International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 05 Issue 12 December 2022
DOI: 10.47191/ijcsrr/V5-i12-01, Impact Factor: 5.995
IJCSRR @ 2022
www.ijcsrr.org

Landing Eyes on Unnoticed Disorder: A Polycystic Ovary Syndrome

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ABSTRACT: Polycystic Ovary syndrome (PCOS) is an underdiagnosed metabolic and endocrine disorder found in women of reproductive age in which ovaries develop follicles and does not release egg regularly. Its symptoms include menstrual irregularity, polycystic ovaries, hirsutism, infertility, insulin-resistance, impaired glucose tolerance. Currently the exact cause for the PCOS is unknown but research suggest that it may be related to lifestyle changes, environmental traits and genetical factors. Prevalence of PCOS in India ranges from 3.7 %to 22.5%. The syndrome is associated with increased gonadotropin-releasing diagnose PCOS till the date. Out of 3 diagnosis criteria, Rotterdam diagnostic criteria is highly accepted by the healthcare providers. Weight loss has been a major contributor in the non-pharmacological management of PCOS. Moderate exercise, behavioral therapy and psychological counselling is suggested for affected women. In pharmacological treatment, combined oral contraceptive pills (COCP), metformin, anti-androgen agents, clomiphene citrate, letrozole as fertility inducing agents are used and surgical options are also considered when necessary. In India, PCOS is still underdiagnosed disorder with long term morbidities involved and its time that it should be discussed more openly and treated holistically.

KEYWORDS: Diagnosis Guideline; Management; Polycystic Ovary Syndrome; Prevalence; Pathophysiology.

INTRODUCTION

Polycystic Ovary syndrome (PCOS) is thought to be complex endocrine disorder found in women of reproductive age. Women with PCOS have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries develop numerous small collections of fluid (follicles) and fail to release eggs regularly [1]. Symptoms of PCOS include menstrual irregularity, polycystic ovaries, hirsutism and also infertility, insulin-resistance, impaired glucose tolerance (Type 2 Diabetes), and dyslipidemia [2]. Due to nature of the disease this can affect reproductive health and fertility of affected patient. PCOS has very low awareness due to which PCOS has a very high percentage of individuals who remain undiagnosed when visiting their doctor, estimated to be as high as 75%. PCOS women have multiple long term risk factors of type 2 diabetes, hypertension, cardiovascular disease and endometrial cancer. There is now clear evidence that 25% to 30% of women with PCOS have been observed with impaired glucose tolerance by the age of 30 and 8% of affected women can develop type 2 diabetes mellitus annually [3]. Furthermore, women with PCOS are more prone to have more extensive coronary artery disease by angiography [4]. Chronic anovulation predisposes women to endometrial cancer and emerging evidence suggests more and more possibilities of ovarian and breast cancer development [5]. Lastly, PCOS impacts women of all races and ethnicities who are of reproductive age and variations have been seen in different regions due different diagnostic criteria.

ETIOLOGY

The exact causes of PCOS has not been completely revealed yet, but there are evidences that shows that genetic factors, environmental factors and lifestyle are associated with the disease occurrence [6,7].

EPIDEMIOLOGY

Globally, 6–12% women of reproductive age are affected from PCOS [8]. Prevalence in India ranges from 3.7 to 22.5% depending on the population studied and the criteria used for diagnosis [9]. According to several studies conducted in different states and cities of India, including Tamil Nadu, Karnataka, Andhra Pradesh, Mumbai, Lucknow, and Chennai respectively, PCOS prevalence is depicted in table- 01 and 02 [10-15].

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Table: 01 Prevalence of PCOS in different states of India

States of India	Prevalence of PCOS
Tamil Nadu	18%
Karnataka	9%
Andhra Pradesh	9.13%

Table: 02 Prevalence of PCOS in different cities of India

Cities of India	Prevalence of PCOS
Mumbai	22.5%
Lucknow	3.7%
Chennai	6%

PATHOPHYSIOLOGY

Polycystic Ovary Syndrome (PCOS) pathophysiology is complicated and multifactorial which involves genetic, environmental traits and transgenerational transmission [16]. In addition to metabolic, reproductive and psychological impairments likely to play a role [17].

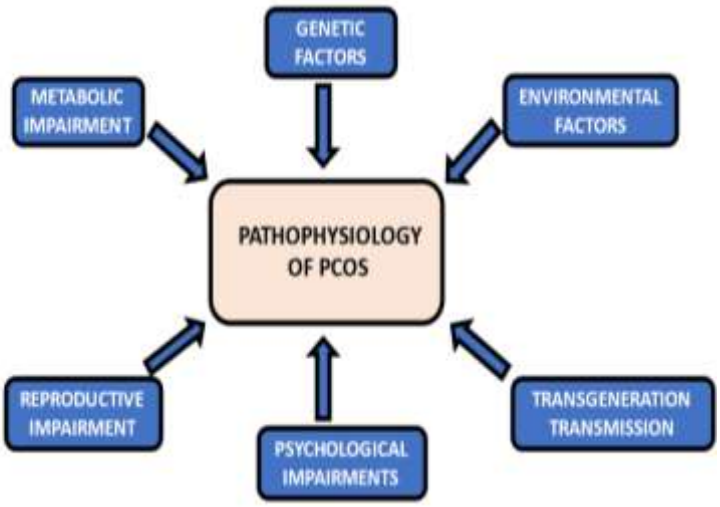

Figure: 01 Factors contributing in pathophysiology of PCOS

Reproductive impairment:

The syndrome has been linked with persistently increased gonadotropin-releasing hormone (GnRH) pulse amplitude that shows excess luteinizing hormone (LH) level and deficiency of follicle-stimulating hormone (FSH), all contribute to high ovarian production of androgen and ovulatory dysfunction which is most likely related to lowered responsiveness to negative feedback of progesterone that is primary regulator of GnRH [18].

Metabolic impairment:

PCOS associated insulin resistance/Hyperinsulinemia aggravates hyperandrogenism by abolishing liver synthesis of sex hormone–binding globulin (SHBG) and augmenting adrenal and ovarian androgen synthesis, promoting hyperandrogenism [19].

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Genetic factors:

Total 19 risk gene loci were discovered by Genome-wide association studies (GWAS) detected in the neuroendocrine, reproductive, and metabolic pathways responsible for PCOS [20-24]. Identified genetic risk loci elucidated less than 10% of inheritance of PCOS, hence other environmental factors should also be considered. First-degree female relatives of women with PCOS are exposed for obesity, insulin resistance/hyperinsulinemia, and type-2 diabetes mellitus (T2DM) [25].

Transgenerational transmission:

Some of human data manifest that, PCOS has transgenerational transmission to daughters born to PCOS mother with the 5-fold risk [26,27].Though mechanism by which daughters are exposed to increased androgen levels still remains unclear, hypothesis suggests that Anti-Müllerian Hormone (AMH) contributes to it. Moreover, increased levels of AMH at late pregnancy developed PCOS in offspring with excessive LH levels and hyperandrogenism was found in one of the recent study [28]. Even if studies showed potential link between high AMH levels in 2nd and 3rd trimester in women with PCOS [28,29], the role of AMH on transgenerational transmission in humans require further research in this area.

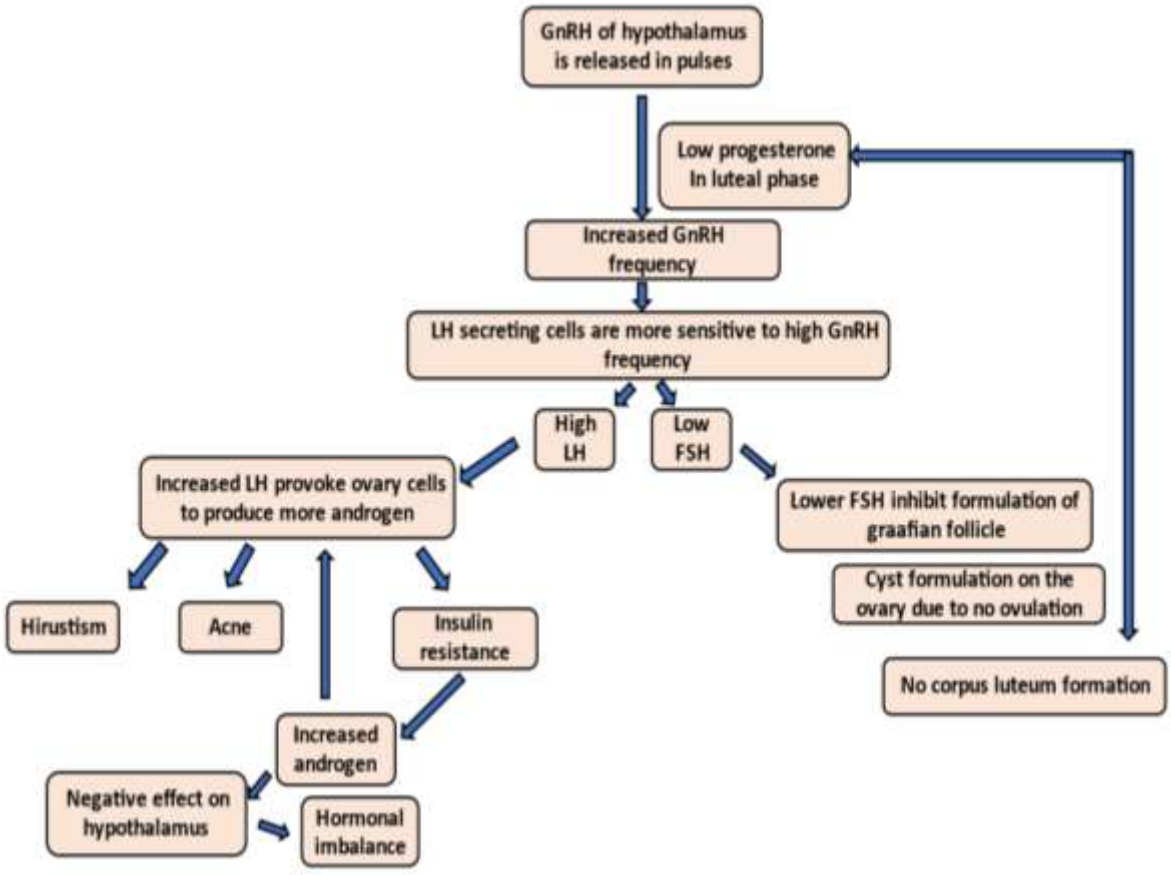

Figure: 02 Pathophysiology of PCOS

Diagnosis

Diagnostic criteria for PCOS are not totally efficient thus, primarily patient history including menstrual history, other comorbid condition, recent fluctuation in the weight and physical examination involving terminal male pattern hair growth, presence of excessive acne and androgenic alopecia should be in prime focus for healthcare provider to determine presence or absence of PCOS [30].

There are three well established diagnostic criteria available to diagnose PCOS till the date [31,32] which are set by National Institutes of Health's (NIH) international conference on PCOS in 1990, the European Society of Human Reproduction and

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Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) in 2003 (referred to as the Rotterdam criteria), and the Androgen Excess Society & PCOS Society (AE-PCOS) in 2006 (see table 03) [33].

Table: 03 Diagnostic criteria of PCOS

Organization/group	Year	Criteria
National Institutes of Health	1990	Both hyperandrogenism and chronic anovulation
Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine-sponsored PCOS consensus workshop group	2003	Two of the following conditions: hyperandrogenism, chronic anovulation, polycystic ovary
Androgen Excess Society	2006	Hyperandrogenism, ovarian dysfunction (including infrequent or irregular ovulation or anovulation) and/or polycystic ovary

Abbreviation: PCOS, polycystic ovary syndrome
Adapted with permission from reference [31].

Out of all three diagnostic criteria, **Rotterdam criteria 2003** is highly accepted tool for the diagnosis of PCOS by the most of the clinicians [34].

Criteria requires at least two out of the three findings of PCOS for the diagnosis (following exclusion of congenital adrenal hyperplasia, androgen-secreting tumor or Cushing's syndrome) that includes:

- Oligomenorrhea (irregular menstruation) or amenorrhea (absence of menstruation)- Periods of more than 35 days apart or having less than 9 menstruations in a year [35],
- Hyperandrogenism (based on clinical and/or biochemical features)- clinically presence of excessive acne, androgenic alopecia, or hirsutism (terminal hair in a male-pattern distribution which are thick, dark, coarse in nature) or biochemically diagnosed by elevated serum levels of total, bioavailable, free testosterone or dehydroepiandrosterone sulphate[DHES] [36].
- Polycystic ovary on the ultrasound- It is characterized by 12 number of immature follicles or more in each ovary with size of 2-9 mm in diameter and/or Ovarian volume of 10 mL or more in at least one ovary [37]. The Rotterdam criteria 2003 inscribed four prominent PCOS phenotype descriptions (see table 04) [33].

Table: 04 PCOS phenotypes based on Rotterdam criteria

Phenotypes	Associated features
Phenotype A (Classic PCOS)	Clinical or biochemical evidence of hyperandrogenism Absent or irregular periods Polycystic ovaries on ultrasound
Phenotype B (Essential NIH Criteria)	Clinical or biochemical evidence of hyperandrogenism Absent or irregular periods
Phenotype C (Ovulatory PCOS)	Clinical or biochemical evidence of hyperandrogenism Polycystic ovaries on ultrasound
Phenotype D (Non-hyperandrogenic PCOS)	Absent or irregular periods Polycystic ovaries on ultrasound

Information from references [36].

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One new tool discovered for diagnosing PCOS is Anti-Mullerian Hormone (AMH) which has an important role in follicular development and maturation. AMH production is about 2-4-fold higher in PCOS women than in healthy women [41,42]. Some of the studies suggested that AMH concentrations can be used as an alternative of ovarian ultrasound [43]. Further, AMH level varies during the reproductive life complexify the diagnosis criteria [44]. Due to limitations in AMH measurement, it is alone not considered as a diagnosis. A recent study subjected to seek a more specific and sensitive integrated biomarker system to categorize the subtypes of PCOS. In the future, the integrated biomarker system may help in developing precise diagnosis strategies for different PCOS subgroups [45]. The diagnostic criteria are still progressive and open for debate in the endocrinology field [46].

MANAGEMENT

1. Supportive therapy:

a) Lifestyle modification

It is a first step towards managing PCOS. Women suffering from PCOS are about 40% to 85% obese or overweight [47]. Obesity sensitizes theca cells to LH stimulation and amplifies functional ovarian androgen production, which causes the symptoms of PCOS such as anovulation, hirsutism, and infertility [48]. It is been said that weight reduction of even 5% can restore regular menstruation and improve ovarian induction and fertility treatment [49] and also useful in treating psychological impairment which have a 3-8-fold increased prevalence in PCOS women. Therefore, it is essential to address and treat obesity in PCOS [48]. With the help of lifestyle modifications like diet, exercise and behavioral therapy one can achieve weight loss [48].

- Diet-

The Mediterranean diet (MedDiet) is said to be the healthiest dietary model which involves consumption of unsaturated fat, low glycemic index (low GI) carbohydrates, fiber, antioxidants, vitamins, and sufficient amount of animal protein [50]. It reduces the inflammatory and oxidative stress markers, improves ovarian form (ovarian volume and follicle number per ovary), insulin sensitivity, lipid profiles, endothelial function, antiatherosclerosis and antithrombotic properties. This shows that MedDiet can be one of the optimal non-pharmacological strategies for treatment of PCOS [50]. Hence a diet moderate in carbohydrates, high in protein and fiber, moderate with respect to monounsaturated and polysaturated fats to be taken at small intervals is recommended to get maximum benefits [48].

- Exercise-

Exercise is one of the important components of lifestyle modification in PCOS [49]. Exercise helps improving cardiovascular, metabolic parameters, hormonal imbalances and regulates menstrual cycles [51]. According to New international PCOS guideline 150min/week of moderate physical exercise or 75min/week intense vigorous and muscle strengthening exercise on 2 non consecutive days/week is recommend for women with PCOS [48]. Physical activity should consist of aerobic and resistance exercise as part of regimen. Even yoga has ability to relieve multiple symptoms of PCOS. Furthermore, acupuncture can also be helpful in treating the symptoms of PCOS [52].

b) Psychotherapy

- Behavioral Therapy-

As PCOS has constellation of symptoms such as hirsutism, alopecia, acne and increased body weight or obesity which severely affects body image. This can lead to anxiety and depression in such women and can impact their quality of life. So, adequate treatment like psychological therapy or behavioral therapy can help in improving self-esteem and symptoms of PCOS [48].

c) Surgical intervention

- Bilateral laparoscopic ovarian surgery-

Monopolar electrocautery (multiple controlled perforation of the ovary) or laser is an acceptable alternative when women are unable to comply with gonadotropin administration [62].

- Laparoscopic ovarian surgery-

It could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors [53]. It restores menstrual regularity in 63%–85% of women, and the beneficial effects on reproductive outcomes seem to last for several years in many women [34].

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- Bariatric surgery-

It has been advocated as a strategy for weight loss in the morbidly in obese women , if spontaneous weight loss cannot be achieved with diet and exercise, bariatric surgery can be offered [34].

- In Vitro Fertilization (IVF)-

It is third line therapy when first or second-line ovulation induction therapies have failed. In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimized [53].

This is the last possibility for achieving a full-term pregnancy in women with PCOS [34]. Several stimulation protocols have been published for the treatment of patients with PCOS undergoing IVF, including combinations or isolated use of clomiphene, human menopausal gonadotropins, recombinant FSH, GnRH agonists, and GnRH antagonists [63]. Myoinositol is widely recommended in improving live birth rate in sub-fertile or infertile women with PCOS undergoing IVF. However, recent Cochrane analysis was not able to conclude benefits on use of myoinositol due to insufficient data [67].

2. Pharmacological treatment:

PCOS is a multifactorial syndrome that affects significantly metabolic and reproductive system. Treatment should be based on the individual patient's clinical presentation. Therapy aims to improve menstrual regulation, infertility and associated co-morbid conditions.

a) Treatment for ovulation induction

- Combined oral contraceptive pills [COCPs]-

It alone should be recommended in adult with PCOS for management of hyperandrogenism and/or irregular menstruation [53]. COCP acts by promoting direct negative feedback on LH secretion, which results in lowered ovarian production of androgens by increasing liver production of sex hormone-binding globulin. The dose of COCPs contain ethinyl estradiol in doses ranging between 15 µg to 35 µg [34]. Newer OCPs contain less androgenic progestins such as norethindrone, desogestrel, and norgestimate and two progestins- cyproterone acetate [CPA], which is more potent thus used in low doses and drospirenone function as androgen receptor antagonists [56]. Other option is antiandrogenic progestin, dienogest which is available in Europe and is combined with estradiol as a COCP [34]. Combination with the COCPs, metformin may be most beneficial in high diabetes risk groups [53].

- Metformin-

Metformin is used as a first-line treatment for prevention of pregnancy related complications, or for the treatment of obesity in PCOS [30]. Mechanism of metformin is to inhibit hepatic glucose production, and it is also decreasing intestinal glucose uptake and increases insulin sensitivity in peripheral tissues [57]. Metformin is started at 500mg daily with food. After 1 week, the dose is increased to 1000 mg for another week and then to 1500 mg daily. The target dose is 1500–2550 mg/day (500 or 850 mg three times daily). Clinical response is usually seen at the dose of 1000 mg daily. It appears that some PCOS patients who do not respond to metformin at a dose of 1500 mg daily will respond favorably to 2000 mg daily [34]. Articles recommend metformin in women with PCOS who have T2DM who fail lifestyle modification . For women with PCOS with menstrual irregularity who cannot take or do not tolerate Contraceptive pills, Metformin is suggested as second-line therapy [30].

- Letrozole-

It should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility [53]. The class of the drug is nonsteroidal competitive inhibitor of aromatase; inhibits conversion of adrenal androgens. Letrozole mechanism is to induce ovulation by blocking estrogen production, leading to increases in follicle-stimulating hormone (FSH) release. The dose of the drug is 2.5 to 7.5 mg for 5 days and adverse effect of the drug is Osteoporosis, thromboembolism, MI, hot flashes, arthralgias [60].

- Clomiphene citrate (CC)-

the first-line treatment of anovulatory infertility in women with PCOS [30]. The mechanism of CC is an estrogen receptor antagonist that interferes with negative feedback of the estrogen-signaling pathway, resulting in increased availability of FSH. Increased FSH leads to follicular growth, followed by an LH surge and ovulation [34]. Doses 50–150 mg are administered for 5 days, starting on days 3 or 5 of a progestin-induced or spontaneous cycle. CC produces ovulation in 75%–80% of PCOS patients. The live birth rate following 6 months of clomiphene ranged from 20% to 40%. Furthermore, the majority of pregnancies occurred within the first six ovulatory cycles following the initiation of treatment [61].

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- Tamoxifen-

It is also oral ovulatory agent that is similar to CC in its mechanism of action, but it lacks its antiestrogenic effect on the cervix and endometrium. It can be used as an alternative to CC in case of CC resistance or failure [34].

- Gonadotrophins-

could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors [53]. The step-up regimen starts with a minimum dose (37.5–50 IU/day), which increases according to the lack of follicle response. The step-down regimen is starts with the maximum recommended dose, which is reduced as a follicle response is achieved. The dose is reduced by 50% each time the regimen is changed [34].

b) Treatment for hyperandrogenemia

- Antiandrogens-

Antiandrogen such as spironolactone, Cyproterone acetate [CPA], or flutamide act as competitive inhibition of androgen-binding receptors or by decreasing androgen production [56]. Spironolactone, which is an aldosterone antagonist, is a dose-dependent competitive inhibitor of the androgen receptor and can also inhibit 5-α-reductase activity. Spironolactone possesses as moderate antiandrogenic effects when administered in large doses (100–200 mg daily) [34]. CPA is a pregestational antiandrogen. CPA competitively inhibits the binding of testosterone and its more potent conversion product 5a-dihydrotestosterone to the androgen receptor. Used in high doses (50–100 mg) and in a reverse sequential regimen (for the first 10 days of cycle), in combination with ethinyl estradiol 20–50 µg (to ensure regular menses), it was shown to be more effective than finasteride, a 5-α-reductase inhibitor [58]. Flutamide is a nonsteroidal, selective antiandrogen without progestogenic effect. It is marketed for the treatment of prostate cancer and is very effective in treating hirsutism. In a dose of 500 mg daily, it was found to be similarly effective as spironolactone 100 mg in women with idiopathic hirsutism, and, in a recent study, the minimal effective dose was found to be 125 mg daily [34]. When COCPs are contraindicated or poorly tolerated, in the presence of other effective forms of contraception, anti-androgens could be considered to treat hirsutism and androgen-related alopecia [53].

- Glucocorticoids-

It is also use and glucocorticoids suppress adrenal androgen secretion and have been used in patients with adrenal hyperandrogenism. Their use is most legitimate in patients with classic congenital adrenal hyperplasia, where they can help prevent and manage hirsutism and allow ovulatory cycles. In non-classic congenital adrenal hyperplasia and functional adrenal androgen excess (a minority of PCOS patients), their role is more limited [59].

- Gonadotropin-releasing hormone agonist (GnRHa)-

It is effective in women with severe insulin resistance who are unresponsive to COCP [64]. It suppresses pituitary hormones, decreases androgen and promotes estradiol secretion, and improves hirsutism [34].

c) Treatment for hirsutism

- Direct hair remove therapy-

It is conventional technique for many years to remove excess hair in PCOS. It works by applying electrical current via fine needle into the hair follicle [34]. Although, laser treatment is more expensive, less painful and much faster results can be seen [65], the side effects associated with its use are higher.

- Eflornithine hydrochloride-

It is an inhibitor of the enzyme ornithine decarboxylase in human skin, has been approved for topical application in hirsutism. It is used in treating facial hirsutism, taking 6–8 weeks for effect to be seen. It can also be combined with laser treatment [34].

d) Treatment for acne

- Oral contraceptives and antiandrogen agents are used successfully in the treatment of acne in conjunction with standard topical acne therapy (e.g., retinoids, antibiotics, benzoyl peroxide) or as monotherapy [68]. Inflammatory acne counts decrease by 30%–60% in 50%–90% of affected patients. OCPs are especially helpful in patients who are relapsed on isotretinoin or has deep-seated acne.

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Future developments in PCOS

Genome-wide association studies (GWAS) is becoming a rising area of PCOS research. The first locus was identified on chromosome 2p16.3, which contains two genes: *GTF2A1L* and *LHCGR*, which plays a role in LH receptors also important for ovulation and maintenance of pregnancy [54]. BM-Hmsc (Human bone marrow mesenchymal stem cells) is another genetic treatment which significantly downregulate steroidal gene expression, decrease inflammation, and restore fertility in PCOS. The anti-inflammatory cytokine interleukin-10 (IL-10) play a key role in mediating the effects of BM-hMSC in PCOS models [55]. Newer drug Quercetin is an herbal bioactive flavonoid used for the treatment of metabolic and inflammatory disorders. The effects of quercetin on reducing the levels of testosterone, luteinizing hormone (LH), and insulin resistance and also effect as an antioxidant [66]. More newer options at present under study on PCOS will hopefully be available soon to maximize current and future health for patients.

CONCLUSION

PCOS is one of the most undiagnosed endocrine disorder in reproductive age women. In India it is needed to be discussed and not to be taken as taboo topic. Prevalence of PCOS in India is ranging from 4-22%. Insights into the pathophysiology of PCOS suggests that, it is complex and multifaceted and genetic, environmental traits and lifestyle contributes to the development of PCOS. The role of impaired AMH levels in the pathophysiology is emerging but is not considered as a diagnostic tool yet. Early identification of women “at risk” for PCOS and those present with the condition should be considered a priority. Although, Evidence-Based Guidelines have clarified the diagnostic criteria and refined the diagnosis of PCOS, clear diagnostic criteria should be developed for timely and precise diagnosis which will ameliorate the concerns of patients which results from delay in diagnosis. Non pharmacological treatment is considered to be first line treatment option for PCOS women. Obesity is major problem in this condition; hence weight loss plays important role in restoring regular menstruation and improve ovarian induction and fertility treatment. Lifestyle modification with diet, exercise and behavioral therapy one can achieve desired outcomes. In pharmacological treatment combined oral contraceptive pills[COCPs]metformin, clomiphene citrate, letrozole are first line agents. Gonadotrophins are second line agents and IVF as third line therapy where the first- or second-line ovulation induction therapies have failed. At last, it is clear that PCOS is an enigma and health care workers should make extensive efforts to fully evaluate the syndrome to provide more successful treatment options and to help in preventing long terms comorbidities of this disease in the patient.

Acknowledgment- None

Conflicts of interest- There were no conflicts of interest between authors.

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International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 05 Issue 12 December 2022
DOI: 10.47191/ijcsrr/V5-i12-01, Impact Factor: 5.995
IJCSRR @ 2022
www.ijcsrr.org

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Cite this Article: Jay Davariya, Hiloni Patel, Shanti Patel, Yash Saraiya, Tarachand Lalwani, Shrikalp Despande (2022). Landing Eyes on Unnoticed Disorder: A Polycystic Ovary Syndrome. International Journal of Current Science Research and Review, 5(12), 4391-4401