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Polycystic Ovarian Syndrome: An Integrative Review Of Pathophysiology And Management

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Abstract: Among women of reproductive age, Polycystic Ovarian Disease (PCOD), commonly known as Polycystic Ovary Syndrome (PCOS), is one of the most prevalent *endocrinologica*l and metabolic condition. which is characterized by insulin resistance, irregular menstruation, hyperandrogenism, and ovarian cyst formation, has a major effect on long-term metabolic health and fertility. The condition has a complex etiology that includes lifestyle, environmental variables, and genetic predisposition. that PCOD, or polycystic ovarian syndrome, is becoming more and more common, this integrated paradigm combines lifestyle therapies centered on nutrition, exercise, and the management of metabolic and psychological problems with medicinal treatment for symptoms such as irregular menstruation and hyperandrogenism. The endocrine problems that accompany polycystic ovarian syndrome are among the most prevalent metabolic spectrum illnesses in the human population. The focus has shifted to genetic and epigenetic alterations as potential causes of the illness due to the variation in phenotypic manifestation across individuals and within family lines.

Index Terms: Polycystic Ovary Disease, Polycystic Ovarian Syndrome, Hormonal Imbalance, Anovulation, Hyperandrogenism, Insulin Resistance, Obesity, Metabolic Syndrome, Infertility, Lifestyle Intervention, Pharmacological Management, Ovarian Dysfunction.

I. INTRODUCTION:

The most prevalent endocrinological disorder in women of reproductive age is polycystic ovarian syndrome (PCOS), which can affect 16–40% of women based on demographic research and diagnostic criteria. Rather than being an illness, PCOS is a condition that causes female ovaries to expand and create a substantial number of cysts (more than 10). Ovarian wall thickening, a symptom of the disorder, occurs and prevents the release of the mature follicles, or anovulation, in order to provide a thorough and detailed explanation of the condition. Approximately 70% of women with PCOS do not receive an early diagnosis.

According to a 2012 World Health Organization (WHO) report, 4–12% of women worldwide suffer from PCOS, and by 2020, the percentage had sharply grown to 26%. The prevalence, diagnosis, aetiology, therapy, clinical procedures, psychological issues, and prevention of PCOS are the most controversial and challenging parts of the condition. Future therapy options and increased diagnostic accuracy could result from a deeper comprehension of DNA/histone methylation and microRNA patterns.[1]

In 1990, the National Institutes of Health (NIH) released criteria that provide a thorough and in-depth justification for the diagnosis of PCOS. Two of the three requirements stated below must be met in order to meet the Rotterdam Criteria 2003, another diagnostic criterion: 1) anovulation or oligomenorrhea; 2) clinical or biochemical hyperandrogenism; and 3) polycystic ovaries, which are 2 to 9 millimetres in size on ultrasonography and contain 12 or more follicles per ovary. The Androgen Excess Association (AES) changed the diagnostic standards in 2006. In 2012, the National Institutes of Health approved the Rotterdam criteria of 2003 for PCOS, which are based on the presence of clinical or biochemical hyperandrogenism and oligo-anovulation or polycystic ovaries.

Approximately 22.4% of female PCOS patients experienced androgenic alopecia, or female baldness, according to retrospective cohort research done in San Francisco, USA. 8. About 15–25% of female PCOS patients also have acne, another clinical manifestation of hyperandrogenism. Menstrual abnormalities include menorrhagia (heavy bleeding), oligomenorrhea (delay in menstrual cycle of more than 35 days), and amenorrhea (total lack of menstruation). PCOS is expected to be present in 91% of women with irregular menstrual cycles. PCOS is also associated with psychological issues such as anxiety, sadness, a distorted body image, and low self-esteem. In order to effectively control PCOS, nutritional management is essential. Evidence-based dietary approaches to enhance PCOS patients' clinical, metabolic, and reproductive results are compiled in this review.[2] Worldwide, a large number of women of reproductive age suffer with the diverse endocrine condition known as polycystic ovarian syndrome (PCOS) Excess androgen levels, insulin resistance, oversized and dysfunctional ovaries, and other conditions are frequently linked to this syndrome. One in ten women are thought to develop PCOS before to menopause and deal with its aftereffects.

The precise etiology and pathophysiology of PCOS are not fully understood, despite the fact that the high ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) and elevated frequency of gonadotropin-releasing hormone (GnRH) are recognized as the fundamental causes of PCOS, Evidence points to the involvement of a variety of internal and external factors, such as genetics, epigenetics, environmental factors, insulin resistance (IR), and hyperandrogenism (HA). Furthermore, it is important to note that PCOS raises the risk of other comorbidities such as metabolic syndrome, depression, anxiety, cardiovascular illnesses, and type 2 diabetes mellitus.

Every woman with PCOS is advised to follow a regular exercise regimen and eat a diet low in fat and sugar because losing at least 5% of body weight is the most important step in managing this illness. Additionally, because of their preexisting beliefs, cheaper prices, etc., using complementary and alternative medicine techniques in conjunction with or without other therapies may be beneficial in some situations.

Oral contraceptives, antiandrogens, insulin sensitizers, and ovulation inducers are frequently used (in combination) by doctors. As of right now, none of the drugs listed are officially approved by the US Food and Drug Administration (USFDA) for PCOS, and they are all taken off-label. Drug repurposing techniques may lead to the discovery of novel drugs, in addition to the imperative need for advancements in the study and development of new drug molecules and new drug discoveries. There are numerous drugs that were previously approved by the USFDA for purposes other than PCOS, and there is currently a desire to use them as therapeutic options in the treatment of PCOS.[3]

These include mucolytic treatments like N-acetyl cysteine, 3-hydroxy-3-methyl-3-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors like simvastatin and atorvastatin, and anti-diabetic pharmaceuticals including pioglitazone, empagliflozin, sitagliptin, and liraglutide. It is crucial to properly examine the pathophysiology of PCOS and identify new pharmacological targets because it is a developing problem that regrettably has many unintended consequences and because current treatments and drugs are not always effective. Repositioning strategies could accomplish this, saving money and time.

The definition, diagnosis, and etiology of PCOS are covered in this overview, with an emphasis on the syndrome's pathophysiology and treatment. Numerous frequently prescribed drugs are listed together with their full prescription information, and both internal and environmental factors that contribute to PCOS have been thoroughly investigated. A few repurposed drugs are then discussed in detail, along with a summary of the relevant clinical trials conducted during the previous five years.

Worldwide, women of reproductive age frequently suffer from polycystic ovarian syndrome, or PCOS (Deans, 2019). Women of reproductive age are disproportionately affected by POS, an endocrine disorder commonly referred to as hyperandrogenic anovulation or Stein-Leventhal syndrome. Symptoms include swollen and malfunctioning ovaries, insulin resistance, and hyperandrogenism (Witchell et al., 2019a). Prior to menopause, 10% of women will get PCOS and associated problems (Singh et al., 2023). In 2012, the WHO projected that 116 million women (3.4%) have PCOS. PCOS is an expensive condition because of its high occurrence, irregular ovulation and menstruation, infertility, hair loss, and metabolic problems.

Important aspects of women's reproductive health include taking care of their bodies, comprehending their cycles, helping them conceive, and protecting their health as well as the health of their unborn child. Supporting women's reproductive health entails treating with consideration, knowledge, and dignity the physical changes, psychological challenges, and life transitions that women go through as they grow from puberty to maturity.

PCOS is a prevalent endocrine condition that is frequently misdiagnosed. Because of its 5–25% incidence, infertility and related clinical and metabolic problems raise healthcare expenses. Although its causes and therapy are yet unknown, PCOS is one of the most prevalent endocrinopathies. Environmental endocrine disruptors may have an impact, according to new research. This article explores the pathogenic mechanisms and critical evaluation of PCOS in order to comprehend its intricate development.[4]

II. RISK AND CAUSE FACTOR:

It is difficult to identify the underlying causes of this multifactorial illness due to its complex and linked pathophysiology. The development, prevalence, and control of the PCOS phenotype can be influenced by environmental pollutants, food and lifestyle choices, genetics, obesity, and gut dysbiosis. These factors could enhance the metabolic syndrome by causing the onset of insulin resistance, partial folliculogenesis arrest, increased androgen secretion from the ovaries, and the continual low-grade release of inflammatory mediators from white blood cells.

Environmental Pollutants' Etiological Role:

Numerous studies have demonstrated the substantial impact that environmental contaminants such pesticides, heavy metals, and endocrine-disrupting chemicals (EDCs) have on human reproduction and health. In fact, there is growing evidence that PCOS is influenced by environmental contaminants. Serum BPA levels were higher in hyperandrogenic women with PCOS than in non-hyperandrogenic women with PCOS and healthy controls, according to Takeuchi and Kandaraki et al. [17,18]. Serum testosterone levels were favourably correlated with elevated blood BPA levels in PCOS women as compared to healthy women, according to a different study. Vagi et al. conducted a case-control study to determine the association between several environmental contaminants and PCOS, and they found that women with PCOS had higher serum levels of perfluorooctanoate and perfluoro octane sulfonate
The group also observed a negative correlation between PCOS and phthalate body burden. More specifically, women with PCOS had decreased urine concentrations of monobenzyl phthalate, which suggests a compromised xenobiotic metabolism. EDCs, such as BPA and phthalates, were previously believed to primarily impact thyroid, estrogen, progesterone, and androgen receptors in the nuclear hormone system.[5] However, further studies have shown that EDCs can also affect nonnuclear hormone receptors, orphan receptors, and neurotransmitter receptors, as well as directly alter steroidogenesis and hormonal metabolism. EDCs are a class of common pollutants that have been thoroughly studied as possible environmental factors that contribute to PCOS pathophysiology. This condition is associated with increased oxidative stress and inflammation, which in turn lead to insulin resistance, obesity, and infertility—all of which can be directly or indirectly linked to exposure to EDC. Furthermore, PCOS exhibits changes in neurotransmitter profiles that are comparable to those observed in animals exposed to EDCs. In vitro and animal studies, endocrine disruptors are linked to the production of reproductive and metabolic disorders that mimic PCOS symptoms. Developmental exposure to specific EDCs may accelerate and/or worsen the natural course of PCOS throughout life cycle exposure, or it may permanently change metabolic, reproductive, and neuroendocrine regulation in ways that favour PCOS development in individuals who are genetically predisposed to it. Additionally, EDCs may cause epigenetic changes in the female reproductive system's DNA that could impact future generations and pass on possible PCOS features. All things considered, EDCs have the potential to disrupt local paracrine and autocrine systems, as well as the hypothalamic-gonadal hormone balance, ultimately leading to PCOS pathogenesis. The incidence of PCOS is positively correlated with smoking and exposure to cigarette smoke, according to numerous research. In a study involving oligo-anovulatory women with PCOS, women with normal anovulation in PCOS, and healthy controls, smoking was found to be dose-dependently linked to ovulatory dysfunction. PCOS and smoking are closely linked to an inflammatory state that is marked by an increase in mononuclear cells, mitochondrial dysfunction, a decrease in GSH (glutathione) and oxygen uptake, and an oxidative state with lower antioxidant levels. Theca cells may undergo steroidogenesis as a result of these inflammatory stimuli changing the enzymes. A significant portion of the air pollutants that are positively connected with the risk of PCOS development are polycyclic aromatic hydrocarbons (PAHs), which are created by burning coal, gas, wood, waste, cigarette smoke, and high-temperature-cooked meat. PCOS may occur as a result of exposure to air pollutants like nitrogen oxides, sulphur dioxide, PAHs, and particulate matter (PM) 2.5, which might change normal steroidogenesis and raise inflammatory mediators in exposed women. Higher exposure to fine air pollutant particles and pollutant gases, including SO2, NO, NO2, NOx, and PM2.5, was linked to an increased incidence of PCOS, according to the findings of a population-based cohort study carried out in Taiwan. Animal models also show a link between

environmental contaminants and PCOS. Recent studies have shown that direct exposure to the insecticide DDT or the fungicide vinclozolin during pregnancy in rats was linked to the development of ovarian anomalies typical of PCOS in three subsequent generations through epigenetic processes.[6]

Dietary and lifestyle factors

Although they are not a substitute for pharmaceutical therapy, lifestyle modifications are the mainstay of care for women with PCOS. In addition to being advised in professional guidelines for a number of conditions, regular physical activity, maintaining a healthy body weight, following a healthy diet, and quitting smoking are all crucial in the prevention and treatment of metabolic illnesses. Sedentary lifestyles and high-calorie diets may be contributing factors to the aggravation of PCOS. By changing gut flora, causing chronic inflammation, raising insulin resistance, and increasing androgen production, high-sugar diets may be a contributing factor to PCOS. Weight gain and obesity exacerbate the syndrome's defining characteristics. Without affecting fasting glucose, HDL-C, weight, or the free androgen index, low-GI (LGI) diets decreased waist circumference, total testosterone, TGs, total and LDL-C, and fasting insulin in PCOS patients as compared to high-glycaemic-index (HGI) meals. Furthermore, HDL, SHBG production, and body fat reduction were enhanced by the addition of an LGI diet, exercise, and/or omega-3 supplements. According to Gonzales et al., eating saturated fat increases the production of peripheral leukocytic suppressor of cytokine-3 (SOCS-3) and TNF-α in the blood, which in turn causes LPS-mediated inflammation and insulin resistance in PCOS.[7]

Therefore, it is essential to exclude saturated fats from these individuals' diets. Through the sex steroid hormone–microbiota–inflammation axis, dietary α-linolenic acid-rich flaxseed oil reduced PCOS in rats, while other α-linolenic acid sources are probably going to have a similar impact. Obesity and PCOS are intimately connected, as evidenced by epidemiological data and, more recently, by genetic studies. Obesity exacerbates PCOS, mainly by increasing insulin resistance (IR). Because of the abnormal activity of the HPO axis, obesity has been associated with the development of PCOS. Hyperinsulinemia, which is linked to obesity, exacerbates the lipid profile and glucose intolerance of PCOS patients. Obesity raises androgen production by inducing LH, which leads to hyperandrogenism. SCF As are released as a result of the metabolic advantages that fermentable fibre provides for the gut flora. Ghrelin and glucagon, two hormones that control appetite, may change as a result of low-GI meals. Low-GI meals increased glucagon and decreased ghrelin in PCOS-afflicted women. High fructose consumption (HFC) may exacerbate endocrine-related phenotypes in PCOS, since it enhanced endocrine changes but not metabolic ones. An LGI diet is a safe, effective, and acceptable solution for IR alleviation, according to a meta-analysis and systematic review, and all PCOS patients should receive professional nutritional counselling. HOMA-IR scores significantly improved, while blood glucose and insulin levels dramatically dropped. TGs, total cholesterol, and LDL levels all drastically decreased while HDL levels increased. Additionally, blood levels of progesterone, SHBG, and steroidal increased while those of LH/FSH ratio, LH total, free testosterone, and DHEAS drastically decreased. A KD may therefore offer even more advantages than a diet with an LGI in PCOS patients who are severely obese or obese and have full-blown metabolic syndrome; however, it can be generally concluded that by adhering to the guidelines of a healthy diet, physiological homeostasis can be managed and a speedier recovery from the condition can be accomplished. Women with PCOS who change their behaviours to lose extra weight had better reproductive outcomes and better control over their periods. [8]The function of genetics and genes, A person's vulnerability to PCOS, a polygenic and complex disorder, has been shown to be influenced by certain genes, gene–gene interactions, or interactions between genes and the environment. Numerous genetic studies have connected a variety of PCOS symptoms to a number of potential genes that have single-nucleotide polymorphisms or mutations. PCOS is linked to all genes and mutations that have a direct or indirect impact on the ovaries.

The most often implicated genes in the pathophysiology of PCOS are those that encode signalling components related to steroidogenesis, steroid hormone action, gonadotrophin action and regulation, insulin action and secretion, energy metabolism, and chronic inflammation. Finding genetic markers could help diagnose this syndrome more accurately, enabling more specialized care and early intervention for co-morbidities associated with the illness and its symptoms. [9] Gut Microbiota Dysbiosis: An Important Connection Comprising approximately 1013–1014 bacteria with a combined gene count nearly 200 times higher than the human genome, the gut microbiome is an "organ" unto itself. Gut dysbiosis appears to be the cause of inflammation and alterations in gut permeability, which can affect a host's health. Immunological function, metabolism, nutrition, and physiology are all impacted by the delicate balance that the gut microbiota and the host maintain under physiological conditions. It also has a significant impact on the prevention of some illnesses. There are notable variations in the microbiome composition of healthy people, and these variations

may make an individual more susceptible to certain diseases. In recent years, many studies have examined the connection between PCOS and alterations in the gut flora. According to these research, PCOS patients' gut microbiota composition was substantially different from that of healthy controls. The variety and structure of the gut microbiome in women with PCOS may be influenced by factors such as insulin resistance, sex hormone levels, and obesity, according to research. The gut microbiota and its byproducts are intimately associated with PCOS. The main cause of the notable difference in the number of species and metabolites produced by PCOS and the control group was a decline in microbial diversity, which was characterized by a rise in pathogenic bacteria (Escherichia and Shigella) and a fall in beneficial bacteria (Lactobacilli and Bifidobacteria).

Among the host tissues whose functions are changed in PCOS include the ovary, liver, skeletal muscle, and adipose tissue. The gut microbiota produces substances that can either act directly on the intestines or enter the systemic circulation by metabolizing the substrates that enter the gut through meals. Short-chain fatty acids (SCFAs), secondary bile acids, and trimethylamine (TMA) are a few guts bacterial metabolites that are altered in PCOS. Numerous research using human and animal models have shown a link between changes in gut microbiota and PCOS, including alterations in some bacterial taxa and a decline in biodiversity, despite the broad variations in 16S rRNA and metagenomic gene sequencing data. [10]

III. COMPLICATION:

1. Reproductive Issue:

Infertility and subfertility are caused by insufficient follicular maturation and chronic anovulation. Amenorrhea, oligomenorrhea, irregular periods, and dysfunctional uterine bleeding are examples of menstrual disorders. Complications of pregnancy: increased risk of miscarriage. heightened vulnerability to gestational diabetes mellitus (GDM). preeclampsia and pregnancy-related hypertension. preterm delivery and low birth weight. Long-term exposure to estrogen without progesterone causes endometrial cancer and hyperplasia. The outcome of assisted reproductive technologies (ART) may be impacted by poor-quality oocytes and embryos.

2. Problems with Metabolism:

Insulin resistance is thought to be the most prevalent metabolic disease. The development of compensatory hyperinsulinemia, which intensifies ovarian androgen production, is common. Women who are affected have a higher chance of developing type 2 diabetes mellitus (T2DM) earlier in life. Central obesity, dyslipidaemia, hypertension, and decreased glucose tolerance are all common symptoms of metabolic syndrome. There is mounting evidence that non-alcoholic fatty liver disease (NAFLD) is a hepatic manifestation of insulin resistance. Obesity and central adiposity are commonly associated and are known to exacerbate endocrine and metabolic problems. Chronic low-grade inflammation is often observed and is likely to worsen insulin resistance. Vitamin D deficiency and aberrant calcium metabolism have frequently been associated with metabolic dysfunction in PCOS.

3. Problems with the Heart:

It is believed that insulin resistance, hyperinsulinemia, and an overactive sympathetic nervous system are the causes of the hypertension that many women with PCOS report suffering. Elevated blood pressure further increases the risk of long-term cardiovascular disease. Commonly observed dyslipidaemia is characterized by elevated triglycerides, elevated low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol. These lipid abnormalities significantly impact the cardiovascular risk profile of affected women and promote atherosclerosis.

Early vascular problems and atherosclerosis are more common in women with PCOS. Clinical studies have consistently demonstrated carotid intima-media thickness, arterial stiffness, and endothelial dysfunction, indicating that subclinical vascular disease develops significantly earlier in this population, while coronary artery disease (CAD) and ischemic heart disease (IHD) are more likely to develop later in life. The combination of obesity, insulin resistance, dyslipidaemia, and metabolic syndrome creates a substantial risk of major adverse cardiac events. Chronic low-grade inflammation is often indicated by elevated inflammatory markers such as C-reactive protein (CRP). This inflammatory condition is believed to accelerate vascular damage and contribute to endothelial dysfunction. [11]

4. Complications related to psychology and neuropsychiatry:

Depression is frequently reported by women with PCOS. The combined reasons are believed to be hormonal imbalances, metabolic dysfunction, body image dissatisfaction (from obesity, acne, and hirsutism), and infertility-related misery.

Among the anxiety disorders that are frequently diagnosed include panic disorder, social phobia, and generalized anxiety disorder. These disorders are sometimes exacerbated by long-term health problems and reproductive uncertainty.

Low self-esteem and issues with body image are sometimes caused by cosmetic manifestations such as obesity, hirsutism, acne, and alopecia. These symptoms are clearly associated with a lower quality of life.

It has been discovered that eating disorders, particularly bulimia nervosa and binge eating disorder, are more common in women with PCOS. The incidence of sleep disturbances including insomnia and poor sleep quality might be largely attributed to hormonal dysregulation and related conditions like obesity and obstructive sleep apnea. These disturbances may lead to a decline in mood and cognitive function. [12]

5. Risks of Oncology

Endometrial hyperplasia and endometrial carcinoma are considerably more likely to occur in women with PCOS. Chronic anovulation, which leads to extended unopposed estrogen exposure without sufficient progesterone opposition, is the cause of this risk. While the precise correlation between PCOS and ovarian cancer remains uncertain, certain studies indicate a marginally increased risk. Hyperandrogenism, ovulatory dysfunction, and chronic gonadotropin stimulation have all been proposed as contributory reasons. Breast cancer Regarding the risk of breast cancer in PCOS, there is conflicting data. Some studies suggest that prolonged exposure to estrogen changes sex steroid metabolism, which raises the risk marginally, particularly in obese and insulin-resistant women. colon cancer. Recent studies have suggested a link between PCOS and an increased risk of colorectal cancer. [13]

IV. PATHOPHYSIOLOGY:

The pathophysiology of PCOS is believed to be complex and multidimensional. Insulin resistance, increased luteinizing hormone (LH), antimalarial hormone (AMH), and ovarian steroid production have all been connected to disruptions in the hypothalamic-pituitary-ovarian (HPO) axis. These routes are believed to interact at different points over the course of the illness. In recent years, PCOS has gained more recognized as a metabolic disorder. The reciprocal relationship between excessive testosterone and hyperinsulinemia is considered to be one significant pathogenic feature. Insulin resistance causes compensatory hyperinsulinemia in about 70% of women with PCOS. Impaired catecholamine sensitivity to lipolysis has been demonstrated to be a precursor to insulin resistance. The ovary becomes sensitized to LH as a result of insulin's interference with normal homologous desensitization to LH. Insulin-like growth factors (IGF) also contribute to follicular maturation and steroid production by interacting with FSH in granulosa cells. [14] It has been shown that P450c17 and other androgen-producing enzymes are overexpressed in PCOS theca cells. Androgen is overproduced as a result. Granulosa cells prematurely lutein ate when insulin and androgen levels are too high. Furthermore, sex hormone-binding globulin (SHBG) is decreased and the liver's IGF-1 binding proteins are altered by hyperinsulinemia, both of which increase the amounts of free androgen. A vicious cycle is created when androgen excess exacerbates IGF-1 imbalance, which in turn leads to impaired follicular maturation and oligo-ovulation.

Increased androgen responses to gonadotropin stimulation are a hallmark of functional ovarian hyperandrogenism (FOH), which affects most women with PCOS. Unusual ovarian reactions and isolated adrenal hyperandrogenism are less common in women. Excess androgens lead to polycystic ovarian morphology (PCOM), which compromises dominant follicle selection while encouraging early follicle recruitment. Excess LH, which stimulates hormone secretion and steroid enzyme activity, is frequently linked to PCOS. But, as theca cells usually become desensitized with prolonged exposure to LH, it is less likely to be the primary cause of androgen excess. Instead, hyperandrogenism, which promotes excess LH, maintains ovarian dysfunction.

When the plasticity of gonadotropin-releasing hormone (GnRH) is changed, the secretion of LH is somewhat larger than that of FSH. By encouraging androgen synthesis and reducing aromatase activity in granulosa cells, this restricts the conversion of androgens to estrogen. Peripheral conversion of androgens to estrogens, mainly estrone, occurs in adipose tissue, and it is particularly noticeable in obese women. Extended exposure to estrogen in the absence of normal cyclic fluctuation is one of the factors causing endometrial hyperplasia. [15] Low-grade chronic inflammation has also been linked to elevated C-reactive protein levels, even in thin

PCOS women. More and more research is being done on the role that inflammatory and autoimmune pathways play in abnormal follicular development and infertility.

The biochemical hallmark of PCOS, hyperandrogenaemia, manifests clinically as hirsutism, acne, and alopecia. High levels of androgens are present in 75–90% in PCOS patients with oligomenorrhea, and these levels frequently increase as the condition worsens. The overproduction of androgen by the ovaries and adrenal glands results in hyperandrogenism. Increased levels of free (unbound) testosterone, a crucial hormone in the pathogenesis of PCOS, are a hallmark of hyperandrogenism. Abnormal adrenal or ovarian function leads to an excess of androgens. Poor folliculogenesis is the first effect of excess androgens interfering with normal androgen production in PCOS. During the early gonadotropin stage, a rise in antral follicles and the development of primordial follicles are encouraged by excess androgens.

Based on the diagnostic criteria, between 8% and 20% of women globally who are of reproductive age suffer from PCOS annually. The pathophysiology of this condition involves alterations in ovarian folliculogenesis, steroidogenesis, neuroendocrine function, metabolism, insulin sensitivity, insulin production, adipose cell activity, inflammatory factors, and sympathetic nerve function. According to Barre et al., excessive carbohydrate intake, hyperinsulinemia, hyperandrogenemia, and persistent low-grade inflammation are the four primary causes of pathophysiological alterations in PCOS. (Figure 1).

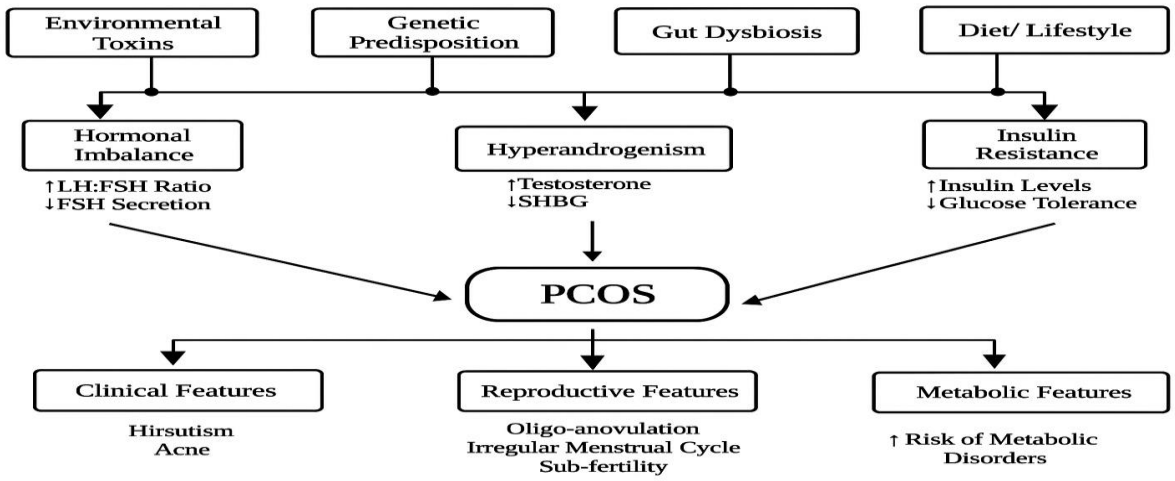

figure 1:the suggested pathogenesis and characteristics of PCOS are depicted in this schematic figure. risk factors that contribute to the pathophysiology of PCOS and subsequent development of clinical, reproductive, and metabolic characteristics in PCOS*[16]*

Figure 1. The suggested pathogenesis and characteristics of PCOS are depicted in this schematic figure. Risk factors that contribute to the pathophysiology of PCOS and the subsequent development of clinical, reproductive, and metabolic characteristics in PCOS patients include genetics, gut dysbiosis, environmental toxins, and food. FSH stands for follicle stimulating hormone, LH for luteinizing hormone, and SHBG for sex hormone binding globulin.

V. NUTRITIONAL ALLOPATHIC REMEDIES:

The following drug classes are utilized or being researched:

- hormone therapy
- hormone-preventive agents
- insulin-sensitive agents
- ovulation-inducing agents
- weight-loss medications
- psychotropic drugs (for associated mental health disorders).

VI. MANAGEMENT ADVANCES

Supplemental Vitamins, A vital mineral, vitamin D is mostly obtained from exposure to sunlight but can also be present in some foods like oily fish and fortified dairy. The metabolism of calcium and the preservation of bone health depend heavily on vitamin D. According to certain research, women with Polycystic Ovary Syndrome (PCOS) may benefit from vitamin D supplementation in terms of insulin sensitivity and hormonal balance, especially if they take it daily. Its effect on inflammation, hyperandrogenism, and lipid profiles is less clear, but. Vitamin B-8 (inositol): Myo-Inositol (MI) and Dchiro-Inositol (DI) are two forms of inositol that are crucial for controlling insulin signalling and glucose absorption in the ovaries. MI and DI abnormalities are common in PCOS-afflicted women, and they may have an impact

on glucose metabolism and reproductive health. It has been demonstrated that using MI supplements improves insulin resistance and lowers fasting insulin levels. Sex Hormone Binding Globulin (SHBG) levels may also rise as a result of MI however this impact is more noticeable after at least 24 weeks of treatment. In women with PCOS, inositol administration has been linked to better ovulation rates, menstrual cycle management, and hormonal balance (Fig. 1). Folate/Folic Acid (Vitamin B-9): Folic acid, a synthetic version of folate, is necessary for the production of DNA and RNA as well as other metabolic processes. Folic acid supplementation has been associated with better glycaemic control, decreased oxidative stress, and inflammation in women with PCOS, especially those who are overweight or obese. It appears that higher folic acid dosages are more successful in enhancing lipid profiles and insulin sensitivity. Vitamin K: Known as K1 from green vegetables and K2 from animal products, vitamin K contributes to blood coagulation and supports healthy bones and arteries. According to certain research, vitamin K supplements—more especially, vitamin K2—may help women with PCOS with their androgen levels and insulin resistance. Nevertheless, additional investigation is required to validate these results.

Vitamin E: Free radicals can be neutralized by vitamin E, an antioxidant. It has demonstrated potential in decreasing insulin resistance and lowering androgen levels in women with PCOS when taken in conjunction with other nutrients such as omega-3 fatty acids or coenzyme Q10. Nevertheless, there aren't many research that only look at vitamin E supplementation in PCOS.

Vitamin A: Also referred to as retinol, vitamin A may have a part in PCOS androgen production and metabolic processes. The precise benefits of vitamin A supplementation in women with PCOS are unknown, nevertheless, as there is currently no direct research on the topic.[17]

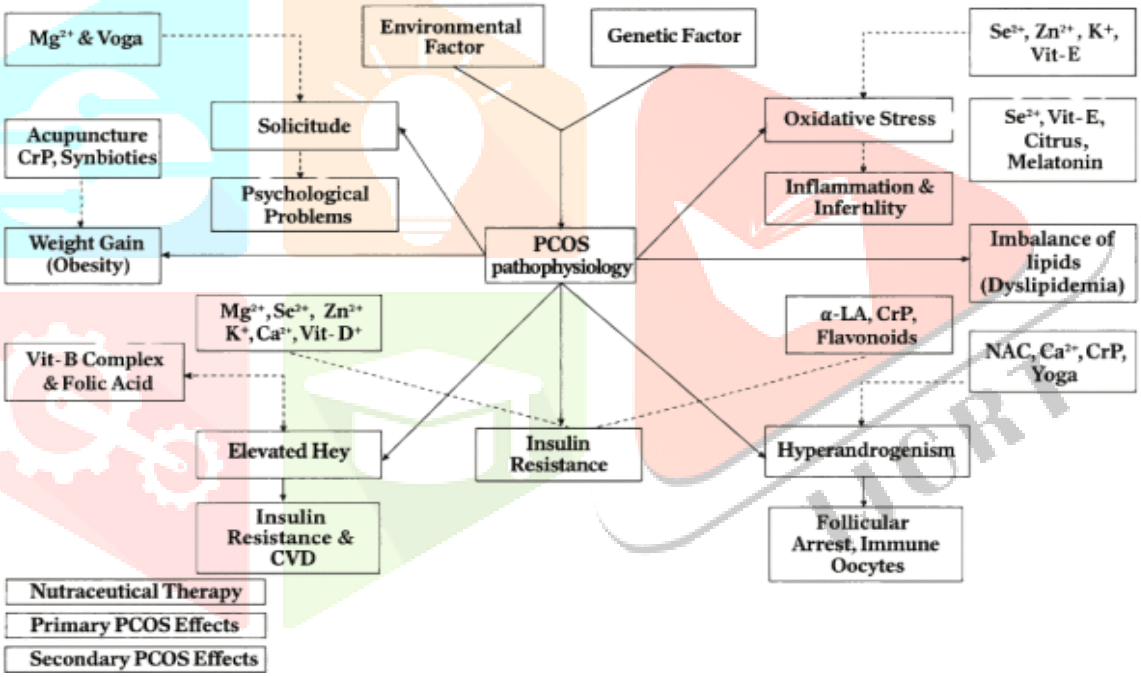

figure 2:alternative treatments and nutritional supplements for polycystic ovarian syndrome may have an impact on risk factors and health. dashed arrows indicate calming effects, whereas solid arrows indicate increasing ones

Like Vitamins Nutrients

Plant-derived polyphenolic chemicals known as bioflavonoids have anti-inflammatory, anti-estrogenic, anti-proliferative, antidiabetic, and antioxidant qualities. A subclass of bioflavonoids known as isoflavones has drawn attention because of its purported neuroplasticity-promoting and cardioprotective properties. Apples, berries, grapes, and onions contain quercetin, which is thought to have anti-inflammatory and metabolic properties. According to certain research, lipid profiles and insulin resistance may be improved by quercetin and isoflavones like genistein in PCOS. To validate their effectiveness, more research is necessary as the evidence is conflicting. Among other metabolic processes, L-carnitine specifically plays a role in the metabolism of glucose and fatty acids. Women with PCOS often have reduced amounts of L-carnitine, which can worsen insulin and androgen-related issues and impact the quality of their eggs. L-carnitine supplementation has shown promise in reducing insulin sensitivity, BMI, and LDL levels in women with PCOS. More research is required to look more closely at its potential benefits. Alpha-lipoic acid is an antioxidant and a crucial cofactor in the citric acid cycle. It has been suggested that controlling body weight can be achieved by increasing energy expenditure and decreasing food intake. In some studies, taking α-LA

supplements have been demonstrated to improve insulin resistance, reduce LDL and triglyceride levels, and perhaps regulate lipid metabolism. A study that paired α-LA with D-chiro-inositol (DI) found improvements in menstrual cycles, ovarian cysts, progesterone levels, BMI, and insulin resistance; however, further research is needed to fully understand its benefits in PCOS. [18] Extra Minerals CrP, which includes essential trivalent chromium, has been shown in numerous Randomized Controlled Trials (RCTs) and systematic reviews to improve glycaemic control, hirsutism, acne, and Insulin Resistance (IR) in women with PCOS. However, there are contradictory results from different studies, and further research is needed to offer conclusive evidence of its efficacy. Women with PCOS often have abnormal calcium levels, which may be caused by differences in parathyroid hormone and vitamin D. When calcium and vitamin D supplements are used together, several PCOS symptoms have improved, including lipid profiles, menstrual regularity, insulin resistance, hirsutism, and testosterone levels.

- ✓ Magnesium is involved in the metabolism of insulin and the nervous system. According to some data, magnesium supplements may help lower IR in women with PCOS; however, more research is needed, especially to determine how it affects feelings of depression.
- ✓ Selenium is a significant trace element that has antioxidant and anti-inflammatory qualities. In women with PCOS, selenium supplementation has been shown to reduce insulin resistance, inflammation, and oxidative stress. However, there are conflicting findings on other PCOS characteristics like BMI and hormone indicators.
- ✓ The synthesis and function of insulin depend on zinc. Zinc supplementation has been associated with improvements in lipid profiles, HOMA-IR, inflammation, and oxidative stress in women with PCOS. In certain trials, there were additional decreases in free testosterone (ft), FSH, and DHEAS. However, because some of these trials incorporated mineral combinations, it is challenging to attribute all stated effects to zinc supplementation alone.

Low-Glycaemic Foods

The Glycaemic Index (GI) measures how quickly the sugar and carbohydrate content of food is absorbed into the bloodstream. meals with a high glycaemic index cause blood sugar levels to rise dramatically and quickly, while meals with a low glycaemic index cause blood sugar levels to rise more gradually and discreetly. To reduce risks and improve PCOS biochemical and clinical outcomes, a low-glycaemic diet is crucial. These diets reduce weight gain and dyslipidaemia while reducing hunger and carbohydrate cravings. Low-processed, high-fibre meals like whole wheat bread, sweet potatoes, chickpeas, lentils, apples, and oats are what define them. They are helpful for effectively managing PCOS, based on long-term data. Table 1:

Table 1: Sources of Low, Moderate and High glycaemic index foods:

Sources	**Index- Low Glycaemic**	**Index- Moderate Glycaemic**	**Index-High Glycaemic**	**References**
Vegetables	Asparagus, Broccoli, cucumber, Cabbage, Eggplant, Green beans Lettuce, Mushrooms, Onions Raw carrots, Tomatoes.	Beetroot	Potato, Pumpkin	[27], [28]
Fruits	Apples, Dried Apricots, Cherries, Grapes, Guava, Kiwi, Oranges, Plums, Peaches, Pomegranate, Strawberries	Bananas, Figs, Mango, papaya, Pineapple, Raisins	Dates, Watermelon	[27],[29]
Dairy	Buttermilk, Curd, Skim Milk, Soy Milk, Whole milk, Paneer, Yogurt	Ice-cream	-	[27],[28]
Beans/Legumes	Chickpea, Red & Green Lentils, Kidney beans	-	-	[27],[28],
Starch	Barley, Quinoa, Popcorn, Peas, Sweet corn, Rice bran	Basmati rice, Brown rice, Instant Cooking Oats, Sweet potato	Carrots, White rice, White bread, Potato	[28],[29]

Vitamin D: According to estimates, vitamin D deficiency affects between 67 and 85 percent of PCOS patients. There is evidence that low vitamin D levels are associated with obesity, and a vitamin D deficiency may indicate an excess of fat tissue. more blood. Increased anti-Mullerian hormone (AMH) levels and other measures of ovarian reserve are associated with higher (OH)D concentrations, suggesting that sufficient vitamin D levels may support ovarian function and potentially prevent early ovarian depletion. Vitamin D supplements can reduce insulin. Research has shown that low vitamin D levels can lead to the development of insulin resistance and PCOS, and that vitamin D is involved in several metabolic processes, including insulin metabolism. There may be a connection between vitamin D levels and hormonal and metabolic issues in PCOS patients, according to recent review research by Thomson et al. [19]

Calcium: The decrease in circulating androgens suggests that calcium and vitamin D may directly affect the pathway that results in the production of ovarian and/or adrenal steroid hormones. Research indicates that 1,25-Dihydroxyvitamin D causes pancreatic β-cells' intracellular calcium levels to rise, which in turn causes an increase in insulin secretion. Because vitamin D promotes the expression of calcium-binding proteins in β-cells, it is necessary for the release of insulin. Blood calcium levels and insulin sensitivity were found to be favourably connected in a healthy population. According to this study, maintaining optimum calcium levels may have an impact on glucose metabolism and insulin sensitivity.

Prebiotics: Prebiotics are non-living, indigestible fibres that can support the growth and activity of the good bacteria in the gut. There is proof that compared to women without PCOS, women with the condition have a less varied gut flora and higher intestinal permeability. Hyperandrogenism and elevated systemic inflammation have been connected to this decrease in gut bacterial diversity. The dysbiosis of the gut microbiota has an impact on the pathogenesis of PCOS. One of the processes that activates the host's immune system is the dysbiosis of the gut microbiota**.**

The Fatty Acids: Dietary polyunsaturated fatty acids (PUFAs) are beneficial for those with PCOS who have insulin resistance, decreased vascular endothelial function, and dyslipidaemia. Omega-3 fatty acids, one of the less prevalent polyunsaturated fatty acids (PUFAs), are found only in deep-sea fish and plant sources (such as green leafy vegetables, seeds, and vegetable oils). According to new research from the Scientific Congress of the American Society of Reproductive Medicine, omega-3 fatty acids can help women with PCOS become more fertile and increase their chances of getting pregnant. [20]

VII. CONCLUSION

It is clear that the etiology of PCOS is complex and multivariate, with little knowledge of its causes. Furthermore, the precise role of adipose tissue is unknown. Utilizing our recently altered understanding of adipocyte physiology/pathophysiology has been advantageous and timely in order to explore its function in greater detail. This review has outlined the main characteristics of this application. The question of whether adipose tissue is an innocent bystander or plays a major part in the aetiology of PCOS remains unanswered, nevertheless.

Similar to type 2 diabetes, weight gain is intimately linked to the development of PCOS. Nonetheless, PCOS can develop in individuals who are neither overweight nor obese. Therefore, although obesity is associated with PCOS, it is not a prerequisite for its beginning. Furthermore, the association between adiposity and PCOS development, particularly in Android, does not imply that adiposity causes PCOS. Indeed, it is commonly known that normal women may develop android adiposity if they are exposed to high levels of testosterone in their serum. It seems likely that the development of android adiposity in women with PCOS is influenced by the effects of hyperandrogenism on the adipocyte. This is supported by experimental results in female sheep and rhesus monkeys that have undergone androgenization during pregnancy. These demonstrate that throughout fatal and postnatal development, genetically controlled hyper-secretion of ovarian androgens results in the deposition of fat in an android distribution. These conclusions are supported by data from human research. Women who are just fat, especially those with android, are not likely to develop PCOS. Therefore, it is incorrect to say that fat is the cause of PCOS. Nonetheless, there is proof that obesity worsens metabolic and reproductive characteristics in many women with the condition, and weight loss remains the most effective treatment. In women who are genetically prone to PCOS, gaining weight may be enough to identify the condition.

It is likely that the prevalence of PCOS will increase in tandem with the obesity epidemic. The complex aetiology of PCOS involves both genetic and environmental factors, particularly dietary ones. Both of these

factors influence adiposity, which in turn influences the severity and presentation of PCOS. Because of the intricacy of adipocyte physiology and pathology, we have most likely only just begun to understand the mechanisms linking obesity and adiposity to PCOS. [21]

REFERENCE:

1. Nagarathna P., Rajan P.R. and Koneri R. A. Detailed study on polycystic ovarian syndrome and its treatment with Natural Products. *International journal of toxicological and pharmacological research*. 2014;5(4):109-120
https://dx.doi.org/10.13005/bpj/3105

2. Teede H.J., Misso M.L., Costello M.F., Dokras A., Laven J., Moran L., Piltonen T. and Norman R. J. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertility and Sterility*. 2018;110(3): 364-379. https://doi.org/10.1016/j.fertnstert.2018.05.004

3. Zeng L.H., Rana S., Hussain L., Asif M., Mehmood M.H., Imran I., Younas A., Mahdy A., Al-Joufi F.A. and Abed SN. Polycystic Ovary Syndrome: A Disorder of reproductive age, Its pathogenesis, and a discussion on the emerging role of herbal remedies. *Frontiers in Pharmacology*. 2022; 13:874914. https://doi.org/10.3389/fphar.2022.874914

4. Bulsara J., Patel P., Soni A. and Acharya S. A review: Brief insight into polycystic ovarian syndrome. *Endocrinology and Metabolism*. 2021;3:1-7.doi: 10.1016/j.endmts.2021.100085 https://doi.org/10.1016/j.endmts.2021.100085

5. Deans R. Polycystic ovary syndrome in adolescence. Med. Sci. 2019; 7:101. doi: 10.3390/medsci7100101 **https://doi.org/10.3390/medsci7100101**

6. Witchell S.F., E Oberfield S., Peña A.S. Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment with Emphasis on Adolescent Girls. J. Endocr. Soc. 2019; 1545–1573. Doi: 10.1210/js.2019-00078 https://doi.org/10.1210/js.2019-00078

7. Khan, M.J.; Ullah, A.; Basit, S. Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives. *Appl. Clin. Genet.* **2019**, *12*, 249–260.
https://doi.org/10.2147/TACG.S200341

8. Wang, T.; Sha, L.; Li, Y.; Zhu, L.; Wang, Z.; Li, K.; Lu, H.; Bao, T.; Guo, L.; Zhang, X.; et al. Dietary α-Linolenic acid-rich flaxseed oil exerts beneficial effects on polycystic ovary syndrome through sex steroid hormones—Microbiota—Inflammation axis in rats. *Front. Endocrinol.* **2020**, *11*, 284.
https://doi.org/10.3389/fendo.2020.00284

9. Victor, V.M.; Rocha, M.; Banuls, C.; Alvarez, A.; de Pablo, C.; Sanchez-Serrano, M.; Gomez, M.; Hernandez-Mijares, A. Induction of oxidative stress and human leukocyte/endothelial cell interactions in polycystic ovary syndrome patients with insulin resistance. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 3115–3122.
https://doi.org/10.1210/jc.2011-0651

10. Yang, Q.; Zhao, Y.; Qiu, X.; Zhang, C.; Li, R.; Qiao, J. Association of serum levels of typical organic pollutants with polycystic ovary syndrome (PCOS): A case–control study. *Hum. Reprod.* **2015**, *30*, 1964–1973
https://doi.org/10.1093/humrep/dev123

11. González, F.; Considine, R.V.; Abdelhadi, O.A.; Acton, A.J. Saturated fat ingestion promotes lipopolysaccharide-mediated inflammation and insulin resistance in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 934–946.
https://doi.org/10.1210/jc.2018-01143

12. Wang, T.; Sha, L.; Li, Y.; Zhu, L.; Wang, Z.; Li, K.; Lu, H.; Bao, T.; Guo, L.; Zhang, X.; et al. Dietary α-Linolenic acid-rich flaxseed oil exerts beneficial effects on polycystic ovary syndrome through sex steroid hormones—Microbiota—Inflammation axis in rats. *Front. Endocrinol.* **2020**, *11*, 284. https://doi.org/10.3389/fendo.2020.00284

13. Barber, T.M.; Hanson, P.; Weickert, M.O.; Franks, S. Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. *Clin. Med. Insights. Reprod. Health* **2019**, *13*, 1179558119874042. https://doi.org/10.1177/1179558119874042

14. Barber, T.M.; Kabisch, S.; Pfeiffer, A.F.H.; Weickert, M.O. The Health Benefits of Dietary Fibre. *Nutrients* **2020**, *12*, 3209. **https://doi.org/10.3390/nu12103209**

15. Szczuko, M.; Zapalowska-Chwyć, M.; Drozd, R. A low glycemic index decreases inflammation by increasing the concentration of uric acid and the activity of glutathione peroxidase (GPx3) in patients with polycystic ovary syndrome (PCOS). *Molecules* **2019**, *24*, 1508. **https://doi.org/10.3390/molecules24081508**

16. Shang, Y.; Zhou, H.; Hu, M.; Feng, H.J. Effect of diet on insulin resistance in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 3346–3360. https://doi.org/10.1210/clinem/dgaa425

17. Shang, Y.; Zhou, H.; Hu, M.; Feng, H.J. Effect of diet on insulin resistance in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 3346–3360. https://doi.org/10.1210/clinem/dgaa425

18. Singh, S.; Sharma, P.; Pal, N.; Kumawat, M.; Shubham, S.; Sarma, D.K.; Tiwari, R.R.; Kumar, M.; Nagpal, R. Impact of Environmental Pollutants on Gut Microbiome and Mental Health via the Gut–Brain Axis. *Microorganisms* **2022**, *10*, 1457. **https://doi.org/10.3390/microorganisms10071457**

19. Yurtdaş, G.; Akdevelioğlu, Y. A New Approach to Polycystic Ovary Syndrome: The Gut Microbiota. **2020**, *39*,371–382 https://doi.org/10.1080/07315724.2019.1657515

20. Liu, R.; Zhang, C.; Shi, Y.; Zhang, F.; Li, L.; Wang, X.; Ling, Y.; Fu, H.; Dong, W.; Shen, J.; et al. Dysbiosis of gut microbiota associated with clinical parameters in polycystic ovary syndrome. *Front. Microbiol.* **2017**, *8*, 324. https://doi.org/10.3389/fmicb.2017.00324

21. Rizk, M.G.; Thackray, V.G. Intersection of Polycystic Ovary Syndrome and the Gut Microbiome. *J. Endocr. Soc.* **2020**, *5*, bvaa177. https://doi.org/10.1210/jendso/bvaa177