management should address on healthy lifestyle with symptomatic medical therapy and psychological bearing with special emphasis on far reaching side effects and long-term metabolic consequences This review article gives a comprehensive overview of PCOS and the morbidities hooked up with it. It has a notable emphasis on the PCOS guidelines, diagnosis, non-pharmacological, and pharmacological treatments.

Keywords: Anovulatory infertility, Hyper-and rogenemia, Hypothalamic-pituitary-ovarian axis, Menstrual irregularity, Psychological trauma

Introduction

Although PCOS was described in 1935, even today there is lack of awareness regarding the condition in India and it often goes undetected for several years. It is estimated that this health condition affects approximately 10 million women globally. In India, one in every 10 women is diagnosed with polycystic ovary syndrome (PCOS), a common endocrinal system disorder among women of reproductive age, as observed by the PCOS Society. And out of every 10 women diagnosed with PCOS, six are teenage girls. As per the study conducted by department of endocrinology and metabolism, AIIMS, it was reported that about 20-25 per cent of Indian women of childbearing age are afflicted by PCOS. While 60 per cent of women with PCOS are obese, 35-50 per cent suffer from fatty liver.

Stein-Leventhal Syndrome or PCOS has emanated its name due to the contribution by the late American gynecologists: Irving F. Stein, Sr., and Michael Leo Leventhal in 1935. They concluded that one of the reasons for the onset of syndrome was the high serum concentrations of luteinizing hormone (LH) to follicle-stimulating hormone (FSH). PCOS hinge-in roughly 75% of premenopausal women who agonize with infertility due to anovulation[1]. The intricacies originate from syndrome heterogeneity in its clinical presentation and laboratory investigation. Polycystic ovary Syndromeis phenotypically represented as an enlarged ovary with string-of-pearl like appearance and clinically represented as obesity, hyperandrogenism, menstrual cycle disturbance, insulin resistance, and infertility. When left untreated, these septic women have potential risk for metabolic and cardiovascular diseases and also bear psychological intrusions and low self-esteem (Table 1). The economic outlay of PCOS is significantly huge due to its presentation heterogeneity. The annual expenditure of the US is around 4 billion dollars and > 800 million dollars is spent by Australians for treating its various morbidities, including hirsutism, infertility, and diabetes mellitus[2,3]. This review article aims to provide an overview of the effects of PCOS in the premenopausal women, focusing largely on the PCOS genesis, diagnosis and evolving nonpharmacological and pharmacological interventions in its management.

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Hypothalamus-pituitary-ovarian axis

A palpitate GnRH stimulus maintains the gonadotrophic synthesis and secretion in the ovulatory cycle. The frequency and the amplitude of GnRH pulses determine the secretion of pituitary gonadotrophs (LH and FSH). The increase in GnRH frequency amid the follicular phase backs LH synthesis before LH surge. Succeeding ovulation, luteal steroids delay GnRH pulses, advancing FSH synthesis. Inconsistent gonadotropin secretion midst ovulatory cycles fits in frequency changes of gonadotroph GnRH stimulation mechanism. Figure 1A and B describes hypothalamic-pituitary-gonadal axis in a normal female and how endocrine abnormalities in women alters it, culminating in PCOS conditions[4,5]. Uprear concentrations of LH (observed in 40% of women), testosterone, androstenedione changes the hormonal milieu of ovary and this upheaval is associated with low or standard concentrations of follicle-stimulating hormone (FSH). In PCOS females, persistently rapid GnRH pulses favor synthesis of LH, hyperandrogenism, and damaged follicular maturation. This in turn, leads to an increase in androgen production by the theca cells within the ovary, which further aromatizes to estrogen[6,7]. This hormonal imbalance of estrogen, androgen, LH in combination with insulin resistance are the key players in shaping up PCOS.

Is PCOS a genetic disease?

The interpretation for the diverse biological and biochemical variability in PCOS is the reciprocity between the environmental components with a small number of anticipated causative genes. Studies prove that genetic and epigenetic changes in PCOS development lead to female infertility. Nonetheless, the nature of the genes remains obscure. The notion that

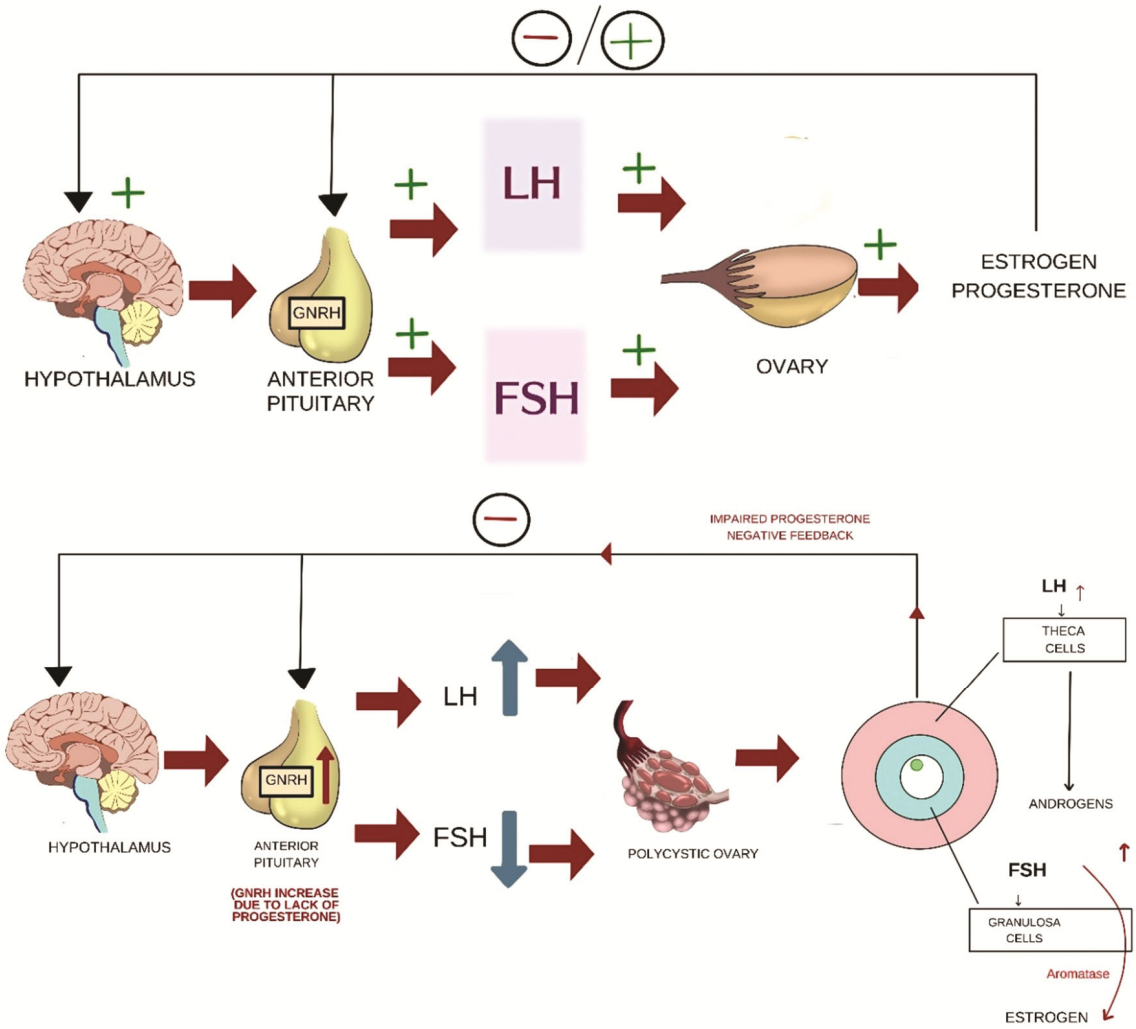

Fig. 1 — (A) HPG axis normal; and (B) Deranged HPG axis in PCOS

PCOS has a genetic component was first introduced in the literature more than 50 years ago[8,9]. Hayes *et al.* emphasized the increased likelihood of insulin resistance (IR) associated with genes such as INSIG2 and MC4R[10]. Cardinal characteristic of PCOS is steroidogenic abnormalities, and the predominant contribution of PCOS development comes from the variation in hormone levels created by increased androgens and insulin combination. Genes implicated in the functioning of HPO axis, like LHCGR, FSHR, and FSHB, have been identified as candidate genes in the pathophysiology of PCOS. PCOS-associated gene identification shows their involvement in metabolic/ androgen biosynthetic pathways. For instance, the ghrelin gene actively functions in appetite suppression, active in along with follistatin impairs stimulation of FSH synthesis and steroid synthesis gene, CYP11A, coding for P450 cholesterol side-chain cleavage and follistatin[11-12].

Pathophysiology

PCOS is a heterogeneous disease involving the interplay of rampant ovarian steroidogenesis, aberrant insulin signaling, extreme oxidative stress, and genetic factors. Figure 2A explains the pathophysiology of PCOS according to several hypotheses. According to the old school, the prime cause for PCOS development is intrauterine androgen. However, research shows no connection between excessive prenatal androgen exposure and PCOS development in adolescent girls[13]. PCOS-suffering women have a high frequency of GnRH pulses, owing to intrinsic activation of steroidogenesis[14-17]. It stimulates the theca cells to produce androgen and escalating estrogen secretion due to negative feedback decreases FSH secretion. Thus, there is concomitant decreases in FSH levels with increasing LH levels. This change in the hormonal milieu further affects the granulosa cells producing four times higher anti-mullerian hormone when compared to healthy individuals that drastically regulates the interim development of follicles[17]. The augmented makeover of ovarian stroma with primordial follicle transition to preantral and small antral follicles in the vicinity of a nonconforming environment with increased LH, insulin, androgen, and AMH levels and inadequate FSH concentrations structures the classic cystic 'string of pearl' morphology of PCOS[18,19]. Additionally, apart from mitochondrial dysfunction, oxidative stress induces insulin resistance and increased production of androgens by decreasing SHBG (sex hormone binding globulin) in patients with PCOS[19,20].

Diagnosis

In the early days, ultrasonographic findings alone were sufficient to analyze the condition and confirm the disorder as "polycystic ovary" (PCO) or polycystic ovarian disease (PCOD). But such terms entirely disregarded the conventional endocrine features. Based on histology, the sweeping diagnostic observable features of PCO are bilateral enlargement, thickening of ovarian capsule, multiple follicular cysts (usually ranging in size between 2-8 mm in diameter), and an increased amount of stroma[21]. The whole ovarian hypertrophy with thickened capsules and an increased number of subcapsular follicle cysts is another possible representation. Adams and colleagues illustrated PCOS as the presence of either multiple cysts (ten or more) from 2-8 mm in diameter distributed evenly around the ovarian periphery with an increased amount of stroma, or (less commonly) multiple small cysts 2-4 mm in diameter distributed throughout abundant stroma (Fig. 2B)[22]. Although the presence of polycystic

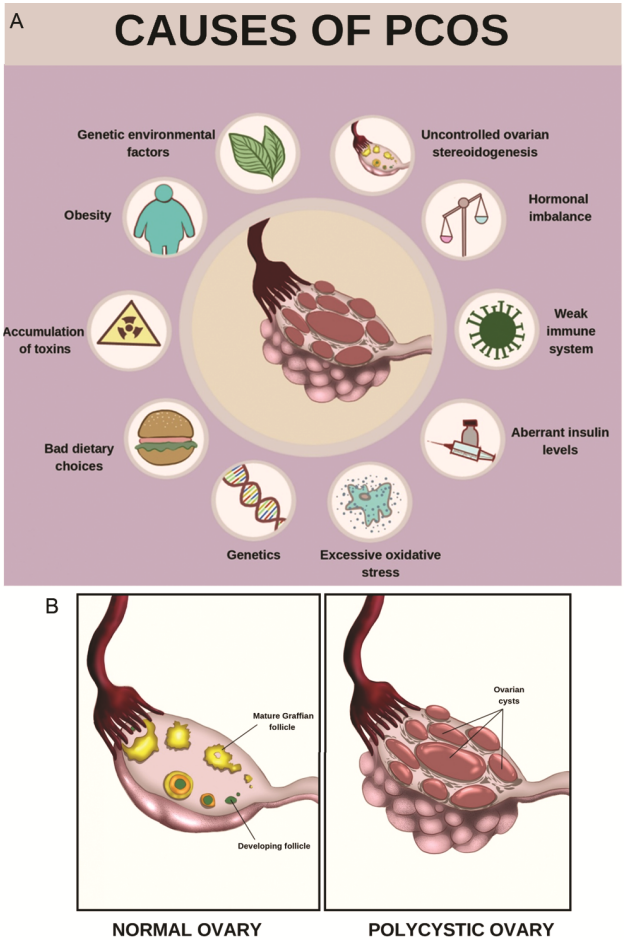

Fig. 2 — (A) Pathophysiology of PCOS; and (B) Diagrammatic representation of normal and PCOS ovary

ovaries is mostly seen in PCOS women, it may also develop in women with other disorders like Congenital Adrenal Hyperplasia (CAH), Cushing's Syndrome, virilising tumours and even extend to healthy women. Thus there seems to be a lack of uniformly acknowledged diagnostic convention. The international consensus revision on the PCOS clinical criterion was held at a workshop (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004) and again at the 2006 Androgen Excess & PCOS (AE-PCOS) Society. They were more elaborate than the diagnostic criteria recommended in the National Institutes of Health-sponsored meeting in 1990 (Fig. 3). It profiles women with hirsutism, hyperandrogenemia, and an ovulation to increased follicle number and ovarian volume. The most recent NIH-sponsored evidence-based methodology workshop on PCOS held in 2012 had an independent panel of experts that recommended PCOM as a diagnostic criterion for PCOS which is still debatable as a diagnostic classification for PCOS. Besides, it also inludedoligo-ovulation and biochemical parameters like hyperandrogenism, and exclusion of other aetiologies notably, Congenital Adrenal Hyperplasia (CAH) and Cushing's Syndrome[14,23]. However, the panel considered the use of multiform criteria perplexing, further obstructing the progress in understanding of PCOS. Also it is interesting to note that despite obesity and insulin resistance being cardinal to PCOS, they are not included in any of the guidelines.

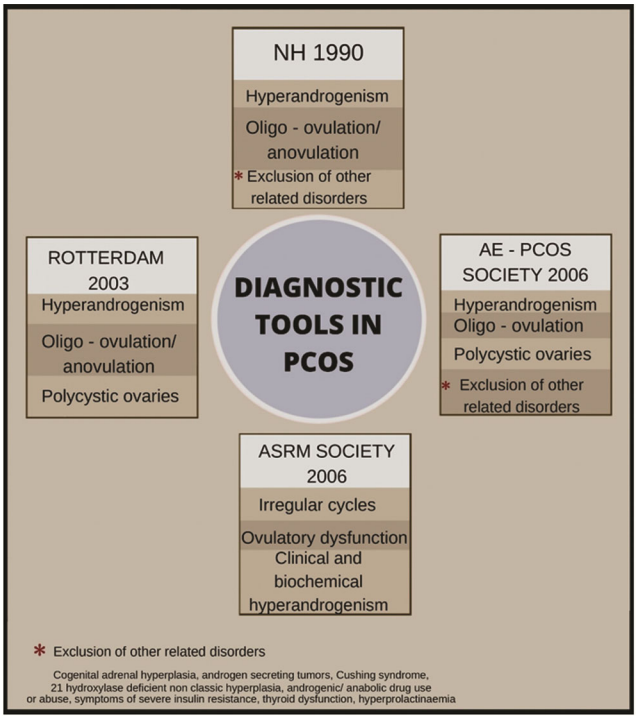

Fig. 3 — Diagnostic tools in PCOS

Morbidities associated with PCOS

Figure 4 illustrates various morbidities associated with the PCOS like obesity, hyperandrogenism, insulin resistance, infertility, cardiovascular diseases and metabolic alterations.

Obesity

Obesity is the most prominent contributor in the metabolic expression of PCOS patients. Girls who suffer from obesity at a younger age have higher chances of developing PCOS and associated complications like hirsutism and hyerandrogenemia. According to research, the excessive adipose deposition of body tissues leads to hormonal imbalance. Thus, it affects the reproductive and metabolic health aspects of women putting them at risk for type 2 diabetes mellitus (DM2), impaired glucose tolerance (IGT) and Cardiovasculardiseases[24,25]. This makes obesity as a potential target and should be the first line of treatment for PCOS.

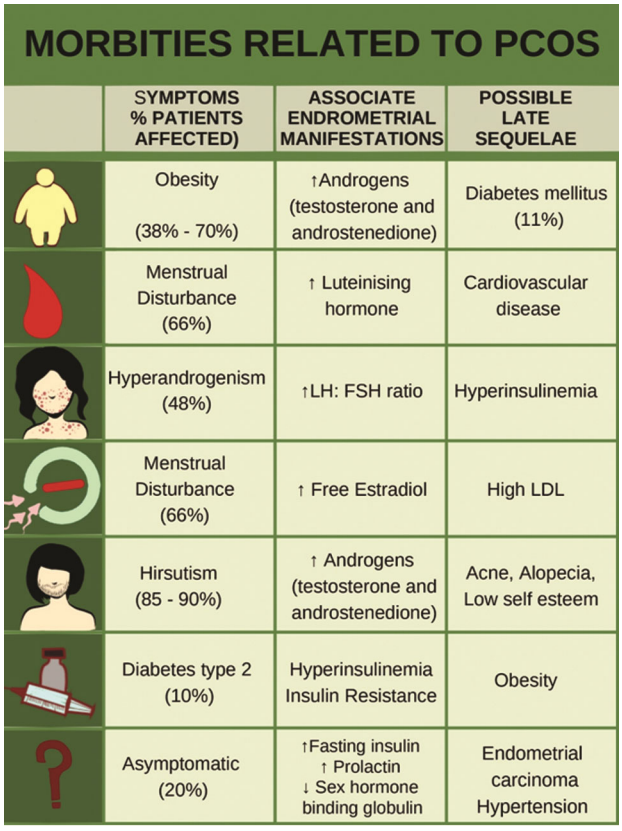

Fig. 4 — Morbidities related to PCOS

Hyperandrogenism

Synergistic effects of elevated levels of luteinizing hormone and insulin in women suffering from PCOS commands the theca cells of the ovary to synthesize an excessive amount of androgens. The ratio of the LH to FSH is high as the ovaries favor the transcription of the beta unit of LH rather than the beta unit of FSH. It further undermines ovarian follicle development. Clinical hyperandrogenism essentially comprises of hirsutism, acne, and male pattern alopecia[15].

Insulin resistance

Insulin Resistance is a pathogenic factor leading to increased metabolic disturbances in 85% of women with PCOS and specifically in obese (95%) as compared to lean (65%)[16]. Increased insulin levels coupled with high levels of LH activates the arrest of follicular growth, which influences the gonadotropin-releasing hormone pulse secretion pattern and also enhances ovarian androgen production in women with PCOS[17]. It is also one of the contributing factors to nonalcoholic fatty liver disease (NAFLD), prevalent in women with PCOS[22].

Infertility

PCOS affected women may have decreased fertility as compared to PCOS unaffected women due to endocrine and reproductive abnormalities that affect ovarian quality and function. PCOS accounts for 90% to 95% of women with anovulatory infertility, however, 60% of women with PCOS are fertile, although time to conceive is often increased. Obesity is more pronounced in women presenting PCOS and independently exacerbates infertility and puts them at a greater risk of miscarriage[18].

Cardiovascular diseases

There is an elevated risk of cardiovascular diseases in PCOS women owing to obesity, dyslipidemia and diabetes. Several studies indicate an increased arterial stiffness and carotid artery thickness associated with PCOS[24]. Evaluations show that PCOS affected women are seven times more likely to develop myocardial infarction as compared to other women. It has been seen that 65% of deaths due to CVD involve patients with IGT, DM2 and who are largely obese. These studies are not universal and further research is needed to study minute relationship between cardiovascular diseases and PCOS.

Cancer

With unopposed estrogen elevations and prolonged anovulation of more than 3 months, endometrial hyperplasia is seen in women with PCOS. Obesity, insulin resistance, diabetes and hypertension further exert their action on endometrium lining and increase the risk of endometrial carcinoma three fold[24,25]. There are also concerns about the likelihood of ovarian cancer in patients taking medication for anovulation and undergoing multifollicular ovulation.

Quality of life

PCOS becomes perceptible in women at a reproductive age when complications start in forming a family. PCOS has gloomy effects as physical appearance takes a heavy toll on the mind. Consequently, it creates self-doubt and anxiety, which indirectly affect the fertility rate in women. It influences the daily routine and life quality, including sleep disorders, daily fatigue, becoming disinterested in everyday chores, and much more[15,20]. Depression and anxiety are the most observed symptoms in women with PCOS. A fourfold increase in the prevalence of depressive symptoms has been recorded in PCOS patients as compared to normal individuals.

Treatment

Till date, no drugs have been developed to cure PCOS but targeted medications are available to relieve the symptomatic and clinical presentation associated with it. The design of the treatment plans should not only eradicate the symptoms but also inhibit the development of long-term complications. Thus the treatment goals revolve around remodelling anovulation, inhibiting the action of androgen on target tissues, and reducing insulin resistance (Fig. 5)

Lifestyle changes, physical exercise and weight loss

Excessive weight can influence the hormonal and reproductive health of women. Incorporating exercises and an energy-restricted diet are predominant parts of the management of obesity in women with PCOS. Evidence suggests that, female fertility significantly decreases with a BMI >30-32 kg/m^2 and regulation of body weight can balance the menstrual cycle, restore ovulation and improve fertility[20]. Lifestyle modifications are economical, convenient first-line treatments in overweight women with PCOS. As per studies, weight loss as little as 5% to 10% has noteworthy clinical benefits and has positive psychological bearings. A moderate energy restricted diet (500 to 1000 kcal/day) with increased fiber intake, low fat content and moderate protein intake reduces body weight by 7% to 10% over a period of 6 to 12 months. Structured exercise for bare minimum 30 min/day and incidental exercise therapy

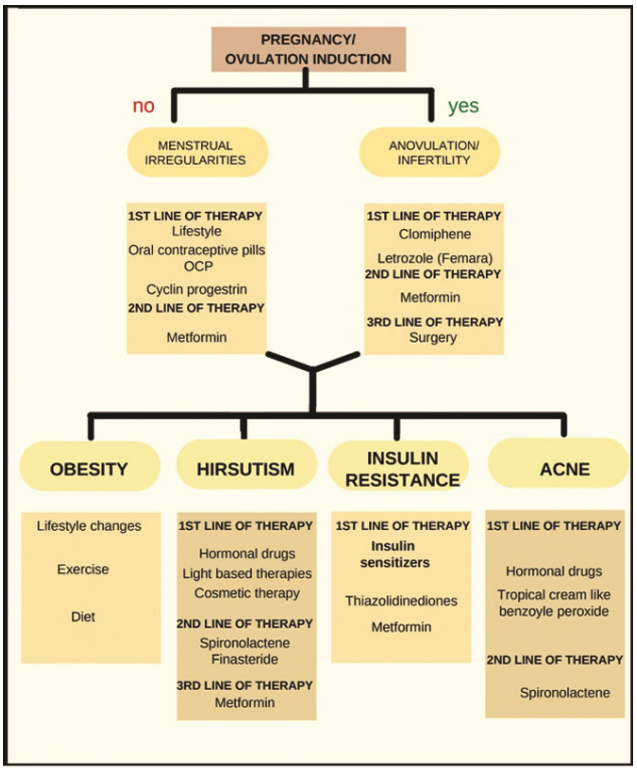

Fig. 5 — Treatment of PCOS

aids in achieving weight loss and improves clinical outcomes in PCOS, compared to diet alone[20].

Pharmacological treatment

Oral contraceptive pills

Oral Contraceptive pills are the most frequently used medications for women with PCOS. According to research, they are the first-line treatment for improving the menstrual cycle abnormalities and hyperandrogenism in women with PCOS. They decrease the LH level and increase the sex hormone-binding globulins thus decreasing the free androgen levels in blood. Further, it improves acne, hirsutism[19]. A combination of estrogen and progesterone are the primary oral contraceptives for PCOS symptom treatment. Presently, newer OCs contain anti-androgenic progestins, such as Bayer's drospirenone (*e.g.*, Yaz) and dienogest (*e.g.*, Natazia) are much more prevalent and these formulations are comparatively more effective in the treatment of androgenic symptoms. It takes a minimum period of 6 months to see the effectiveness of these pills[26,27].

Ovulation inducing agents

- **Clomiphene**

Clomiphene citrate is an anti estrogenic molecule that directly influences the hypothalamic-pituitary axis and increases FSH level by negative feedback mechanism and treats anovulatory PCOS. However around 20%-25% of anovulatory sterile women with PCOS do not respond to CC and are considered to be "clomiphene-resistant". Due to its favorable expense, ease of administration and minimal side effects, Clomiphene citrate is considered as a first-line therapy over Human menopausal gonadotrophins (HMG) and FSH for inducing ovulation[26,27]. But it also causes multiple pregnancies and ovarian hyperstimulation syndrome (OHSS).

- **Aromatase inhibitors**

Patients use aromatase inhibitors only if they have clomiphene resistance or they are prone to congenital abnormalities that are directly or indirectly linked with clomiphene or gonadotropin medications. Letrozole is considered as an effective aromatase inhibitor for patients with hormone-responsive breast cancer, but it is also effective for ovulation induction in women with PCOS[28,29]. In a study, wherein efficacy of anastrozole was compared with clomiphene for ovulation induction, the latter one showed significant results[29].

Antiandrogens

Antiandrogens chiefly act either by competitive inhibition of androgen binding receptors or by inhibiting 5-alpha-reductase enzymes, further decreasing androgen production. Antiandrogens such asspironolactone, flutamide, cyproterone acetate, finasteride along with ovarian suppression, are known to alleviate hirsutism and androgenic alopecia in women with PCOS.

- **Spironolactone**

Spironolactone is one of the most effective antiandrogens that shows a noticeable effect on hirsutism[28]. It is generally coupled with oral contraceptive pills to correct menstrual irregularity. But there are no specific recommendations for spironolactone use in PCOS management. Spironolactone is an aldosterone antagonist administered at a large dose of 100-200 mg/day.

- **Flutamide**

It has the same effectiveness as spironolactone and is very well tolerated. Flutamide and metforminare used synergistically.

- **Cyproterone acetate**

Cyproterone acetate (CPA) combined with ethinylestradiol (EE), is effective in the treatment of PCO related hyperandrogenic skin symptoms such as

acne and/or hirsutism, in women of reproductive age. Additionally, it is efficient in restoring the menstrual cyclicity.

Insulin sensitisers

- **Metformin**

It is the most recommended drug for controlling the metabolic outcomes of PCOS. It helps in insulin-sensitizing and acts as a hypoglycemic agent.[26,27] But according to recent studies, metformin plays a minimal role in reducing BMI compared with placebo. Antiandrogen combined with oral contraceptives is more beneficial in reducing BMI as compared to only metformin. Further, it plays an insignificant role in decreasing body adiposity, and it does not work on reducing waist circumference[28,30]. Glucagon-like peptide-1 (GLP-1) analogs assist in glycemic control and insulin resistance coupled with weight loss and helps in balancing the menstrual cycle[29,31-33].

Bariatric surgery

Bariatric Surgery is considered one of the most useful treatments for patients with unnatural obesity. This surgical procedure aims at reducing body weight, insulin resistance, and other metabolic domains related to the syndrome[34,35]. However, it has its pros and cons in the longer run. Due to the development of novel alternatives like laparoscopy, surgery-associated complications have significantly reduced in the majority of the population. The surgery application is for patients with extreme metabolic comorbidities. Also, for those who do not show any therapeutic improvements even after lifestyle and pharmacological interventions. A recent study on 234 obese patients with PCOS opted for bariatric surgery for their treatment. The study concluded that bariatric surgery corrected BMI, fluctuating glucose levels, IR, and hypertension in PCOS patients.[36] It had great results in hyperandrogenism, associated clinical symptoms, ameliorated menstrual cycles, and ovulation rates. The mechanism of action for these effects is still unclear. Nonetheless, after the surgery, an increase in circulating GLP 1 and peptide YY levels is observed, which may result in advantageous reproductive consequences due to the ability of these gut peptides to decrease food intake[34-39].

Conclusion

PCOS is an established disorder, prevalent among Indian women of reproductive age with lifelong complications. The ambiguous criteria for diagnosis and enormous complexity of the exhibited characteristics are the most challenging aspects of PCOS. The current techniques are not fault-free and might not recognize the difference between normal development and pathogenesis. Since proper diagnosis is the stepping stone for successful treatment, further study and clinical research will update the criteria for diagnosis and provide therapeutic plans and diagnostic tools which can recognize all PCOS phenotypes and complaints. Prior to heading to pharmacological options, proper guidance and awareness related to healthy lifestyle must be provided to all women diagnosed with PCOS irrespective of their weight, menstrual irregularities, or any other presenting symptoms.

The new refined therapeutic options with hypocaloric diet and exercise regimens provide contemporary and advanced directions towards the disease medications and will benefit women population worldwide. Despite the importance of role of medical practitioners in the diagnosis PCOS and educating patients about PCOS, the time and cost for treatment and diagnosis discourages many young women to seek help. Affected women should have an open discussion with their doctor about mood swings, change in eating and sleeping patterns and body image concerns as it is vital to the health and well-being of patients with this PCOS condition. In future, it warrants further research in the field of genetics, *in silico* analysis and drugs modification targeting hypothalamic –pituitary-ovarian axis to have better understanding of the etiology of PCOS and, as a result, targeting the underlying mechanism by appropriate medication.

Conflict of interest

All authors declare no conflict of interest.

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