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Review Article

Effects of Hyperandrogenism in PCOS: A Review Analysis

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Abstract

The endocrine condition known as Poly Cystic Ovary Syndrome (PCOS) is becoming more common in the local areas of Pakistan. Concerningly, the prevalence of PCOS among women who are fertile has been increasing. It plays a significant role in the worldwide population's infertility and subfertility. PCOS patients frequently exhibit a variety of symptoms, including ovarian cysts, hyperandrogenism, irregular menstruation, and ovulatory abnormalities. The symptoms are frequently misdiagnosed or disregarded, and they take longer to manifest. Due to PCOS's complex nature, its cause is yet unknown. Several scientific associations have developed diagnostic standards for PCOS and have identified three distinct phenotypes. The primary symptom of PCOS in all phenotypes is hyperandrogenism, or an excess of androgen production. This review focuses on hyperandrogenism and the several variables that cause hyperandrogenic states in Pakistani women with PCOS. Additionally, this review addresses and summarises new and prior research on the connection between hyperandrogenism and PC This review's objective is to evaluate the evidence-based relationship between hyperandrogenism and PCOS critically in Pakistan. The PRISMA flowchart approach was used to document the study selection process. The research from the last six years that exclusively addressed hyperandrogenism and PCOS met the inclusion criteria. Studies that do not concentrate on PCOS or hyperandrogenism are among the exclusion criteria. 34 of the first 50 studies that were found were included in the final evaluation following screening. Information was taken from Pakistani locals. Using qualitative methodologies, data was synthesised so that similar themes and patterns from several studies could be found. In the future, additional research into the fundamental causes of PCOS may open the door to more specialised and efficient therapies in the local areas of Pakistan. Patients with PCOS frequently have extra testosterone, which can have negative effects. However, more long-term research is needed to fully understand its implications for the treatment of this illness in Pakistan.
Key words: Ovulation, infertility, hyperandrogenism, hirsutism, phenotype.

Introduction

PCOS, or polycystic ovarian syndrome, is a hormonal condition that typically affects women who are fertile. The most prevalent symptom, along with irregular menstruation, ovulation issues, and many ovarian cysts, is clinical or biochemical hyperandrogenism. According to reports, PCOS affects 5-20% of women who are of reproductive age. Almost 70% of women do not receive a diagnosis.[1] it is reported that up to 15% of women in reproductive age are affected when applying the Rotterdam criteria.[2] In Pakistan, between 5% to 10% of this age group were influenced by the ages of 18 and 44. The most prevalent issue in the world is infertility, which is defined as the inability to conceive after a year of uninterrupted exposure to regular, unprotected coitus at the proper stage of the menstrual cycle.[3] About 30-40% of all cases of infertility in humans are female. Despite being a highly common and family endocrine illness, the lack of a clear pathogenic mechanism impedes the search for a solution.[4] Symptoms that change depending on the patient's age and a need for individualised treatment plans, PCOS is a diverse and incredibly frequent disease. Chronic oligo-anovulation, micropolycystic ovarian morphology, and/or hyperandrogenism with ovarian dysfunction are examples of its usual expression. Guidelines mostly address the symptoms of PCOS, but they are less clear when it comes to the

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SSS conceptualized the project. AKK did the data collection. SZ performed the statistical analysis. SSS, HS, AKK & MS did the literature search. Drafting, revision & writing of manuscript were done by HS, SAIR & MS.

underlying causes of the illness, such as insulin resistance, which is a common ailment in PCOS that is exacerbated by the buildup of adipose tissue linked to hyperandrogenism.[5]

Methodology

The resources like PubMed, Web of Science, and Google Scholar to perform an extensive literature search were used. "Ovulation," "hirsutism," and "polycystic ovaries" were among the search terms used. In order to incorporate papers published in English between 2019 and 2024, filters were implemented. The PRISMA flowchart approach was used to document the study selection process. Studies were chosen on the basis of their caliber, type, and applicability to the subject. The research from the last six years that exclusively addressed hyperandrogenism and PCOS met the inclusion criteria. Included were studies that examined the metabolic and reproductive effects of PCOS. Studies that do not concentrate on PCOS or hyperandrogenism are among the exclusion criteria. Studies without precise definitions or diagnostic standards for PCOS and hyperandrogenism were also excluded. The 34 of the first 50 studies that were found were included in the final evaluation following screening. Particularly in metropolitan areas, data was taken from Pakistan's indigenous areas. Using qualitative methodologies, data was synthesised so that similar themes and patterns from several studies could be found.

Standards for diagnosis

The diagnosis of PCOS is predicated on the variable presence of three particular elements: oligoanovulation, androgen excess, either clinical or biochemical, and the ultrasound assessment of ovarian morphology. There is no one diagnostic test that can definitively identify PCOS. The Rotterdam criterion, which requires the presence of two of the three diagnostic criteria for a diagnosis in adult women, has been endorsed by the International Evidence-Based Guideline. It is advised to rule out thyroid disease (defined as TSH, thyroid stimulating hormone), hyperprolactinemia (defined as prolactin), and nonclassic congenital adrenal hyperplasia (defined as 17-hydroxy progesterone screening). In patients with amenorrhea and more unusual symptoms, further testing is advised to rule out hypogonadotropic hypogonadism or Cushing illness. In cases where the androgenic picture is more severe, an assessment for androgen-producing tumors should also be considered. Serum androgen measurements above two times the upper limits of normal according to the local clinical assay standard indicate the presence of severe androgenic profiles.[6]

The typical female androgen physiology

The typical female androgen physiology in addition to supporting female sexual function, muscle mass, and bone density, androgens are important for the health of women. The most physiologically active are testosterone and dihydrotestosterone. The ovaries (25%) and adrenal glands (25%) as well as peripheral tissues (50%) like the skin, fat, and liver are the sites of androgen production. As high androgen levels are the most consistent symptom of PCOS, hyperandrogenism represents a primary characteristic, with the majority of patients (60%) demonstrating hyperandrogenism (Rotterdam definition). The serum levels of several androgens, such as testosterone (T), androstenedione (A4), dehydroepiandrosterone sulfate (DHEAS), and the enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD), which is necessary to convert pro-androgens to bioactive androgens, are elevated in women with hyperandrogenic PCOS.[7] Insulin resistance and hyperinsulinemia can lead to a decrease in sex hormone binding globulin levels, which in turn increases free androgens and unfavorable metabolic profiles. This can result in excess androgens.[8]

Hirsutism

A woman's abnormal amount of terminal hair distributed in a male pattern is called hirsutism, and it is the primary sign of hyperandrogenism in women with polycystic ovarian syndrome. Although mild acne and female pattern hair loss are not advised as diagnostic criteria in adolescents due to the lack of data in this population, progressive hirsutism is still the primary marker of hyperandrogenism. Acne and female pattern hair loss are also clinical manifestations of hyperandrogenism.[9] Adults have two distinct forms of hair: terminal and vellus. Human cheeks and necks, which are largely "hairless," are covered in vellus hair, which is fine, short, and pigmented. Terminal hair is longer, more stiff, highly pigmented, and has a blunter tip. It is present on the scalp, eyebrows, eyelashes, axilla, and pubic regions.[10] While there are numerous disorders that might cause hirsutism, over 85% of cases are caused by polycystic ovarian syndrome and idiopathic hyperandrogenism. Idiopathic hirsutism, non-classic congenital adrenal hyperplasia, androgen-secreting tumors, drugs, hyperprolactinemia, thyroid conditions, and Cushing syndrome are less frequent causes.[11]

Androgen's physiological impact on women

Biological effects are caused by the levels of free testosterone in the blood.[12] The defining characteristic of PCOS is hyperandrogenism, which presents clinically as hirsutism, acne, and alopecia. Hyperandrogenism is a result of both the adrenal glands and the ovaries producing too much androgen. PCOS women experience abnormalities in the neuroendocrine system, such as elevated gonadotropin-releasing hormone pulse frequency and pituitary stimulation leading to an excess of luteinizing hormone production compared to follicle-stimulating hormone.[13] One of the main characteristics of PCOS is hyperandrogenism, as high androgen levels are the most consistent sign, and most patients (60–65%) have hyperandrogenism (Rotterdam definition). Insulin resistance and hyperinsulinemia can lead to a decrease in sex hormone binding globulin levels, which in turn increases free androgens and unfavourable metabolic profiles. This can result in excess androgens.[14] As per the standard, there are four phenotypes of PCOS: (1) hyperandrogenism, PCOM, and chronic anovulation; (2) PCOM, chronic anovulation, and no clinical or biochemical indications of hyperandrogenism; (3) hyperandrogenism, chronic anovulation, and normal ovaries; and (4) hyperandrogenism, PCOM, and normal ovulation. The significance of hyperandrogenism in PCOS is demonstrated by these diagnostic criteria and manifestations.[15] There is little information available about how PCOS affects psychological health, and much of the research has been done on adult individuals. Based on available data, women with PCOS are more likely to experience hormonal imbalances, which may be related to co-morbidities and variables implicated in the development of the condition.[16] A deeper comprehension of the underlying mechanisms is still required and may help improve this disease's care.[17] This review will give a quick rundown of the pathogenesis of PCOS, the current standard of care for PCOS, and a synopsis of recent research on new and developing therapeutic approaches for PCOS management by concentrating in particular on peripheral metabolic pathology, central neuroendocrine dysfunction, and pharmaceutical treatment of androgen excess.

The current review highlights the negative impacts of PCOS and androgenism on a typical lifestyle, identifies knowledge gaps, and suggests areas for future investigation. Thus, this review's objective is to evaluate the evidence-based association between hyperandrogenism and PCOS rigorously.[18]

Management

In addition to medicine, such as insulin sensitizers, lifestyle changes for weight loss and better eating habits are among the management treatments aimed at the metabolic phenotype. Cosmetic operations and the combination of oral contraceptives with or without antiandrogens are used to treat hyperandrogenic phenotype. Clomiphene citrate, aromatase inhibitors, and dietary and lifestyle changes are all part of the treatment approach to reproductive phenotype. Herbs, acupuncture, resveratrol, myo-inositol, and dietary supplements are examples of alternative therapies.[19]

Discussion

Aldosterone may be the underappreciated component in PCOS diagnosis and treatment, according to Alamgir N. et al. Research has demonstrated that elevated levels of aldosterone, and specifically the aldosterone/renin ratio, are frequently observed in individuals with PCOS. This may contribute to the development of certain metabolic and cardiovascular problems by exacerbating the underlying inflammatory condition.[20] A variety of pharmaceutical approaches that target androgen excess, central neuroendocrine dysfunction, and/or metabolic pathology are being developed as promising novel therapeutics for PCOS.[21]

According to research by Hassan Mulk et al., the primary neuroendocrine feature of PCOS is the persistently elevated frequency of GnRH's pulsatile secretion, which causes an increase in LH production and the associated alterations in the LH/FSH ratio. Regardless of their main or secondary genesis, neuroendocrine disorders play a crucial role in the development and progression of PCOS. One of the primary features of PCOS is the existence of large polycystic ovaries with a high antral (2-8 mm) follicle number. This typical ovarian shape is caused by endocrine abnormalities such as hyperandrogenemia, hypersecretion of LH, and hyperinsulinemia, which hamper follicular development and prematurely stop follicular expansion. Because of this, 60-80% of the patients experience irregular menstruation in addition to anovulatory infertility.[22]

According to a study by Selma Feldman et al., women with PCOS were more likely to use in vitro fertilization and ovulation induction, had pre-existing medical issues, and had difficult pregnancies than those without the disease. Infants born to women with PCOS were more likely to

experience perinatal death, congenital abnormalities, and preterm birth than infants born to women without PCOS. Obesity and/or gestational diabetes mellitus complicate PCOS-afflicted women's pregnancies frequently.[23]

According to Kabir M. et al., clomiphene citrate (CC) is usually used for the treatment of PCOS-associated anovulatory infertility. It is still widely considered as the first-line treatment globally since it is a cheap, easy-to-use medication with few side effects. His research, which focused on treating PCOS patients' infertility, also showed that 68% of respondents considered clomiphene citrate to be the first line of treatment. Clomiphene citrate works by lessening the negative feedback that estrogen has on the hypophysis and the hypothalamus. As a result, the hypophysis secretes more follicle-stimulating hormone (FSH), which promotes follicular development and ovulation.[24]

The study by Faiza S. et al., claims that a variety of herbs can be utilized to treat different elements of PCOS. Herbs that affect menstrual and ovulatory dysfunctions, obesity, insulin resistance, lipid-metabolism dysfunction, and disorders associated with testosterone excess include Cinnamomum verum, Trigonella foenum-graecum L., and Vitex agnus-castus.

Table 1. Herbs used in the treatment of associated PCOS complications. [25]

Symptom/Complication associated with PCOS	Herb used for Treatment
Hormonal imbalance	*Bauhinia variegata*
Regulation of hormones	*Phyllanthus emblica, Terminalia bellirica, Terminalia chebula, and Commiphora wightii*
Anti-oxidant	*Cinnamon cassia, Ocimum sanctum*
Reproductive dysfunction	*Tribulus terrestris*
Depression & Mood swings	*Hypericum perforatum*
Menorrhagia	*Commiphora myrrha*
Cholesterol	*Nigella sativa*
Estrogenic action	*Saraca asoca*
Folliculogenesis	*Asparagus racemosus*
Regulation of menstrual flow	*Tinospora cordifolia*

According to research by Rana Athar A. et al., estoprogestins (EPs) are thought of as a first-line therapy for PCOS management and have been shown to reduce hyperandrogenism and irregular menstruation. Intriguingly, all estoprogestins can increase hepatic production of sex hormone binding globulin (SHBG), which lowers free testosterone levels and also reduces peripheral hyperandrogenic manifestations (seborrhea, acne and hirsutism). These effects include decreasing ovarian production of androgens, inhibiting T binding with androgen receptors (AR), reducing 5alpha-reductase activity, and finally decreasing androgen bioavailability.[26]

According to Kathiuska et al., clomifene citrate, anti-oestrogen medication, has long been the first-line treatment for anovulatory PCOS. It is hypothesized that clomifene citrate reduces the normal ovarian-hypothalamic feedback by binding to and blocking the oestrogen receptors in the hypothalamus for extended periods of time. By increasing GnRh pulsatility, this blockage causes the pituitary to secrete more gonadotrophins, which in turn encourage the formation of ovarian follicles.[27]

Letrozole is a non-steroidal aromatase inhibitor that Mitwally and Casper introduced for ovulation induction in 2001, according to Poly Begum et al. It works by reducing the ovary's ability to convert testosterone and androstenedione to estrogen. Letrozole has a 48-hour elimination period and a brief half-life. Letrozole is therefore less harmful to the endometrium and cervix and is typically eliminated from the body before implantation. Numerous clinical trials have been conducted since the drug's launch to determine how well letrozole works as an ovulation induction agent.[28]

According to Mehwish B. et al., the most widely used insulin sensitizer, metformin, is the standard off-label medication used globally to treat polycystic ovarian syndrome. However, gastrointestinal side effects may be the main factor restricting its utilization. Another well-known dietary supplement that is an evidence-based treatment for PCOS in women is myo-inositol.[29]

Oral contraceptive pills, which have been shown to lessen androgen excess, acne, and hirsutism, should be the first line of treatment for adolescents with PCOS, according to Ahmed Zia et al. After three months, the oral contraceptive pills treatment raises sex hormone binding globulin levels, and after six months, hirsutism is reduced. Moreover, oral contraceptive pills may be recommended to treat irregular menstruation in thin PCOS girls who do not exhibit metabolic comorbidities.[30]

Reducing the levels of androstenedione and testosterone in the bloodstream is essential for treating PCOS, according to Nouman A .et al. A number of tactics can be suggested to achieve that aim, such as altering theca cells' sensitivity to LH stimulation and attenuating important enzymes involved in the synthesis of androgens. Attenuation of anti-müllerian hormone level, downregulation of GnRH gene expression in hypothalamic GnRH neurons, and reduction of GnRH pulse frequency, which may impair LH production and balance the LH/FSH ratio. The most promising scientific findings

that could serve as solid foundations for cutting-edge treatments are outlined below.[31]

According to Sidra tul Muntaha et al., women with PCOS may benefit from a micronutrient supplement that includes folic acid, selenium, vitamin E, catechin, glycyrrhizin, and co-enzyme Q10, provided for at least three months. The supplements may also help with PCOS-specific parameters, such as the LH:FSH ratio, serum testosterone, and serum AMH.[32]

In their study, Hishmat Ullah et al. noted that the international evidence-based guideline for the assessment and management of PCOS, which was published in 2020, states that metformin, combined oral contraceptive pills, anti-obesity agents, anti-androgen agents, and isosorbideone are among the therapeutic pharmacological options for non-infertility indications. These agents address various clinical manifestations. Oral contraceptive pills were the mainstay of conventional treatment in the past.[33]

Myo-inositol, a common stereoisomer of inositol that is abundant in plants and animal tissues, has emerged as a newer nonhormonal alternative for PCOS, as proven by a study by Ramanan et al. By addressing insulin resistance, myo-inositol treatment has been demonstrated in numerous studies to regulate hormone fluctuations and enhance fertility in PCOS patients. By lowering hyperandrogenism or a variety of other closely linked modes of action, inositol improves skin condition.[34]

Conclusion

The growing number of cases of PCOS in Pakistan highlights how important hereditary and pathological variables are in the development of illnesses linked to infertility. The focus is still largely on comprehending the intricate hormonal imbalances that are present in PCOS and their consequences for general health and quality of life, even though environmental factors that affect infertility are frequently disregarded. Enhancing disease management and improving outcomes for those afflicted by this complex disorder requires advances in research and treatment strategies targeting hyperandrogenism and other symptoms of PCOS. In the future, additional research into the fundamental causes of PCOS may open the door to more specialized and efficient therapies in the local areas of Pakistan. Patients with PCOS frequently have extra testosterone, which can have negative effects. But figuring out how it affects this disorder's care will take more time.

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