WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

REVIEW ON: POLYCYSTIC OVARY SYNDROME

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ABSTRACT

A sizable fraction of the world's population is affected by the infertility disorder polycystic ovarian syndrome (PCOS), which is frequent. It is the most prevalent endocrinopathy affecting reproductive-aged women, with a prevalence of 8–13 percent depending on the criteria used and population studied. It is the primary cause of anovulatory infertility in women. Due to the disease's complex multifactorial nature and overlapping symptoms, diagnosis is frequently challenging. PCOS's aetiology has been linked to numerous causes. Since there are numerous pathways and proteins involved in the pathophysiology, it is impossible to develop a single genetic diagnostic test. Although improvements have been made in PCOS care and diagnosis, little is understood about the underlying biological mechanisms and signalling networks. PCOS is a polygenic and complex syndromic condition, in conclusion.PCOS has been linked to numerous genes that, either directly or indirectly, impair fertility. However, research on PCOS patients from various families was unsuccessful in identifying a completely penetrant variation (s). Reviewing the current genetic understanding of the disease was the goal of the current investigation. The clinical gamut, the genetics, and the discovered variations linked to PCOS have all been covered in this review. It is yet unknown how the genetic variations that cause PCOS increase risk as well as how the physical and genetic components of the condition interact with one another. Our grasp of the pathophysiology of PCOS will undoubtedly grow as genetic players and cellular pathways that underlie this condition are revealed. The research also evaluates the state of the present in PCOS.

1. INTRODUCTION

A diverse endocrine condition known as polycystic ovary syndrome (PCOS) affects many women around the world who are of reproductive age. This syndrome is frequently accompanied by enlarged and dysfunctional ovaries, high levels of testosterone, insulin resistance, etc. According to estimates, 1 in 10 women will experience PCOS before menopause and struggle with its implications. The fundamental causes of PCOS are known to be a high luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio and an increased frequency of gonadotropin-releasing hormone (GnRH), however the precise aetiology and pathophysiology are not fully understood. Evidence points to the importance of several internal and external factors, including as genetics, epigenetics, environmental factors, hyperandrogenism (HA), and insulin resistance (IR) .It is important to note that PCOS raises the risk of other issues like heart disease, type 2 diabetes, the metabolic syndrome, depression, and anxiety. The most important step in managing this illness is to drop at least 5 percent of your body weight, so every woman with PCOS is advised to follow a regular exercise regimen and diet that is low in fat and sugar. Additionally, because to their Prior beliefs, cheaper costs, etc., complementary and alternative medicine practises can occasionally be preferred over conventional therapies. Oral contraceptives, antiandrogens, insulin sensitizers, and ovulation inducers are frequently prescribed by medical professionals. There are currently no drugs licenced by the US Food and Drug Administration (USFDA) particularly for PCOS. These treatments range from 3-hydroxy-3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors like simvastatin and atorvastatin to 3-hydroxy-3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors like pioglitazone, empagliflozin, Sitagliptin, and liraglutide, as well as mucolytic Given that PCOS is a problem that is unfortunately often accompanied by undesired complications and that current treatments and drugs are not always effective, it is crucial to carefully research its pathophysiology and identify new pharmacological targets. Repositioning techniques could do this while saving money and time. The definition, diagnosis, and aetiology of PCOS are covered in this review, with an emphasis on the pathogenesis and treatment of this syndrome. Comprehensive research has been done on the internal and environmental aspects that contribute to PCOS, and a number of frequently prescribed drugs are listed along with their full drug information. Following that, a few repurposed

One of the most prevalent endocrine system conditions affecting women of reproductive age is polycystic ovarian syndrome (PCOS), also known as hyperandrogenic anovulation (HA), or Stein-Leventhal syndrome. Since Stein and Leventhal (1935) first described it, the disease has been defined as one in which at least one ovary has an ovarian volume greater than 10 ml and at least one ovary develops an estimated 10 tiny cysts with a diameter ranging from 2 to 9 mm (Balen and Rajkowha) According to systematic screening of women using National Institutes of Health (NIH) diagnostic standards, 4–10% of women of reproductive age have PCOS. Despite the fact that it was formerly thought to be a condition of adult women In the United States, almost 4 billion dollars are spent yearly on the disease's many morbidities, including hirsutism, infertility, and diabetes mellitus. Every year, the Australian health system spends more than $800 million to treat the illness. Compared to those without PCOS, those with it are twice as likely to be admitted to the hospital. As a result, PCOS must be accurately and promptly diagnosed in order to both prevent and lessen the financial burden and cost of future health problems. We will briefly discuss the pathophysiology of the condition and outline the most pertinent and current publications linked to PCOS in this review. Polycystic ovaries are a physical or primarily biochemical manifestation of the illness (hyperandrogenemia). Anovulation, microcysts in the ovaries, follicular development suppression, and menstrual abnormalities can all be attributed to hyperandrogenism, a clinical feature of PCOS. At least 7 percent of adult women have 2PCOS, a diverse condition. The Office of Disease Prevention at the National

Institutes of Health estimates that 5 million American women of reproductive age suffer from PCOS. The detection and management of PCOS is estimated to cost the American healthcare system $4 billion annually. 4 According to research, PCOS affects 5 to 10% of females between the ages of 18 and 44, making it the most prevalent endocrine condition in American women of reproductive age. 5 women requesting medical assistance. Numerous drugs that were previously approved by the USFDA for purposes other than PCOS are included here, and there is currently a desire to use them as therapeutic choices in the management of PCOS. These treatments range from 3-hydroxy-3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors like simvastatin and atorvastatin to 3-hydroxy-3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors like pioglitazone, empagliflozin, sitagliptin, and liraglutide, as well as mucolytic Given that PCOS is a developing problem that unfortunately has many unfavourable side effects and that the present treatments and drugs are not always effective, it is crucial to carefully research its pathophysiology and identify novel pharmacological targets. Repositioning techniques could do this while saving money and time.One of the most significant areas of research in female reproductive endocrinology is PCOS, a field in which our research team has conducted experiments using rats in prolonged estrus mimicking states of chronic anovulation. 3 Even though the illness has received a lot of research, there is still a lot of disagreement over its classification and pathophysiology. As a result, the objective of the present study was to carry out a non-systematic assessment of published literature using PubMed and SciELO searches. Publications on polycystic ovaries have covered the pathogenesis, clinical symptoms, diagnosis, and treatment aspects of the condition as well as its links to arterial hypertension and cardiovascular disease. The new study might also help spread knowledge about polycystic ovarian syndrome patients' increased risk of developing hypertension.

2. PREVIOUS HYPOTHESIS

Many theories have been developed to try to understand the pathophysiology of PCOS. At first, it was believed that an excess of intrauterine androgen was the main cause of the condition. However, recent research on humans failed to find a link between high levels of prenatal androgen exposure and the onset of PCOS in young people or an increase in androgen levels in the cord blood of girls born to mothers with PCOS (Anderson et al., 2010). Another theory, the adipose tissue expandability hypothesis, proposed that newborns with spontaneous catch-up growth and intrauterine growth restriction (IUGR) may experience diminished tissue expandability, which would prevent them from properly storing lipids in their fat tissues. As a result, insulin resistance may develop, perhaps causing PCOS and hyperandrogenemia (de Zegher et al., 2009). Though this Another theory, the adipose tissue expandability hypothesis, proposed that newborns with spontaneous catch-up growth and intrauterine growth restriction (IUGR) may experience diminished tissue expandability, which would prevent them from properly storing lipids in their fat tissues. As a result, insulin resistance may develop, perhaps causing PCOS and hyperandrogenemia (de Zegher et al., 2009). Patients with PCOS who did not have IUGR or who had but did not have spontaneous catch up growth are not covered by this rule (Ibáez et al., 1998, 2009).

3. A MULTIFACETED DISEASE

The greatest understanding of PCOS's pathogenesis views it as a complex condition involving abnormal insulin signalling, excessive oxidative stress, uncontrolled ovarian steroidogenesis, and hereditary and environmental variables. Hyperandrogenemia in PCOS patients may be partially explained by an inherent abnormality in theca cells. In fact, even in the absence of trophic stimuli, theca cells in PCOS patients continue to release excessive quantities of androgens due to an innate stimulation of steroidogenesis (Nelson et al., 1999). Granulosa cells are also impacted by this inherent dysregulation since they release up to four times as much anti-mullerian hormone in PCOS patients as compared to healthy controls (Pellatt et al., 2007; Azziz et al., 2009; Villarroel et al., 2011) .Additionally, studies reveal that women with PCOS have an increased number of follicles, especially pre-antral and tiny antral follicles (Webber et al., 2003). PCOS individuals have an increased number of mature follicles due to a malfunction in apoptotic mechanisms (Das et al., 2008). As an alternative, PCOS has been linked to lower insulin sensitivity caused by a postreceptor binding problem in the insulin signalling pathways, which is unrelated to fat (Dunaif, 1997). Microarray gene analysis revealed changes in the gene expression of some participants in the insulin signalling pathways (Croton et al., 2007, 2008). Additionally, PCOS has been linked to an increase in glycooxidative stress as a result of mitochondrial malfunction (González et al., 2006). (Victor et al., 2009). Patients with PCOS may experience insulin resistance and hyperandrogenism as a result of oxidative stress (Victor et al., 2009).

The occurrence of PCOS in families (Azziz et al., 2004; Chen et al., 2011) and the finding of PCOS susceptibility loci in the genome (Chen et al., 2011) provide evidence for the involvement of genetics in the aetiology of this condition. According to several research, PCOS patients' high androgen levels have a hereditary component (Legro et al., 1998; Escobar-Morreale et al., 2005; Yildiz et al., 2006). Additionally, a polymorphic marker for PCOS associated with the fibrillin 3 gene, D19S884, has been discovered in separate groups of families with the condition (Urbanek et al., 2007; Segars et and Decherney, 2010)

4. EVALUATION

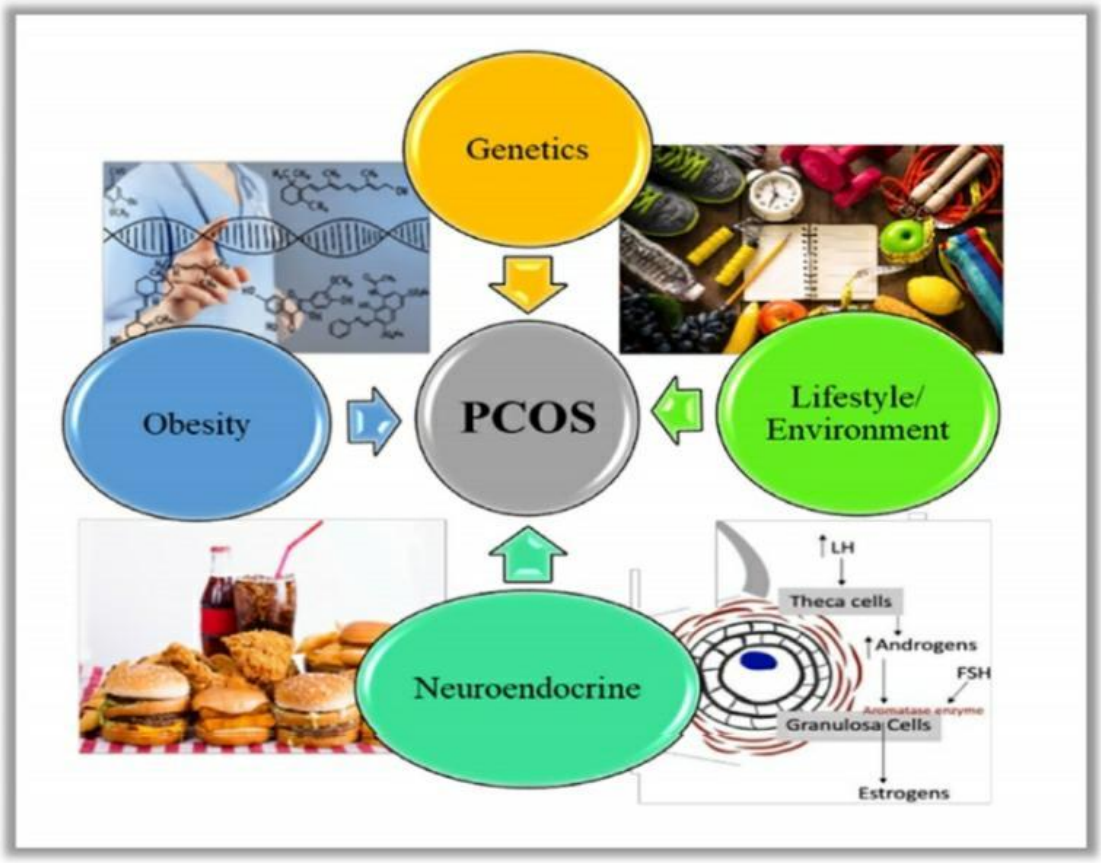
Recent research from numerous studies, particularly in neonates who have risk factors associated with PCOS development, suggests that PCOS may begin in utero. This includes infants who are underweight at birth (Ibáez et al., 1998; Melo et al., 2010) and infants who are overweight at birth (Cresswell et al., 1997) who later catch up on development or who continue to gain weight postpartum (de Zegher and Ibáez, 2009). Signs of early pubarche, early adrenarche (elevated DHEAS), and metabolic syndrome (insulin resistance and visceral obesity) can result from these risk factors plus a genetic predisposition (Verkauskiene et al., 2007; Ibáez et al., 2009). The illness will change to its more prevalent form in adolescence with signs and symptoms of hyperandrogenism and/or anovulation. Later, as a person grows into adulthood, the image The complexity of this condition is better understood by using PCOS as a model that goes through a step-by-step transformation during growth. In spite of the fact that science has shed light on the causes of PCOS, we still don't fully understand it. For instance, the sickness in newborns without IUGR cannot be explained by the adipose tissue expandability concept. How therefore do we account for the absence of a link between prenatal androgen exposure and the emergence of PCOS in humans, given that unchecked ovarian steroidogenesis that results in hyperandrogenism is one component of the disease? Should too much androgen be present at a period of growth when PCOS can develop later on? What age range falls inside this susceptibility window, if this is true? Does the disease

have penetrance and how is its genetic component inherited? One day, may we test newborns for PCOS? To fill in the gaps between ovarian dysregulation, androgen excess, genetics, and numerous susceptibility factors that may contribute to PCOS, additional research is unquestionably necessary.

5. DIAGNOSIS

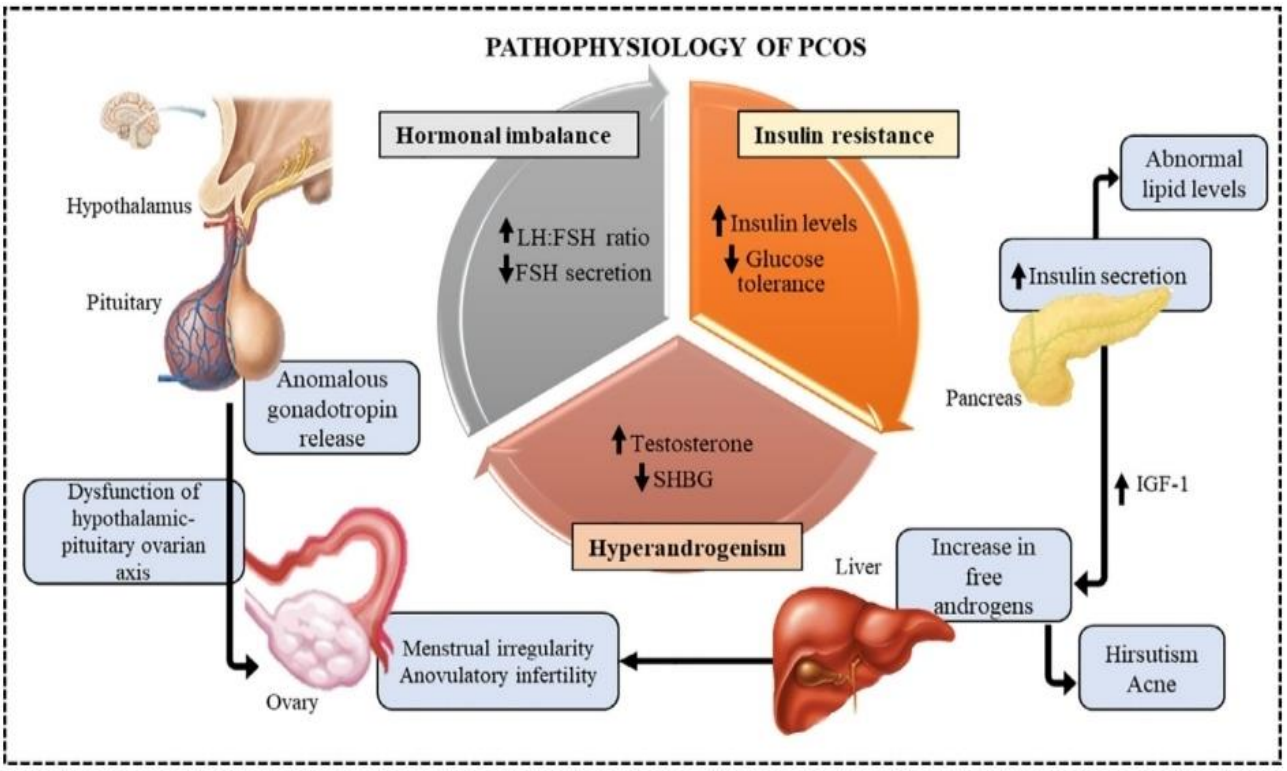
Adults with PCOS can be diagnosed using one of three different criteria, which are shown in Figure. Despite the fact that obesity and insulin resistance are conditions that are thought to be intrinsic to PCOS, neither is listed in the recommendations and should therefore be used for diagnostic purposes (Witchel et al., 2015). Ovarian cysts, anovulation, and endocrine variation are the hallmarks of the heterogeneous endocrine condition known as polycystic ovarian syndrome (PCOS), which negatively affects a woman's quality of life (Escobar-Morreale, 2018, Franks, 1995). The normal menstrual cycle is disrupted by disturbances in the reproductive hormones LH, FSH, oestrogen, and testosterone, which can also cause oligomenorrhoea and amenorrhea-like disorders. Over 116 million women globally (3.4 percent), according to the World Health Organization (WHO), are plagued by PCOS (Bharathi et al., 2017). PCOS is characterised by hyperandrogenism, irregular menstruation, and ovarian cysts of various sizes, albeit there are significant individual variations. Adolescents who are at high risk for developing a number of comorbidities, such as obesity, type II diabetes, infertility, endometrial dysplasia, cardiovascular problems, and mental disorders, initially acquire this multifactorial condition (El Hayek et al., 2016, Goodrich et al., 2011). Due to the complexity of this condition, a number of sets of diagnostic criteria have been developed, and they are shown in Fig. 1 below (Lizneva et al. 2016, Rotterdam ESHRE/ASRMSponsored PCOS Consensus Workshop Group 2004). AMH is a prominent hormonal indication that plays a significant role in the maturation and growth of ovarian follicles in PCOS patients, in addition to the three diagnostic criteria (Broekmans et al., 2008). The follicular growth is hampered by excessive AMH secretion, which leads to ovarian dysfunction.

6. PATH PHYSIOLOGY AND RISK CONSIDERATIONS



The prevalence of androgen in PCOS patients is a defining characteristic of this illness. An important hormone that plays a role in the pathogenesis of PCOS, free (unbound) testosterone levels in the bloodstream are elevated in hyperandrogenism. The primary pathophysiological components of this complex disorder are broken down (Ibáez et al., 2017). As shown in Some women have a higher risk of having PCOS due to prominent genes, the predisposing risk factors for the development of Polycystic syndrome include genetics, neuroendocrine, lifestyle/environment, and obesity (van Hooff and Lambalk, 1998). Numerous findings from genome-wide association studies identified certain loci and alleles that are crucial for identifying the PCOS phenotype (Hayes et al., 2015, Shi et al., 2012, Dumesic et al.,2015).Depending on the population, environmental factors including physical activity, lifestyle, and diet might differ greatly (Escobar-Morreale et al., 2005). Endocrine-disrupting substances and glycotoxins are other environmental variables that can result in genetic variation, disturbance of the metabolic and reproductive pathways, and the development of PCOS

symptoms and associated difficulties (Rutkowska and DiamantiKandarakis, 2016). The LH: FSH ratio can be negatively impacted by androgen exposure, which can increase the high pulse frequency of GnRH and cause follicular arrest and dysplasia (Dumesic et al., 2015,Cheung, 2010). These elements contribute to the development of the metabolic syndrome by increasing levels of hyperinsulinemia, hyperandrogenism, oxidative stress, and



irregular menstrual cycles.

6.1. PCOS and Hyperandrogenism:

Surplus androgens that interfere with normal androgen production cause impaired folliculogenesis. At the early gonadotropin stage, the excess androgens encourage the growth of primordial follicles and a rise in the antral follicles (Rosenfield and Ehrmann, 2016). The release of gonadotropin hormones from the pituitary is triggered by GnRH production from the brain. In order to increase androgen production in ovarian theca cells, luteinizing hormone activates the LH receptor. At the same time, follicular stimulating hormone acts on the FSH receptor in ovarian granulosa cells to convert androgens to estrogens, which stimulate follicle growth (Ashraf et al., 2019). The dysregulation of the neuroendocrine system is thought to cause an imbalance in the hypothalamic-pituitary-ovarian axis, which then leads in an excess of gonadotropin. The LH:FSH ratio in PCOS increases significantly hormonally as a result of the rise in GnRH, which encourages the synthesis of LH over FSH (Walters et al., 2018, Tsutsumi and Webster, 2009).

6.2. Insulin resistance and Type 2 diabetes:

As insulin directly mimics the action of LH and indirectly raises GnRH, hyperinsulinemia is the primary cause of excessive androgen production (Puttabyatappa and Padmanabhan, 2018, Barber et al., 2016). sex hormone binding globulin (SHBG), a key circulatory protein regulating testosterone levels, is decreased by insulin. Therefore, a lower SHBG would lead to a higher level of free androgens, which cause clinical symptoms such hirsutism, alopecia, and acne (Rojas et al., 2014). Patients with PCOS are at an increased risk for diabetes and cardiovascular disease due to insulin resistance, which can also induce dyslipidemia (Rocha et al., 2019, McCartneyMcCartney and Marshall, 2016). According to NIH standards, AE-PCOS definition, and ESHRE/ASRM criteria, PCOS is present in 19%, 37%, and 41% of women with type 1 diabetes, respectively (Escobar-Morreale and RoldánMartn, 2016). IGT incidence among American women is up to 35%, while T2D prevalence is up to 10%, according to a cross-sectional study (Legro et al.,1999). Numerous investigations demonstrated that reducing insulin resistance will eventually result in less excess androgens and an improvement in the disease (Ashraf et al., 2019, Baillargeon et al., 2004).

6.3. Obesity and PCOS:

Obesity has been linked to the development of PCOS due to aberrant hypothalamic-pituitary-ovarian axis function (Legro, 2012). Obesity is associated with hyperinsulinemia, which worsens PCOS patients' glucose intolerance and lipid pro-androgen levels. By boosting LH, obesity increases androgen production, which in turn causes hyperandrogenism (Glueck and Goldenberg, 2019). Obese PCOS women's neuroendocrine and reproductive health are directly impacted by leptin, an adipokine that regulates hunger (Rojas et al., 2014, Barber et al., 2006). Additionally, hyperleptinemia may prevent the development of ovarian follicles (Barber et al., 2006). Therefore, lowering visceral fat would decrease lipolysis, raise SHBG, and regulate glucose levels, appetite, and androgen action in the ovary.

6.4 Stress in PCOS:

Women with PCOS experience symptoms while they are still able to become pregnant. Women with the condition have changes in their hormone levels and tend to produce more male hormones than usual. They skip their cycles and have problems getting pregnant as a result of the hormonal imbalance. A few of the classic symptoms of PCOS include body or facial hair development. It leads to the development of cysts in the ovaries, the female reproductive organs that make oestrogen and progesterone. A change in food and lifestyle can effectively manage PCOS. A low-calorie diet, regular exercise, and weight loss can all be helpful. According to MayoClinic, lowering even 5% of your body weight can help with PCOS. The benefits of weight loss include

7. EXTERNAL FACTORS

7.1 Epigenetic Mechanism:

The term "epigenetic" describes heritable changes in the genome and gene expression that do not involve changes in the DNA sequence. Chemical components on DNA or histones are added or removed in these modifications. An observed feature in PCOS women is increased LH activity. It can be connected to the frequent issues with follicular development and HA. LH/choriogonadotropin receptor (LHCGR) controls the steroidogenesis pathway in theca cells in PCOS patients. Because of this receptor hypomethylation, gene expression is increased, and LH sensitivity increases. Hypomethylated regions are linked to the overexpression of LHCGR on the surface of theca cells, according to a study on PCOS patients. Epoxide hydrolase 1 (EPHX1) is another enzyme that is involved in the breakdown of aromatic chemicals.. The gene Promoter hypomethylation boosts the expression of the enzyme The reduction in the conversion of testosterone to estradiol caused by excessive EPHX1 synthesis has been linked to PCOS [1Play. Peroxisome proliferator-activated receptor gamma (PPAR-) also contributes to the activity of the ovaries. Patients with PCOS who exhibit HA are shown to have hypermethylation of PPAR, hypomethylation of nuclear co-repressor 1, and altered acetylation of histone deacetylase 3. Granulosa cells from PCOS women showed these changes.

7.2. Environmental Toxicants:

Endocrine disrupting chemicals (EDCs) are defined as "an exogenous agent that interferes with the synthesis, sequestration, transport, binding, action, or elimination of natural hormones in the body that Are responsible for the maintenance of homeostasis, reproduction, development, and/or behaviour" by the United States Environmental Protection Agency (USEPA). When interacting with hormone receptors, EDCs can either bind as an agonist or an antagonist. Almost everything we use in a day-to-day basis includes an EDC. They mimic the actions of steroid hormones since their structures are made of phenols or halogens like chlorine and bromine. Studies have confirmed that women with PCOS have higher serum concentrations of EDCs. Exposure to EDCs from foetal life through adolescence can increase a person's risk of developing PCOS.. For instance, bisphenol A (BPA) BPA is a synthetic substance found in polyvinyl chloride (PVC), epoxy resins, dental fillings, food and beverage packaging, and polycarbonate plastics that affects metabolism via a variety of ppathways. By interacting with the G-protein coupled receptor 30 (GPCR30), Non-classical membrane ER, and oestrogen receptors (ER) and, BPA has a direct impact on oogenesis. Additionally, it stimulates androgen release and prevents the breakdown of testosterone in theca cells. Overproduction of androgens is another consequence of BPA on interstitial theca cells. Via dysregulation of steroidogenic acute regulatory protein, cholesterol side-chain cleavage enzyme P450scc, and 17-hydroxylase (P450c17). The impact of BPA on granulosa cells is reflected in a decrease in oestrogen synthesis and aromatase enzyme expression.Additionally, BPA replaces testosterone and is a strong ligand for the sex hormone-binding globulin (SHBG), increasing the concentration of free testosterone. Hormones and BPA have a reciprocal relationship; excessive testosterone decreases hepatic clearance of BPA and inactivates the enzyme uridine diphosphate-glucuronosyl transferase. This procedure increases the blood's free BPA concentration and exacerbates its harmful effects on the ovaries. Additionally, it's thought that BPA might have obesogenic properties. Its obesogenic effects include the activation of adipocytes and the overexpression of adipogenesis-related genes [30]. Differentiation amplifies the lipid buildup in the cells involved in the Medical Syndrome and activates the phosphatidylinositol 3-kinase pathway, turning target cells become adipocytes. The activation of the glucocor gene causes adipogenesis in response to BPA.

8. THERAPEUTIC OPTIONS FOR PCOS

However, some interventive medications are used to treat the clinical symptoms of PCOS (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2004) There is currently no pharmacological therapy that can cure the syndrome (Legro et al., 2013). Pharmacological treatments and a change in lifestyle help to improve the overall situation. The approach to treating ovulatory dysfunction, hyperandrogenism, insulin resistance, and infertility differs depending on the clinical symptoms and underlying aetiology (Zimmerman et al., 2019).

8.1. Oral contraceptives (OCPs):

Progesterone-only pills and mixed pills with estrogen (estradiol dose up to 50 g) and progesterone (norethisterone, desogestrel) are available in the OCPs (Society, 2018). They are the first line of treatment for females who do not wish to ovulate and are experiencing irregular menstruation. OCPs increase SHBG, which lowers the levels of androgens in the blood (Geller et al., 2011). OCP use lowers the risk of ovarian cancer in women with PCOS, who are predisposed to cancer (Grimes and Economy, 1995). Although the use of OCPs does not increase insulin resistance, it does cause lipid profiles to be variable, which may result in metabolic abnormalities (Geller et al., 2011, Halperin et al., 2011). Therefore, OCP consumption should be in accordance with the risk grade and discontinued right once if there is any discrepancy.

8.2. Antiandrogen:

Spironolactone, flutamide, and cyproterone acetate are among the medications in this class that are favoured as first-line treatments for hirsutism because they reduce androgen output by inhibiting androgen receptors (Badawy and Elnashar, 2011). At high concentrations, the aldosterone antagonist spirolactone has an antiandrogenic effect. Because spirolactone alone results in more frequent menstrual periods, it is typically used with OCPs to create a synergistic effect and address the issue (Rittmaster, 1999). Prostate cancer is treated with flutamide, an anti-androgen that is well tolerated. It is equally as effective as spironolactone.

8.3. Insulin sensitizers:

This class of medications is typically used to treat metabolic co-morbidities linked to PCOS by reducing insulin resistance and restoring normal insulin levels. Lowering IR will result in a drop in related androgen levels, which will enhance the menstrual cycle (Geller et al.,2011).

8.4. Metformin:

Metformin is a biguanide produced on a massive scale that is used to treat insulin resistance and restore irregular menstruation in PCOS (Lauretta et al., 2016). Metformin improves insulin resistance in PCOS patients by increasing glucose absorption and utilisation (Geller et al., 2011, Moghetti et al., 2000). It controls the level of glucose, in contrast to other insulin-regulating medications whose side effects include either hypoglycemia or hyperglycemia (Sivalingam et al., 2014). Metformin works indirectly by lowering insulin levels while CYP17 cytochrome activity, which is essential for the production of androgens, is reduced. It also raises SHBG, which further reduces free testosterone (Lashen, 2010, Nestler and Jakubowicz, 1996). A minor improvement in the lipid profile of PCOS patients is another consequence of metformin (Wulffelé et al., 2004, Loverro et al., 2002). Metformin use during pregnancy has no teratogenic effects, and it also lessens pregnancy-related inflammation and problems (SivalingamSivalingam et al., 2014, Isoda et al., 2006, Glueck et al., 2002). Infertile PCOS patients were found to have higher rates of ovulation and conception when coupled with clomiphene citrate (Dasari and Pranahita, 2009). Flutamide is not considered to be safe for use in laboratory animals, but it has been shown to have a synergistic impact in obese PCOS women when used with metformin (Gambineri et al., 2004, Pasquali and Gambineri, 2006). Improvements in hyperandrogenism were noted in PCOS women receiving dexamethasone and metformin treatment coupled with lifestyle changes (Pasquali and Gambineri, 2006, Vanky et al., 2004). Oocyte quality improved when metformin was added to the ovulation-inducing protocol for IVF PCOS patients (Qublan et al., 2009). The long-term illnesses linked to PCOS in women, such as endometrial cancer, type 2 diabetes, cardiovascular disorders, and hypertension, can be prevented with metformin (Sahra et al., 2008, Salpeter et al., 2008).

This class of drugs, sometimes known as glitazones, includes rosiglitazone and pioglitazone, which reduce the activity of the 11-ß-HSD enzyme, which converts cortisol (Lauretta et al., 2016, Stabile et al., 2014). They are the second-line treatment option for PCOSPCOS women who are insulin-resistant (Stout and Fugate, 2005). TZDs increase the activity of PPAR-gamma, which increases the sensitivity of adipose tissue to insulin (Day, 1999). Women with PCOS who are clomiphene-resistant are prescribed TZDs because they show promise for increasing ovulation and conception rates (Stout and Fugate, 2005, Froment and Touraine, 2006, Cataldo et al., 2001). By raising SHBG levels and redistributing adipose tissue, TZDs reduce excess androgens. issue (Brettenthaler et al., 2004). TZDs reduce the inflammatory mediators that diabetes and obese women's bodies exacerbate more (Haffner et al., 2002). Studies examining the combined effects of metformin and TZDs found no evidence of superiority; both drugs increased ovulation rates, insulin resistance, and menstrual cycle regulation (Yilmaz et al., 2005). Since TZDs are category C medications, their usage should be monitored because it may put the developing foetus at danger in experiments with animals (Froment and Touraine, 2006).

8.5. Ovulation inducing agents:

The main medicine of choice for treating anovulatory sterile women is clomiphene citrate (CC) (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). (Badawy and Elnashar, 2011, Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008) CC raises the FSH level by blocking the oestrogen receptor through a negative feedback mechanism. It is recommended for the management of anovulatory PCOS patients, but pregnancy rates vary greatly depending on BMI, with a lower BMI of 30 increasing the likelihood of pregnancy and a higher BMI of 30 decreasing it (Legro et al., 2007). There is no risk of hyperstimulation with clomiphene, and the likelihood of multiple pregnancies is up to 8% (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008; Eijkemans et al., 2003). When clomiphene citrate fails to work or a patient does not respond to it, anovulation is treated with tamoxifen, which works similarly (Borenstein et al., 1989, Dhaliwal et al., 2020). Tamoxifen, as opposed to clomiphene, has beneficial effects on the endometrium and cervical mucus (Borenstein et al., 1989). The combination tests of clomiphene and tamoxifen demonstrated a noticeably higher pregnancy rate because of tamoxifen's potentially beneficial effect on the uterine lining (Dhaliwal et al., 2020). With either clomiphene or tamoxifen, the rates of ovulation or pregnancy are identical (Steiner et al., 2005).Letrozole is an off-label aromatase inhibitor that blocks the mechanism for turning testosterone into oestrogen and promotes FSH, which helps in folliculogenesis (Kar, 2013). Letrozole has an advantage over clomiphene since it does not deplete oestrogen receptors and does not have an antiestrogenic effect on the endometrium (Casper and MF, 2011). Letrozole therefore works similarly to clomiphene in ovulation induction and is a preferable medication alternative (Holzer et al., 2006) According to studies, letrozole is superior to CC in treating anovulatory infertility in PCOS individuals (Legro et al., 2014). Letrozole had increased pregnancy rates compared to anastrozole when the two aromatase inhibitors were compared (Al-Omari et al., 2004). For anovulatory infertile PCOS women, gonadotropins like recombinant FSH and human menopausal gonadotropin (HMG) are the second line of treatment (Melo et al., 2015). According to Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008) and Homburg and Howles (1999), low dose FSH medication is appropriate for PCOS patients' ovulation induction and improving pregnancy rates. A clinical trial revealed the low-dose step-up HMG strategy had positive outcomes (Andoh et al., 1998). Gonadotropins may be too expensive to provide during a timely intercourse, so intrauterine insemination or invitro fertilisation are used instead (Melo et al., 2015, Veltman-Verhulst et al.2016). Laparoscopic surgery is a second-line surgical option for women with PCOS who are clomiphene-resistant or who do not react to clomiphene to induce ovulation (Seow et al., 2008). By using a laser or diathermy, laparoscopic ovarian drilling (LOD) ruptures the ovary several times (Farquhar et al., 2012). LOD lowers the chance of multiple pregnancies and ovarian hyperstimulation (Api et al., 2005). Although ovarian adhesion in women is a long-term risk factor for LOD (Greenblatt and Casper, 1993). The ovary is further harmed by ovarian drilling since it reduces the size and volume of the ovarian tissue, however research has shown that depletion in ovarian size in PCOS women indicates good ovarian function (Amer et al., 2002). Without any connected

complications, in-vitro fertilisation (IVF) is advised as a third-line therapy option for treating infertility in PCOS women (Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008, Melo et al.

8.6 Lifestyle Intervention:

Since PCOS is a chronic condition with a higher likelihood of having associated comorbid conditions like type II diabetes, changing one's lifestyle is the most important and practical course of action for PCOS sufferers (Carmina, 2012). Studies have shown that dietary, physical activity, and attitudinal modifications have a positive effect on body weight, insulin resistance, and testosterone levels (Moran et al., 2011).

9. CONCLUSION

The review makes it quite obvious that PCOS is a complicated condition. It's challenging to comprehend and articulate the central mechanism. As a result, no treatment can be hailed as a miracle cure because it only addresses the clinical symptoms rather than the underlying illness. Knowing the mechanisms of action of herbal or medicinal plants should be considered as alternatives to pharmaceuticals. It is important to conduct additional research on the pathophysiology and the medications that affect it in order to better predict the long-term effects on the patient's health. Changing one's lifestyle may help with PCOS-related symptoms.

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