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# Comprensive review on Pathophysiology and Emerging Treatment of Polycystic Ovarian Syndrom

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**Abstract:** Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder distinguished by the manifestation of ovarian cysts, anovulation, and endocrine variation that severely impact the life of a woman1 (Escobar-Morreale, 2018, Franks, 1995) The disturbance in the reproductive hormones like LH, FSH, estrogen, testosterone interrupts the normal menstrual cycle and would lead to oligomenorrhoea, amenorrhea like irregularitie According to the World Health Organization (WHO) estimation revealed over 116 million women (3.4%) are affected by PCOS worldwide (Bharathi et al., 2017) . PCOS is diagnosed with hyperandrogenism, menstrual irregularities, and varying size of cysts in ovaries, although substantial differences exist between individuals. This multifactorial condition initially develops in adolescents who are at high risk for the emergence of several comorbidities including obesity, type II diabetes, infertility, endometrial dysplasia, cardiovascular disorders, and psychotic disorders (El Hayek et al., 2016, Goodarzi et al., 2011)

**Keywords**: PCOS, ovaries, WHO, hyperinsulinemia, hyperandrogenism,

**Introduction**: Owing to the intricacy of this condition, various sets of diagnostic criteria have been initiated for the confirmation of PCOS which are listed below in Fig. 1 (Lizneva et al., 2016, Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group 2004). Other than three diagnostic criteria, Anti- Mullerian hormone (AMH) is also a marked hormonal indicator and important in maturation and development of ovarian follicles in PCOS women (Broekmans et al.,

2008). Over secretion of AMH hinder the follicular development which results into ovarian malfunction

The marked feature of this condition is the abundance of androgen found in PCOS patients. Hyperandrogenism is evidenced by raised levels of free (unbound) testosterone in the bloodstream, a key hormone contributing to the pathophysiology of PCOS. This complex condition is deconstructed into its main pathophysiological elements (Ibáñez et al., 2017). The predisposing risk factors include genetics, neuroendocrine, lifestyle/environment, obesity that contributes to the development of Polycystic syndrome as depicted in Fig. 2. Some women have a higher risk of developing PCOS due to predominant genes (van Hooff and Lambalk, 1998). Several data on genome-wide association revealed specific loci and alleles that play a major role in PCOS phenotype identification (Hayes et al., 2015, Shi et al., 2012, Dumesic et al., 2015). Environmental factors including physical exercise, lifestyle, and food may vary widely according to the population (Escobar-Morreale et al., 2005). Environmental factors also include endocrine-disrupting chemicals and glycotoxins that may cause genetic variance and disruption of the metabolic and reproductive pathways, which can develop PCOS phenotypes and related complications (Rutkowska and DiamantiKandarakis, 2016). Androgen exposure can impede the hormone levels to increase the high pulse frequency of GnRH affecting the LH: FSH proportion and leads to follicular arrest and dysplasia (Dumesic et al., 2015, Cheung, 2010).

These factors lead to the cause of hyperinsulinemia, hyperandrogenism, oxidative stress, irregular periods eventually upsurging the metabolic syndrome. PCOS was named so because it indicated multipleovarian cysts (undeveloped follicles) on ultrasound examination. The follicles evolved from primitive follicles, but due to disrupted ovarian function, the development ceased at an early stage (Fig. 3).

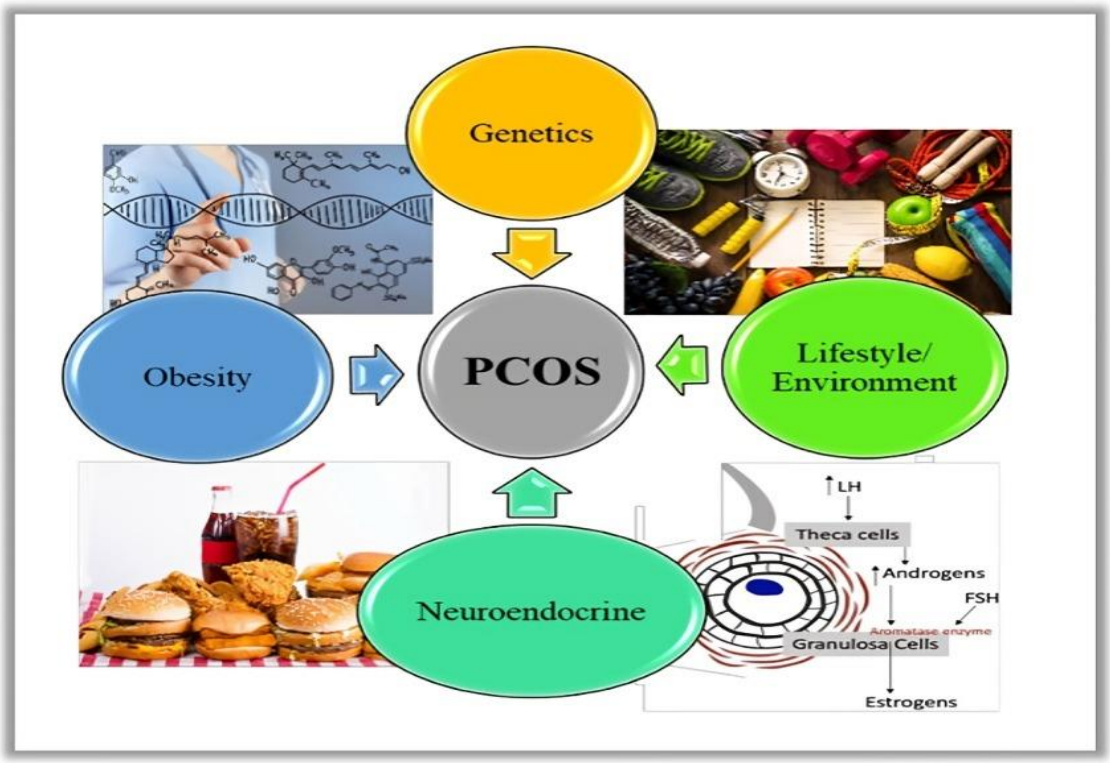


Fig. 1 Risk inducing factor of PCOS

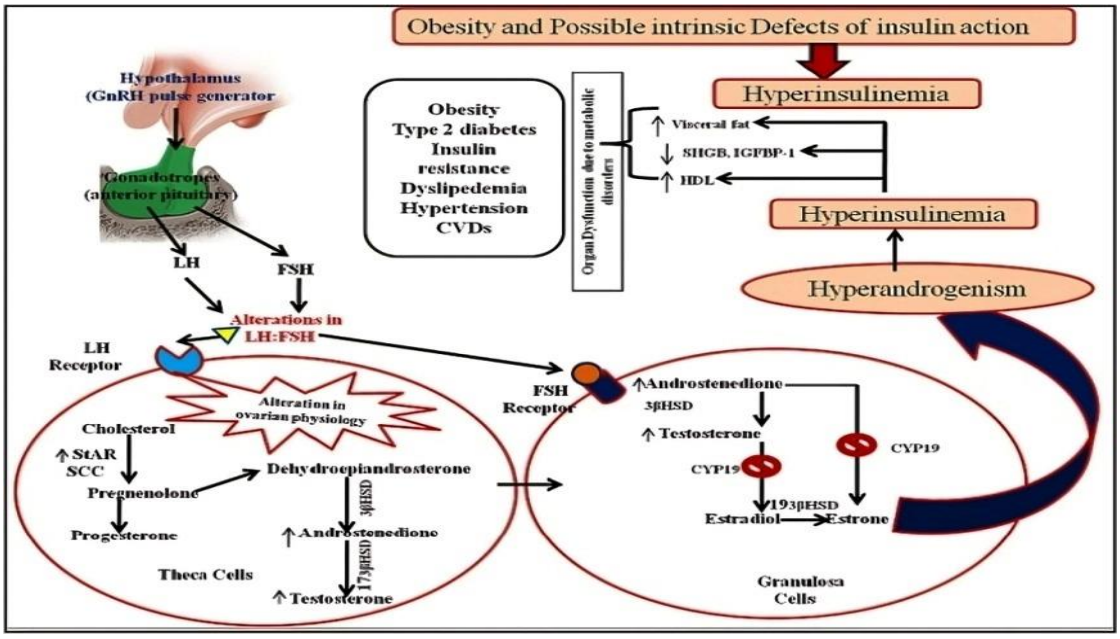


Fig 2. Showing Pathogenesis and development of PCOS

2.1. PCOS and Hyperandrogenism Impaired folliculogenesis is the result of surplus androgens that disrupt normal androgen synthesis. The excess androgens promote the development of primordial

follicles and increase in the antral follicles at the early gonadotropin stage (Rosenfield and Ehrmann, 2016). The secretion of GnRH from the hypothalamus will activate the gonadotropin hormone release from the pituitary. Luteinizing hormone activates the LH receptor to promote androgen production in ovarian theca cells, and the follicular stimulating hormone acts on the FSH receptor simultaneously in the ovarian granulosa cells to transform the androgens to estrogens, which promote the follicle growth. (Ashraf et al., 2019). It has been assumed that the dysregulation in the neuroendocrine system results in an imbalance of the hypothalamic-pituitary-ovarian axis leading to a surplus level of gonadotropin. The rise in the GnRH promotes the production of LH over FSH, resulting in a marked hormonal increase in the LH:FSH ratio in PCOS (Walters et al., 2018, Tsutsumi and Webster, 2009)

2.2. Insulin resistance and Type 2 diabetes Hyperinsulinemia is the root cause of excess androgens as insulin directly simulates the action of LH and raise the GnRH indirectly (Puttabyatappa and Padmanabhan, 2018, Barber et al., 2016). Insulin decreases the sex hormone binding globulin (SHBG), a main circulatory protein controlling the testosterone levels. So reduced SHBG would result in a raised level of free androgens that produce clinical manifestations like hirsutism, alopecia, and acne (Rojas et al., 2014). Insulin resistance can cause dyslipidemia and the patients with PCOS are at high risk for cardiovascular disease and diabetes (Rocha et al., 2019, McCartney and Marshall, 2016). In women with type 1 diabetes, the prevalence of PCOS is 19%,37%,41% according to NIH criteria, AE-PCOS definition, and ESHRE/ASRM criteria respectively (Escobar-Morreale and RoldánMartín, 2016). According to a cross-sectional study in U.S. women, the prevalence of IGT is up to 35% and T2D is up to 10% (Legro et al., 1999). Several studies revealed that controlling insulin resistance eventually would decrease the excess androgens and improve the condition (Ashraf et al., 2019, Baillargeon et al., 2004).

2.3. Obesity and PCOS Obesity has been correlated with abnormal hypothalamic-pituitaryovarian axis function leading to PCOS development (Legro, 2012). Obesity is linked to hyperinsulinemia which further increases the lipid profile, glucose intolerance in PCOS patients. Obesity augments the androgen production by stimulating LH, which in turn leads to hyperandrogenism (Glueck and Goldenberg, 2019). Leptin, an appetite-controlling adipokine has a direct impact on the neuroendocrine and reproductive function of obese PCOS women (Rojas et al., 2014, Barber et al., 2006). Furthermore, hyperleptinemia may hinder ovarian follicular growth (Barber et al., 2006). So, decreasing the visceral fat would control the appetite, glucose levels, lipolysis, and increase the SHBG, thereby regulating the androgen action in the ovary.

3. Therapeutic options for PCOS To date, there is no pharmacological therapy that can cure the syndrome but some interventive medications are used to treat the clinical symptoms of PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004). Pharmacological therapies along with a change in the lifestyle ameliorate the overall condition. The treatment strategy varies according to the clinical symptoms and underlying cause which can be divided by

treating ovulatory dysfunction, hyperandrogenism, improving insulin resistance, and infertility (Zimmerman et al., 2019)

3.1. Oral contraceptives (OCPs) The OCPs are divided into progesterone-only pills and combined pills containing both estrogen (estradiol dose up to 50μg) and progesterone (norethisterone, desogestrel) (Society, 2018). They are first-line therapy for women who do not want to ovulate and are facing menstrual irregularities. OCPs decrease the circulating androgens by raising the SHBG (Fig. 5) (Geller et al., 2011). Women with PCOS are prone to cancers, but the use of OCPs diminishes the risk of ovarian cancers (Grimes and Economy, 1995). The use of OCPs do not affect insulin resistance but show variability in lipid profiles which may lead to metabolic disturbances (Geller et al., 2011, Halperin et al., 2011). So, the usage of OCPs should be according to the risk grade and stopped immediately if any contradiction occurs

3.2. Antiandrogens This category includes spironolactone, flutamide, cyproterone acetate which decreases the androgen secretion by androgen receptor inhibition and is preferred as first-line drugs for hirsutism (Badawy and Elnashar, 2011). Spironolactone, an aldosterone antagonist produces an antiandrogenic effect at high doses. Spironolactone alone leads to more frequent menstruation cycles, so it is generally used in combination with OCPs to produce a synergistic effect and overcome the problem (Rittmaster, 1999). Flutamide is a well-tolerated anti-androgen used to treat prostate cancer. It has the same effectiveness as spironolactone in managing hirsutism (Badawy and Elnashar, 2011, Rittmaster, 1999, Erenus et al., 1994). Flutamide is used in combination with metformin as it causes hepatotoxicity when used alone (Ibáñez and de Zegher, 2006). Cyproterone acetate is an antiandrogen with potent progestogenic activity (Badawy and Elnashar, 2011, Rittmaster, 1999). Cyproterone acetate in combination with ethinylestradiol is used as a remedy for acne and hirsutism (Franks et al., 2008). Finasteride is a 5-$\alpha$-reductase inhibitor showing lower scores of hirsutism (Lakryc et al., 2003). But finasteride is limited for its use in women because of its teratogenic effects. It is used in postmenopausal women or those who do not want to ovulate (Rittmaster, 1999, Pasquali and Gambineri, 2014).

3.3. Insulin sensitizers This class of drugs is generally used to treat PCOS-associated metabolic co-morbidities by decreasing insulin resistance and normalizing insulin levels. By lowering the IR, the associated androgen level will decrease resulting in improvement in the menstrual cycle (Geller et al., 2011)

3.3.1. Metformin Metformin is a large-scale manufactured biguanide used to treat insulin resistance and reinstate the menstrual irregularities in PCOS (Lauretta et al., 2016). Metformin increases the glucose uptake and its utilization which in turn ameliorates insulin resistance in PCOS patients (Geller et al., 2011, Moghetti et al., 2000). It regulates the glucose level, unlike other insulin-regulating drugs which lead to either hypoglycemia or hyperglycemia as its side effect (Sivalingam et al., 2014). Metformin functions indirectly by lowering the insulin level with a decrease in CYP17 cytochrome activity which is involved in the production of androgens and also increases the SHBG further decrease in the free testosterone (Lashen, 2010, Nestler and Jakubowicz, 1996). The effects

of metformin also include slight improvement in the lipid profile of PCOS patients (Wulffelé et al., 2004, Loverro et al., 2002). The use of metformin in pregnancy do not show any teratogenic effect, also reduces inflammation and complications related to pregnancy (Sivalingam et al., 2014, Isoda et al., 2006, Glueck et al., 2002). When combined with clomiphene citrate, the ovulation and pregnancy rate were found to be increased in infertile PCOS patients (Dasari and Pranahita, 2009). Combining metformin with antiandrogens like flutamide shows a synergetic effect in obese PCOS women, though flutamide is not observed safe for laboratory animals (Gambineri et al., 2004, Pasquali and Gambineri, 2006). A beneficial effect was remarked by improving hyperandrogenism in PCOS women when treated with dexamethasone and metformin along with lifestyle modification (Pasquali and Gambineri, 2006, Vanky et al., 2004). Further including metformin in ovulation stimulating regimen for IVF PCOS patients showed better oocyte quality (Qublan et al., 2009). Metformin has a preventive role in the long-term diseases associated with PCOS women including endometrial cancer, type 2 diabetes, cardiovascular diseases, hypertension (Sahra et al., 2008, Salpeter et al., 2008).

3.3.2. Thiazolidinediones (TZDs) This class is commonly named glitazones comprising of rosiglitazone, pioglitazone which decrease the 11-ß-HSD enzyme activity responsible for conversion of cortisol (Lauretta et al., 2016, Stabile et al., 2014). They are the second-line choice of drugs for treating PCOS women who are resistant to insulin (Stout and Fugate, 2005). TZDs stimulate peroxisome proliferator-activated receptor-gamma (PPAR$\gamma$) that elevates insulin sensitivity in adipose tissue (Day, 1999). TZDs indicated positive effects on the ovulation and pregnancy rate and are used in clomiphene-resistant PCOS women (Stout and Fugate, 2005, Froment and Touraine, 2006, Cataldo et al., 2001). TZDs diminish the excess androgens by increasing the SHBG levels and by redistribution in adipose tissue (Brettenthaler et al., 2004). TZDs decrease the inflammatory mediators that are aggravated more in diabetic and obese women (Haffner et al., 2002). Studies comparing the effect of metformin and TZDs together signified no superiority, both increased the ovulation rate, insulin resistance, and regulation of the menstrual cycle (Yilmaz et al., 2005). TZDs are category C drugs that tend to have a risk to the growing fetus in experimental animals, so their use should be surveilled (Froment and Touraine, 2006).

3.4. Ovulation inducing agents Clomiphene citrate (CC) is the prime choice of drug for treating anovulatory sterile women (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). CC increases the FSH level by inhibiting the estrogen receptor through a negative feedback mechanism (Badawy and Elnashar, 2011, Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). It is suggested for the management of anovulatory PCOS patients but pregnancy rates differ significantly according to the BMI, for BMI less than 30 increased the rate of pregnancy and vice-versa (Legro et al., 2007). Chances of multiple pregnancies are up to 8% and risk of hyperstimulation with clomiphene is nil (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008, Eijkemans et al., 2003).

Tamoxifen acts similarly to clomiphene which is used to treat anovulation in patients who fail or not respond to clomiphene citrate (Borenstein et al., 1989, Dhaliwal et al., 2020). Unlike clomiphene, tamoxifen has a positive on the endometrium and cervical mucus (Borenstein et al., 1989). Due to the promising effect on uterine lining by tamoxifen, the combined studies of clomiphene and tamoxifen revealed a marked increase in pregnancy rate (Dhaliwal et al., 2020). There is no variance found in the rate of ovulation or pregnancy with either clomiphene or tamoxifen (Steiner et al., 2005).

Letrozole is an off-label aromatase inhibitor, that obstructs the androgen to estrogen conversion pathway and aid in folliculogenesis by stimulating FSH (Kar, 2013). Letrozole is advantageous over clomiphene as estrogen receptors are not depleted and the antiestrogenic effect on the endometrium is not observed (Casper and MF, 2011). So, letrozole is a better drug option in ovulation induction used as a substitute drug to clomiphene showing similar effects (Holzer et al., 2006). Studies suggest that letrozole is more effective in anovulatory infertility than CC in PCOS patients (Legro et al., 2014). While comparing the two aromatase inhibitors that is anastrozole and letrozole, higher pregnancy rates were found with letrozole (Al-Omari et al., 2004)

Gonadotropins such as recombinant FSH, human menopausal gonadotropin (HMG) are the second-line choice of treatment for anovulatory infertile PCOS women (Melo et al., 2015). Low dose FSH therapy is suitable for ovulation induction and improving pregnancy rates in PCOS patients (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008, Homburg and Howles, 1999). An interventional study indicated that the low-dose step-up HMG protocol gave beneficial results (Andoh et al., 1998). Gonadotropins can be too costly for timely intercourse administration, so instead, intrauterine insemination or invitro fertilization is done (Melo et al., 2015, Veltman-Verhulst et al., 2016).

Laparoscopic surgery is a second-line surgical procedure for ovulation in clomiphene-resistant PCOS women or non-responders to clomiphene (Seow et al., 2008). Laparoscopic Ovarian Drilling (LOD) is rupturing the ovary multiple times by laser or diathermy (Farquhar et al., 2012). The risk of multiple pregnancy and hyperstimulation of the ovary is reduced by LOD (Api et al., 2005). Although the long-term risk of LOD includes ovarian adhesion in women (Greenblatt and Casper, 1993). Ovarian drilling leads to a decrease in size and volume of the ovarian tissue, further damaging the ovary but it is concluded through studies that depletion in the ovarian size indicated normal functioning of the ovaries in PCOS women (Amer et al., 2002).

In-vitro fertilization (IVF) is recommended as a third-line choice of therapy for treating infertility in PCOS women without any associated complications linked (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008, Melo et al., 2015). Adjuvant metformin treatment for a short period of time ameliorates pregnancy rates in PCOS women receiving IVF (Tang et al., 2006). IVF involves complicated procedures with concerning side effects mainly hyperstimulation of the ovary and high-cost treatment (Heijnen et al., 2006)

3.5. Lifestyle Intervention PCOS is a long-term disease with greater chances of other comorbidities like type II diabetes linked with it, so lifestyle modification is the crucial and simple approach for implementation in women with PCOS (Carmina, 2012). Studies revealed that changes in the lifestyle, including diet, exercise, and, attitude have a positive impact on body weight, insulin resistance, and testosterone levels (Moran et al., 2011).

4. Conclusion

Polycystic Ovarian Syndrome (PCOS) remains a complex endocrine disorder characterized by a spectrum of clinical manifestations, including hyperandrogenism, anovulation, and polycystic ovarian morphology. PCOS looks different for everyone to some extent. It is currently incurable and continues way beyond the childbearing age or post-menopause. Given the intricate interplay of genetic predisposition, environ mental factors, and hormonal signaling pathways in the pathogenesis of PCOS, the review encountered challenges in fully dissecting the multi factorial etiology. Additionally, the lack of uniformity in diagnostic criteria and the existence of phenotypic variations among individuals with PCOS posed a challenge in accurately categorizing and comparing study populations, potentially impacting the generalizability of findings and the overall conclusions derived from the reviewed literature. It is clear from the review that PCOS is a complex condition. The central mechanism is difficult to understand and state. Thereby no treatment can be claimed as a magic bullet as it targets the clinical symptoms rather than curing the syndrome. Alternative drugs such as herbal or medicinal plants should be considered by knowing their mechanism of action. Further investigation regarding pathophysiology and drugs acting on it should be done for improvising the abiding consequence on patient's health. Improvising lifestyle could ease the PCOS related symptoms.

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