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Polycystic Ovary Syndrome: Insights and Advances in Diagnosis and Management

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Abstract

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, characterized by its chronic and complex nature. This condition is marked by a combination of ovarian dysfunction and symptoms related to excess androgen, often classified as heterogeneous due to its varied manifestations. PCOS poses significant public health challenges, as it is associated with multiple long-term metabolic issues and a range of comorbidities. The prevalence of PCOS appears to be rising, underscoring the need for effective management strategies.

Research indicates that certain medications may be beneficial for managing PCOS symptoms. These include thiazolidinedione's, dipeptide peptidase-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors, HMG-CoA reductase inhibitors, mucolytic agents, and various dietary supplements. However, there is a pressing need for further studies, including well-designed clinical trials involving diverse populations and clearly defined outcomes. Gaining a deeper understanding of PCOS will enable researchers to explore new therapeutic avenues and potentially develop innovative treatments targeting previously unrecognized pathways.

Keywords: Polycystic Ovary Syndrome (PCOS); Endocrine Disorder; Ovarian Dysfunction; GLP-1 Receptor Agonists; SGLT-2 Inhibitors; HMG-CoA Reductase Inhibitors

Abbreviations

PCOS: Polycystic Ovary Syndrome; GNRH: Gonadotropin-Releasing Hormone; LH: Luteinizing Hormone; HA: Hyperandrogenism; IR: Insulin Resistance; PCOS: Polycystic Ovary Syndrome; LHCGR: Luteinizing Hormone/ Choriogondotropin Receptor; EPHX1: Enzyme Peroxide Hydrolyses 1; PPAR-γ: Peroxisome Proliferators-Activated Receptor Gamma; EDCs: Endocrine-Disrupting Chemicals; BPA: Biphenyl A; USEPA: US Environmental Protection Agency; PVC: Polyvinyl Chloride; GPCR30: G-Protein Coupled Receptor 30; ER: Estrogen Receptor; HPA: Hypothalamic Pituitary Adrenal; SFAs: Saturated Fatty Acids; RNS: Reactive Nitrogen Species; NF-KB: Nuclear Factor- Kappa; NEFAs: Non-Esterfied Fatty Acids; TAUS: Transabdominal 2-D Ultrasound; NIH: National Institute of Health; AMH: Antimullerian Hormone; OHSS: Ovarian Hyper Stimulation Syndrome; GI: Gastrointestinal; OCs: Oral Contraceptives.

Introduction

A diverse endocrine condition that affects many women worldwide who are of reproductive age is called polycystic ovarian syndrome (PCOS).This syndrome is frequently linked

to insulin resistance, high levels of testosterone, oversized and malfunctioning ovaries, etc. According to estimates, one in ten women will experience PCOS prior to menopause and struggle with its aftereffects.

The primary causes of PCOS are recognized to be the elevated frequency of gonadotropin-releasing hormone (GNRH) and the high ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH), however the precise path physiology and etiology are still unclear. A variety of internal and external factors, such as genetics, epigenetics environmental factors, hyperandrogenism (HA), and insulin resistance (IR), are implicated in the phenomenon. Furthermore, it's important to note that PCOS raises the likelihood of developing other issues such as metabolic syndrome, anxiety, depression, type 2 diabetes mellitus, and cardiovascular illnesses.

Effective management of PCOS requires a multi-faceted approach starting with a 5% weight loss through regular exercise and a balanced diet low in fat and sugar some women may also prefer complementary and alternative medicine due to personal belief or cost considerations conventional treatments include oral contraceptives. Ant androgen agent's insulin sensitizers and ovulation inducers although no medication is specifically FDA- approved for PCOS. To address this research are exploring new drug development and repurposing existing FDA approved medications for alternative indications including PCOS management this approach aims to identify novel therapeutic options for PCOS treatment.

Due to the limitations of current treatment for polycystic ovary syndrome (PCOS) and its associated complications. Further research is crucial to understand its understanding its underlying causes and identify new therapeutic targets this review aims to provide a comprehensive overview of PCOS including its definition, diagnosis and etiology with a focus on its pathogenesis and management the discussion encompasses both internal and external factors contributing to PCOS as well as commonly prescribed medications and their effects additionally the review highlights the potential of repurposed medications supported by clinical trials conduct over the past five years which may offer new hope for improving PCOS treatment outcomes.

Causes and Contributing Factors

External Factors: Mechanism of epigenetic: The term "epigenetic" describes heritable modifications to the genome and the expression of genes without affecting the sequence of DNA. These modifications entail the addition or removal of chemical elements from his tones or DNA one phenomenon associated with PCOS women is increased LH activity. It might be connected to the issues with HA and follicle development that PCOS patients frequently experience the process of steroid genesis in cell is controlled by the LH\choriogondotropin receptor (LHCGR). Higher gene expression and sensitivity to LH top resulted from this receptor hypomethylation. According to a study on PCOS patients hyper ethylated sites are linked to LHCGR over expression on the surface of theca cells. Furthermore the enzyme peroxide hydrolyses 1(EPHX1) is active in the degradation of aromatic compounds. Enzymes expression is increase due to hypomethylation of its gene promoter. Reduced testorone to oestradiol conversion due to overproduction of EPHX1 may exacerbate PCOS. Moreover, the function of the ovaries is influenced by peroxisome proliferators-activated receptor gamma (PPAR-γ), hypomethylation of PPAR γ, hyperpolymethylation of nuclear co repress or, and modification in histones deacetylase 3's acetylating are noted. These changes were observed in the granulose cells of women with PCOS.

Environmental Toxicants: Endocrine-disrupting chemicals (EDCs) are defined as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior" by the US Environmental protection agency (USEPA).

When EDCs bind to hormone receptors, they may function as either agonists or antagonists. Nearly every item we use on a regular basis contains an EDC. They mimic the effects of steroid hormones since their structures are made of phenols or halogens like chlorine and bromine. Research has demonstrated that women with PCOS had increased serum concentrations of EDCS. From pregnancy through puberty, prolonged and continuous exposure to EDCs can increase a person's risk of developing PCOS.

The overproduction of androgens caused by dysregulation of steroid genic acute regulatory protein, cholesterol side-chain cleavage enzyme (P450c17) is another consequence of BPA on interstitial theca cells. The reduction of aromatase enzyme expression and estrogen production is the effect of BPA on granulose cells. The indirect effect of BPA on HA is attributed to the down regulation of the liver-level enzymes testosterone 6b-hydroxylase and testosterone 2a-hydroxylase, which results in a greater concentration of testosterone.

As an illustration, consider biphenyl A (BPA), a synthetic chemical found in polycarbonate plastics, epoxy resins, food and drink packaging, dental filling, baby bottles, and polyvinyl chloride (PVC). BPA influences metabolism in a variety

of ways. By interacting with G-protein coupled receptor 30 (GPCR30), non- classical membrane ER, and estrogen receptor (ER) α and β, BPA directly impacts oogenesis. Additionally, it inhibits the breakdown of testosterone in theca cells and initiates androgen production.

Physical and Emotional Stress: Stress on the body and mind while little is known about how stress contributes to PCOS it is well recognized the PCOS negatively impacts mental and self-esteem. Adipocyte hyperplasia and hypertrophy are the outcomes of persistent stress. The effect of glucocorticods on the maturation pre-adipocytes is responsible for this phenomenon. Additionally adipokine production attraction and activation of stromal fat immune cells are linked to chronic stress. Furthermore it triggers an inflammatory state by elevating inflammatory cytokines such a TNF-α and IL-6and by upsetting the equilibrium between antioxidants and oxidants. Furthermore persistent stress is a major factor in IR. The hypothalamic –pituitary-adrenal (HPA) axis releases cortisol in response to stress.

Diet: Nutrition studies have demonstrated a correlation between certain nutritional levels and PCOS indices, notwithstanding the unclear role that nutrition plays in PCOS. Consuming saturated fatty acids (SFAs) increases the risk of PCOS by increasing inflammation and decreasing insulin sensitivity by raising the level of TNF-a in the blood and expressing a particular cytokine suppressor taking SFAs causes inflammation. A lack of vitamin D may make PCOS or the co morbidities it causes worse insulin receptors are up regulated at the mRNA and protein levels by calcitriol. Additionally it both directly and indirectly raises in-insulin sensitivity .by activating PPAR-8, a receptor involved in the metabolism of fatty acids in skeletal and adipose tissue the direct effect is achieved intracellular regulation is the indirect effect.

Internal Factors

Insulin Resistance: Resistance to insulin an inadequate cell response to insulin is referred to as IR. Iris not influenced by a patient's level of testosterone body fat composition or adiposity thin persons have also been found to experience it should be noted that IR is tissue specific an in PCOS women even while ovaries, skeletal muscles adipose tissue and liver and adrenal gland retain their sensitivity to insulin.

Conversely, hyperinsulineia raises blood levels of free testosterone while decreasing hepatic SHBG furthermore the hepatic synthesis of IGF-1binding proteins is inhibited by hyperinsulineia. The production of androgens in thecal cells is initiated by IGF-1. A greater concentration of this material in the blood stream and subsequently a higher production of androgens in thecal cells are the results of inhibiting the formation of IGF-1binding proteins the more IGF-1 up regulation suppresses particular miRNA.which quickness the death of granulose cells and prevent folliculogenisis. The development of follicles is inhibited by both HA and hyper insulin –mica. Menstrual irregularity, ovulatory sub fertility, and the accumulation of immature follicles are the reason for this cessation.

Excessive Masculinity: In general hyperandrogenism (HA) raises the concentration of free test estrogen by lowering the SHBG level women with PCOS have been found to have greater plasma amount of testosterone which can be converted to oestrogen in adipose tissue ovulatory dysfunction is brought on by increased oestrogen to oestradiol change which affects follicle development and raises the LH to FSH ratio.

Oxidative Stress: Oxidative stress is an imbalance between pro-oxidants and antioxidants oxidative molecules include different chemicals such as reactive oxygen species and reactive nitrogen species (RNS) ROS plays a role in different mechanisms like signaling pathways cell growth and differentiation as well as RNS.RONS also act on ovaries function like steroid genesis and affects neurons responsible for feeding behavior to induce hunger over production of oxidative chemicals cause various damage to vital molecules such as lipids proteins and DNA. Several studies have reported increased OS in PCOS patients nuclear factor- kappa (NF-KB) is activated by elevated OS levels NF-KB is implicated in inflammatory pathways and influences the synthesis of pro inflammatory cytokines such as TNF releases however rather of the typical tyrosine phosphorylation of IRS increased OS activates some protein kinases that cause serine/ threonine phosphorylation. As a results OS causes IR and the insulin signaling pathway is blocked. OS contributes to obesity as well it causes adult adipocytes to enlarge which in turn promotes pre-adipocytes growth adipocytes differentiation additionally enforces.

Obesity: One important factor in low grade chronic inflammatory is obesity adipocytes accumulation in visceral fat results in hypoxia and subsequent necrosis which triggers the release of inflammatory cytokines. An inflammatory state results from the death of adipocytes due to hypertrophy adipose tissue mononuclear cells release cytokines that promote inflammation. The inflammatory disease is also caused by excess abdominal fat.

Additionally, obesity contributes to the development of IR.HA and hyperinsulineia. Blood levels of non-esterfied fatty acids (NEFAs) rise in relation to visceral obesity. NEFAs are absorbed by skeletal muscles in place of glucose as energy source. Hyperinsulineia and a pancreatic fast response are caused by this hyperglycemia. Furthermore visceral fats

lipolytic reaction to catecholamine's results in lipotoxicity and decreased insulin clearance and activity.

Diagnosis: Due to the inherent features of polycystic ovarian syndrome, such as its heterogeneity and unpredictability across age groups, the illness is challenging to diagnose. In adolescent and menopausal women, PCOS is challenging or impossible to diagnose since puberty can resemble the symptoms and indicators of polycystic ovarian syndrome. It is quite simple to confuse menarche with the presence of many tiny antral follicles. Because of biological hyperandrogenism, menopausal women's memory of their menses is incredibly erroneous.

PCOS is characterized by infertility, oligomenorrhea or amenorrhea, and the existence of cystic ovaries, which are first detected via a laparotomy and then verified by biopsy. TV scanning has generally replaced transabdominal 2-D ultrasound (TAUS) due to its higher resolution and, frequently, patient desire. A transabdominal scan provides a comprehensive view of the pelvic cavity and could be helpful in identifying any uterine or ovarian developmental abnormalities that may be related. The interior structure of the ovaries can be seen more clearly and with more resolution with a transvaginal scan, particularly in obese women .The ultrasonographic examination makes it possible to assess the internal and exterior elements of the ovary. One of the most obvious signs of PCOS is excess androgens, or hyperandrogenism, which can be identified by a physical examination or laboratory testing to check for elevated androgen levels in the serum [1].

There have been Numerous Revisions to the Diagnostic Standards for PCOS:

The National Institute of Health (NIH) 1990 Established the Following Criteria:

- Chronic an ovulation
- Clinical, biochemical, and hyperandrogenism

Rotterdam Criteria 2003:

- Polycystic ovaries in imaging
- Oligo or anovulation
- Clinical or biochemical symptoms of hyperandrogenism

The 2009 AES Criterion is:

- Hyperandrogenism, which includes hirsutism and/or hyperandrogenaemia.
- Ovulatory dysfunction including oligo or anovulation and or PCO exclusion id any other androgen excess or related disorders.

Polycystic Ovaries or Ovulation Morphology on Ultrasound:

- The inclusion of ultrasonographic evidence of PCO morphology is contentious.
- Ovulatory failure, including oligo or anovulation and/or PCO exclusion of any other androgen excess or related illnesses.

Hyperandrogenism:

- It might be challenging to determine HA in females during clinical and biochemical evaluation.

Menstrual Disturbances Associated with Oligo/ Anovulation:

- Important diagnostic indicators include the lack of menstrual or more and/or 8 or more menstrual cycles annually.
- One of the most reliable surrogate markers of PCOS is oligomenorrhea. Excessive hair growth, irregular bleeding, obesity, hair loss, acne, and infertility are further traits.

Current Diagnostic Metrics:

- Levels of antimullerian hormone (AMH) have been suggested as a measure to take the place of ultrasonographic evaluation. The evaluation of ovarian stromal volume, which is expressed as the ratio of stromal area to the total area of the ovary (S/A ratio), is another diagnostic metric.
- It is necessary to perform a physical examination that includes taking your height, weight, and blood pressure. Along with palpating the thyroid gland for lumps or enlargement, a standard and comprehensive physical examination should have been performed to identify the existence of secondary sex characteristics. To identify the precise hormonal imbalance, laboratory measurements of prolactin, dehydroepiandrosterone, thyroid-stimulating hormone, and FSH, LH, and testosterone levels can yield additional diagnostic information. HDL and total cholesterol were also measured. The existence of 12 or more 2–9 mm diameter follicles in each ovary, as well as an elevated 10 ml ovarian volume, as determined by sonography.

Diagnosis Differentiation:

Exogenous androgens are one option the clinician needs to think about.

- Tumours that release androgen.
- Primeval.
- Cushing's illness.
- Failure of the ovaries.
- Dysfunction of the thyroid.

Assessment and Work-Up of the Diagnosis:

- Standard physical examination.
- Obese is defined as BMI < 30.
- Recording blood pressure.

Experiments Conducted in the Lab Include:

- S: estradiol and FSH estimates.
- Biochemical hyperandrogenaemia demonstrated.

The Laparoscopy is

- A laparoscopy is often performed on people with PCOS, especially those who are having problems getting pregnant.
- A brief general anesthetic is administered to the patient before to a laparoscopic procedure, which involves

making a small incision in the umbilicus and inserting a telescope to view the uterus, tubes and ovaries.

Methods

A thorough search of various databases, including Pub Med, Google scholar, science direct, TRIP database, and up to date, was conducted to identify relevant publications on PCOS, focusing on recent studies (since 2016) and excluding non – English language articles and animal studies. Additionally, was searched to gather information on completed or ongoing clinical trials investigating repurposed drugs for PCOS treatment within the last five years.

Treatment

Non Pharmaceutical Methods: Treatment for PCOS focuses on symptoms management because the underlying cause remains unknown, although there are treatment options for the syndrome, not all of them are effective, and the patient's desire to become pregnant may keep her from seeking help even when her symptoms are present, [83] Reducing insulin resistance, stopping androgens effects on target tissues, on target tissues, and reversing anovulation should all be treatment objections.

For obese PCOS patients, losing weight has several advantages. Reduced insulin, luteinizing hormone (LH), and testosterone levels are associated with weight loss. Additionally, by regulating ovulation, it enhances the likelihood of becoming pregnant. Multiple perforations are made on the ovarian surface and stromal during laparoscopic ovarian drilling, an outpatient surgical procedure. This intervention is thought to destroy tissue that produces androgen. It has been demonstrated to have the same level of effectiveness as medical therapies without raising the chance of repeated pregnancies.

Pharmacological Methods

An Augmentation

Clomiphene: Although the exact mechanism of action of clomiphene citrate (citrate, Sanofi) is unknown, it is the medication of choice for promoting ovulation in PCOS patients. First, a 50 mg/day dose is administered for five days. For the next cycles, use 50mg/day for 5 days if ovulation occurs but pregnancy does not occur. However, the dose may be raised to 100mg per day for five days at least thirty days following the previous course of medication if ovulation does not occur after the first cycle.

After three therapy courses, additional treatment is typically not advised; however, up to six cycles may be tried before additional treatment is taken into considerations. About 30% of pregnancies with clomiphene are successful; yet 20% of these pregnancies end in spontaneous absorptions or stillbirths. Multiple pregnancies, ovarian hyper stimulation syndrome (OHSS), hot flashes, gastrointestinal (GI) distension, bloating, and pain are among the possible adverse effects.

Oral contraceptives: If a woman with PCOS doesn't want to get pregnancy, she should think about using oral contraceptives (OCs). Menstrual period control is the primary mechanism of action of oral contraceptives used to treat PCOS-related hirsutism and acne are combinations of estrogens and progestin.

Data on the presence of anti-androgenic progestin in some of the more recent ocsare limited, but they include Bayer's drosperenone (e.g., Yaz) anddienogest (e.g., Natazia). In theory, these medications work better than previous formulations to address androgenic symptoms. Clinical improvement is typically observed by hirsutistic women after around six months of octreatment. Additionally, the results point to the protentional for synergy between ocs and antiandrogens.

Management

Since there is no cure for PCOS that addresses all clinical manifestation and cures the hormone imbalances that cause it, medical care only addresses certain symptoms and is only used in conjunction with lifestyle modifications.

PCOS lifestyle management

Dietary plan: A diet plan works to control weight and lowers the long-term risk of PCOS.
Cardiovascular illness, type-2 diabetes etc.
The Following Goods should be Avoided:
The addictive substances nicotine, caffeine, and alcohol
Products made from: they prevent ovulation
Normal testosterone processing is hampered by milk protein, which results in level stories
Red meat, dairy products, and saturated fats all raise the production of oestrogen
High glycaemia index foods, such potatoes and white rice.
Consuming the Following Goods is Recommended:
Whole grains: red rice, ragi.
Rich in vitamins, minerals, and nutrients are green leafy vegetables.
Dry fruits: figs and dates.
Whole fruits with low glycamic index: pears, apples, grapes, oranges, and plums.
Vibrantly collared veggies, such as salad, carrot, capsicum, and beets.
Proteins and carbohydrates.

Exercise: 10 minutes of exercise can help with PCOS.

Pharmacological Supervision

Citrate clomiphene: For PCOS patients, it is the first-line medication for inducing ovulation. The oestrogen receptor antagonist is the one that increases the availability of FSH by interfering with the oestrogen signaling pathway's negative feedback. Follicle growth is caused by increases FSH. It includes the initial phase of the menstrual cycle.

Gonadotropin-Producing Hormones: When clomiphene citrate is no longer effective, it is used as a second line of treatment. With the careful administration of FSH, it promotes follicle growth, maintains ovulation, and begins treatment with modest dosages.

Glucocorticoids: To induce ovulation, prednisone and dexamethasone have been utilizes. Use low dosedexamathasone (0.25-0.5 mg) at bedtime in PCOS patients with elevated adrenal androgen.

Cytokine n- acetyl (NAC): It contains antioxidants necessary for the body to produce glutathione, which reduces oxidative stress and keeps hyperinsulinemia from occurring.

Conclusion

Premenopausal women frequently suffer from PCOS, an endocrine condition. In addition to acne and irregular menstrual cycles, it is linked to type 2 diabetes, cardiovascular disease, and diabetes mellitus; it is still unclear what PCOS's underlying flaw is. Combining pharmacological treatments that raise insulin sensitivity and hyperandrogenism with lifestyle changes can help promote a normal menstrual cycle, increases fertility, and prevent cardiovascular disease among other issues.

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