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Polycystic Ovary Syndrome (PCOS): Insights into Etiology, Genetic, Diagnosis, Treatment, and Future Directions (A Comprehensive Review)

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Abstract

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that affects women of reproductive age. PCOS characterized by hormonal imbalances, ovulatory dysfunction, and metabolic disturbances. PCOS is estimated to affect 6-20% of women worldwide, presenting challenges for those affected and healthcare providers. The disorder has a complex etiology, involving environmental, genetic, hormonal, and metabolic factors. Family and twin studies show a strong hereditary component, with genetic predisposition playing a significant role. Wide genomic studies have identified multiple genetic loci linked to PCOS susceptibility, providing insight into its molecular mechanisms. The symptoms of PCOS can differ greatly, from irregular periods and high levels of male hormones to infertility and metabolic issues. PCOS can lead to real health problems such as diabetes, obesity, heart disease, and endometrial cancer, emphasizing the importance of holistic treatment approaches. Diagnosis involves a thorough evaluation of symptoms, hormone levels, imaging tests, and menstrual history. Treatment focuses on managing symptoms, balancing hormones, and reducing long-term risks through lifestyle changes, medications, and fertility treatments. Despite the progress made in understanding PCOS, there are still gaps in our knowledge that emphasize the necessity for more research to clarify the complex pathophysiology and enhance treatment strategies for this prevalent and complicated condition. This article offers a summary of the epidemiology, etiology, diagnosis, treatment choices, and preventive actions for PCOS, with an emphasis on recent developments and upcoming research.

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1. Introduction

Although polycystic ovaries (PCO) and polycystic ovary syndrome (PCOS) sound similar, the two conditions are not the same. PCO occurs when there are an increased number of small cysts in the ovaries. PCOS is an endocrine disorder that causes women to produce excess androgens and cause menstrual irregularities [1]. It affects many women of reproductive age, and in the estimations, PCOS affects at least (5%) to (15%) of adult women globally [1]. This condition is characterized by hormone imbalances, irregular ovulation, and ovarian cysts, often leading to metabolic disturbances and fertility challenges [2].

Stein and Leventhal first identified PCOS in 1935 as a condition characterized by symptoms like excessive hair growth, missed periods, and cysts on the ovaries ultrasound examination [4]. Since then, our knowledge of PCOS has expanded to include a wider range of signs and symptoms such as hyperandrogenism, insulin resistance, irregular periods, and difficulty getting pregnant [2].

PCOS can have a range of different symptoms that make it difficult to diagnose and treat. Some common signs include menstrual abnormalities [such as oligomenorrhea or amenorrhea], hirsutism, acne, alopecia, and difficulty getting pregnant [2,

3]. In the long term, this syndrome may lead to problems such as diabetes, obesity, heart disease, cancer of the uterus lining, and mental health issues like depression and anxiety [2, 3].

The causes of PCOS are not yet fully revealed, but it is believed to be the result of a combination of environmental factors, genetic, hormonal, and metabolic. Genetics seems to play a major role, as studies involving families and twins have shown a strong hereditary component to the condition [5, 6]. Research has also identified various genetic loci linked to PCOS susceptibility through genome-wide association studies (GWAS), particularly those related to ovarian function, insulin signaling, and hormone regulation [5, 6- 9, 14].

PCOS is a common yet often overlooked health condition that can have serious consequences. It is crucial to increase awareness, detect it early, and effectively manage it. This review aims to provide a comprehensive overview of PCOS, covering its epidemiology, clinical presentation, diagnosis, treatment options, and preventive measures, with a special emphasis on recent developments and future research directions.

2. PCOS Etiology

The etiology of this syndrome is multifactorial. As the exact cause of PCOS remains not fully understood, several key factors contribute to its pathogenesis:

A. Hormonal Imbalance

This syndrome is characterized by hormonal imbalances, with high levels of androgens [male hormones like testosterone] and luteinizing hormone (LH), and lower levels of follicle-stimulating hormone (FSH). This disruption in the hypothalamic-pituitary-ovarian (HPO) axis drives increased production of androgen by the ovaries, which hinders regular follicular development and ovulation [10, 11].

B. Hyperandrogenism

It is a key factor of [PCOS], marked by high levels of androgens like testosterone and DHEAS. This disorder results in symptoms like excessive hair growth [hirsutism], acne, and male-pattern hair loss. Androgens also interfere with the regular development of follicles and ovulation, causing irregular MC (menstrual cycles) and the formation of small multiple ovarian cysts [11-13].

C. Insulin Resistance

Insulin resistance is a frequently seen metabolic problem in women with PCOS, mainly in those who are overweight or obese. This condition causes the body to produce more insulin to make up for decreased insulin sensitivity, leading to hyperinsulinemia. Hyperinsulinemia then triggers the production of androgens by the ovaries and plays a role in the development of PCOS [15-17 and 24].

D. Ovarian Dysfunction

Numerous women with PCOS experience issues with their ovaries, such as having more small antral follicles and halted follicular development [18]. These issues lead to irregular periods, ovulation problems, and difficulties getting pregnant for women with PCOS [19].

E. Environmental Factors

Diet, lifestyle choices, and exposure to certain chemicals can affect the development and progression of PCOS according to studies [20-22]. In women with PCOS, obesity can worsen insulin resistance and hormonal issues, further complicating the condition [23, 24].

F. Inflammatory and Immunological Factors

Chronic low-grade inflammation and alterations in immune function have been implicated in the pathogenesis of PCOS. Inflammatory cytokines and adipokines produced by adipose tissue contribute to insulin resistance, dysfunction of the ovary, and hyperandrogenism in PCOS women [25- 28].

3. PCOS In Genetic

Polycystic ovary syndrome [PCOS] has a significant genetic part, with heritability estimated to be around 50-70%. Women who have a family history of PCOS are more likely to develop the condition themselves. Mothers and sisters of PCOS women are at a greater risk of being diagnosed with PCOS compared to women who do not have affected family members. [29].

There are many genes related to the development of PCOS. These genes play a role in hormonal balance, insulin regulation, ovarian health, and metabolism [14, 30]. For example, variations in genes encoding for insulin receptors (INSR), insulin signaling molecules (IRS1, IRS2), androgen receptors (AR), follicle-stimulating hormone (FSH) receptors (FSHR), and anti-Müllerian hormone (AMH) have been associated with PCOS susceptibility [31]. PCOS is considered a complex genetic disorder, meaning that multiple genes interact with each other and with environmental factors to influence disease risk [32].

Changes in how genes are expressed, known as epigenetic modifications like DNA methylation and histone modifications, can impact gene expression without altering the DNA sequence itself [33, 34]. These modifications may have contributed to the development and advancement of PCOS, potentially affecting how environmental factors affect gene expression and susceptibility to disease [34]. While genetics contributes to PCOS risk, environmental factors also play a crucial role in disease development [35, 36]. Lifestyle factors such as diet, exercise, and stress can interact with genetic predispositions

to modulate PCOS risk and severity. For example, obesity and insulin resistance can exacerbate genetic predispositions to hormonal imbalances and metabolic dysfunction [37].

Moreover, through epigenetic mechanisms, evidence suggests that PCOS-related traits may be passed from one generation to the next [38]. Maternal PCOS status and intrauterine exposures during pregnancy may influence the risk of PCOS and metabolic dysfunction in offspring, emphasizing the significance of taking into account the impact on multiple generations in PCOS research and treatment [39].

Understanding the genetic basis of PCOS may help identify individuals at higher risk, inform personalized treatment approaches, and uncover potential targets for therapeutic interventions aimed at addressing the underlying molecular mechanisms of the disease.

4. Diagnosis

There are 4 types of PCOS: Insulin-resistant PCOS, Inflammatory PCOS, and Pill-induced PCOS.

- Insulin-resistant PCOS

This is the most prevalent form of PCOS, which is attributed to factors such as smoking, excessive sugar consumption, pollution, and trans fats. In this type, elevated insulin levels hinder ovulation and stimulate the ovaries to produce testosterone. Women who experience heightened insulin levels and are overweight may be diagnosed with PCOS linked to insulin resistance [17, 18].

The intake of sugar (small) is beneficial, but consuming large quantities can contribute to insulin resistance. Inositol drug can be used to prevent PCOS associated with insulin resistance. It typically takes about six to nine months to see a positive response [40].

- Pill-induced PCOS

This variant is the second most prevalent form of PCOS. It develops as a result of birth control pills, which suppress ovulation. While most women resume ovulation shortly after discontinuing the pill, some may experience prolonged absence of ovulation lasting months or even years. Diagnosis usually occurs when menstruation ceases for three or more months after stopping birth control pills, alongside normal insulin levels and signs of PCOS such as acne, a high LH to FSH ratio, or potential polycystic ovaries observed on pelvic ultrasound [41].

- Inflammatory PCOS

In PCOS due to inflammation, ovulation is prevented, hormones get imbalanced and androgens are produced also Increased abdominal adiposity contributes to the inflammatory load in PCOS [42]. Inflammation in PCOS can be triggered by stress, environmental toxins, and inflammatory diets containing substances like gluten. Symptoms such as headaches, infections, or skin allergies, as well as vitamin D deficiency and elevated thyroid levels, indicate the presence of inflammatory PCOS.

Several biomarkers are used for diagnosing polycystic ovary syndrome [PCOS], including hormonal, metabolic, and imaging markers. First of all the Luteinizing Hormone (LH) to Follicle-Stimulating Hormone (FSH) Ratio. Women with PCOS often have high LH levels and an LH/FSH ratio greater than 2:1, which indicates hormonal imbalances [41]. This is due to dysregulation of the HPO axis, leading to issues with ovarian function and excess androgens [41].

Also, Elevated serum levels of androgens, such as testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione, are hallmark features of PCOS [11].

Another diagnostic test is the Anti-Mullerian hormone. (AMH) is made by the granulosa cells in the ovaries and is used to indicate the ovarian reserve and follicle recruitment. High AMH levels are often found in polycystic ovary women [PCOS] and show that there are more small antral follicles, which is a key aspect of PCOS [43].

Moreover, Insulin Resistance Markers are a frequent issue with PCOS. Biomarkers like fasting insulin, glucose, and HOMA-IR can be high in overweight or obese women with PCOS [44]. Oral glucose tolerance testing (OGTT) may be performed to assess glucose metabolism and insulin sensitivity, especially for those at risk of developing reduced glucose tolerance or type 2 diabetes mellitus (T2DM) women [45].

In PCOS women, Dyslipidemia is common and it's characterized by elevated levels of triglycerides and low-density lipoprotein cholesterol (LDL-C) and reduced levels of high-density lipoprotein cholesterol (HDL-C) [46]. Assessment of lipid profiles can help evaluate metabolic risk and cardiovascular health.

Also, Ovarian Ultrasound helps to diagnose PCOS. Transvaginal ultrasound examination may reveal characteristic features of PCOS, including polycystic ovaries (defined as the presence of ≥12 follicles measuring 2-9 mm in diameter and/or increased ovarian volume ≥10 mL) and/or ovarian stromal hypertrophy [47].

It's important to consider individual patient characteristics, symptoms, and laboratory findings when making a diagnosis of PCOS and to rule out other conditions that may mimic PCOS. Irregular menstrual cycles, oligomenorrhea [cycles >35 days], and/or amenorrhea [absence of menstrual periods] are common clinical manifestations of PCOS and may serve as diagnostic criteria in conjunction with other biomarkers [48].

5. Treatment

Treatment for PCOS is individualized based on the woman's symptoms, reproductive goals, and overall health status. A multidisciplinary approach involving gynecologists, endocrinologists, reproductive specialists, nutritionists, and mental health professionals may be necessary to provide comprehensive care for women with PCOS.

Treatment of PCOS aims to manage symptoms, improve hormonal balance, restore ovulation, and reduce long-term health risks. Below are some common treatments for this syndrome:

A. Modification of lifestyle

Making changes in the lifestyle by eating a healthier diet, being more active, and maintaining a healthy weight can have positive effects on insulin sensitivity, menstrual cycles, and symptoms of PCOS. Losing weight, even just a little bit, can help balance hormones, improve fertility, and regulate metabolism for overweight or obese women with PCOS [20, 21].

B. Hormonal contraceptives

The primary medical treatment recommended for the ongoing management of PCOS is combined oral contraceptive (OC) pills [49]. Patches, vaginal rings, and contraceptive injections containing estrogen and progestin can aid in the regulation of menstrual cycles, reduce androgen levels, improve acne healing and hirsutism in women with PCOS. The possible negative cardiovascular and metabolic impacts of oral contraceptives (OCs) have led to questions regarding their long-term safety in treating PCOS. Nevertheless, existing evidence indicates that, in most cases like Bulent O. Yildiz's (2015) study, the advantages of using oral contraceptives outweigh the potential risks for women with PCOS [49].

C. Insulin Sensitizing

Insulin-sensitizing medications, such as metformin [51], can improve insulin sensitivity, lower insulin levels, and regulate menstrual cycles in PCOS women, particularly those with IR (insulin resistance) or glucose intolerance. Metformin may also help with weight loss and reduce the risk of developing T2DM.

D. Induction of Ovulation

For any PCOS woman who is trying to get pregnant, it may be necessary to consider fertility treatments. Medications like clomiphene citrate or letrozole can help stimulate ovulation and increase your chances of conceiving [52]. In some cases, gonadotropin injections or assisted reproductive technologies like in vitro fertilization may be suggested for women who do not respond to oral medications.

E. Anti-Androgen Medications

Anti-androgen medications like spironolactone, flutamide, finasteride, and cyproterone acetate (CPA) have been used to reduce symptoms associated with hyperandrogenism. These medications work in three ways: either by competitively inhibiting androgen receptors, or androgen production (though the exact mechanism is not fully understood), or by inhibiting 5-α-reductase in the skin, an enzyme responsible for converting testosterone into its active form, 5-α-dihydrotestosterone (DHT) [50]. Using anti-androgen medications could alleviate the hyperandrogenic symptoms of PCOS and improve various conditions linked to excess androgen levels.

F. Laparoscopic ovarian drilling

Laparoscopic ovarian drilling (LOD) is considered beneficial for PCOS women who don't positively respond to medication and don't have any other causes of infertility. This surgical procedure, a less invasive modification of ovarian wedge resection, involves destroying the vascular stroma [53]. Its goal is to stimulate follicular growth by decreasing androgen levels, lowering luteinizing hormone (LH), and enhancing follicle-stimulating hormone (FSH) and sex hormone-binding globulin (SHBG) [54].

Several studies have indicated that laparoscopic ovarian drilling (LOD) is a beneficial second-line treatment option for inducing ovulation in women with clomiphene-resistant PCOS [55]. It has been shown to increase pregnancy rates by temporary stimulation of ovulation, reduce the incidence of ovarian hyperstimulation syndrome (OHSS) in subsequent IVF cycles, decrease cancellation rates, and improve outcomes in IVF cycles [56]. However, conflicting evidence exists as some studies have not observed improvements in pregnancy, miscarriage, and live birth rates [57, 58], leading to ongoing debate on its efficacy.

A recent study by Moini *et al*. (2023) found that performing LOD prior to IVF/ICSI rounds did not enhance pregnancy outcomes in PCOS women, highlighting the need for larger clinical trials to substantiate these findings [59].

G. Surgery

For women with PCOS who are not ovulating with medication, doctors may recommend ovarian drilling as a minimally invasive option. This procedure involves creating tiny holes on the surface of the ovaries using heat or laser energy [60]. The goal is to lower androgen levels and enhance ovulation.

H. Social Support

(PCOS) can greatly affect the overall quality of life and a person's mental health. Providing psychosocial support through counseling, support groups, and education on PCOS can assist individuals in managing the emotional and psychological challenges associated with the disorder [61].

Regular follow-up and monitoring are important to assess treatment response, adjust therapy as needed, and address any complications or concerns.

Medical science (recent progress) has unlocked the chances of novel therapeutic alternatives. The effects of new various drugs and their limitations have been made by phase II clinical trials. Even though some medications, such as elagolix, some individuals may not achieve complete regulation or control of their menstrual cycle with elagolix alone and may require additional treatments or adjustments. This highlights the need for extra studies to explore different dosage programs and combinations of medications to positively figure out the hormonal irregularities linked to PCOS [60].

6. PCOS and subfertility

PCOS can show up at any age, but it is usually identified during adolescence or early adulthood, often after puberty and the start of menstrual cycles. However, some women may only get diagnosed later in life, particularly if they have mild or unusual symptoms. The criteria for diagnosing PCOS may also change as women age since hormone levels and reproductive function evolve with time. In younger women, irregular periods, acne, and excess hair growth may be more noticeable due to hormone changes linked to puberty and early reproductive years. As women get older, issues like infertility, weight gain, and metabolic problems may become more serious, this reflects the continuing impact of PCOS on reproductive and metabolic health.

PCOS is a common cause of infertility in women of reproductive age. It can be especially worrisome for younger women with this syndrome who are trying to get pregnant, but advancing age can also create additional obstacles due to natural declines in ovarian reserve and egg quality [63]. Women with PCOS who wait to have children may encounter difficulties in conceiving as they age.

7. Future Directions

Research in the field of Polycystic Ovary Syndrome is continually advancing, with ongoing exploration of various future paths to enhance our understanding and management of this complex condition. PCOS is characterized by its diverse nature, as it manifests differently in each individual. Future studies may concentrate on identifying specific subtypes of PCOS based on underlying genetic, metabolic, and hormonal factors. This personalized approach could pave the way for tailored treatment plans designed to address the unique requirements of each patient. Additionally, progress in genetic research could reveal new genes linked to PCOS, offering further insights into the condition's underlying mechanisms. A comprehensive genetic components understanding of this syndrome may facilitate the development of precisely targeted therapies.

As the emerging evidence suggests a potential link between gut microbiota and PCOS, Currently, the evidence strongly supports the involvement of gut microbiota composition and disturbances in secondary bile acid production in the development of PCOS [64]. Supplementation with prebiotics, probiotics, and synbiotics in PCOS women seems to enhance various biochemical markers and may have beneficial effects, although the precise mechanisms remain unclear. Further research is essential to clarify the potential of these interventions in treating or even preventing PCOS, and to investigate the role of the gut microbiome in the pathogenesis of this condition [64].

When formulating lifestyle guidelines for managing PCOS, it is crucial to consider and communicate evidence not only related to diet, physical activity, and behavioral interventions, but also regarding psychological health, sleep patterns, and TCIM (Traditional, Complementary, and Integrative Medicine) approaches. This approach will enable clinicians to provide patient-centered care by offering women more choices and autonomy in their treatment options. This approach is consistent with the primary goals outlined in the 2018 PCOS guideline, which aimed to address the unmet needs of PCOS women by involving consumers in the development, implementation, translation, and dissemination of guidelines [65].

One important area of research is finding better ways to help women with PCOS improve their chances of getting pregnant. In the future, researchers may look into new fertility treatments like methods to stimulate the ovaries, mature eggs outside the body, and assisted reproduction techniques designed specifically for women with PCOS.

Traditional treatments for PCOS often involve hormonal therapies, but some women may prefer non-hormonal approaches. Further studies could explore the effectiveness of alternative treatments like acupuncture, herbal supplements, and dietary supplements in reducing PCOS symptoms. Additionally, research in the future may concentrate on creating methods for detecting and preventing associated health conditions early in women with PCOS.

8. Conclusion

To sum up, PCOS is a complex condition that can have various symptoms and serious effects on reproductive and metabolic health. It's important to have a deep understanding of its causes, symptoms, diagnosis, and treatments to effectively help women with PCOS. Further serious studies are needed to uncover the intricate reasons behind PCOS and create personalized therapies for those affected.

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10. References

[1] L.I. Rasquin, C. Anastasopoulou, J.V. Mayrin, “Polycystic Ovarian Disease”. In: StatPearls [Internet]. Treasure Island (FL): 2024 StatPearls Publishing, 2022, https://www.ncbi.nlm.nih.gov/books/NBK459251/

[2] H. J. Teede, M.L. Misso, M.F. Costello, et al., "Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome," Clinical Endocrinology, 89[3], 251-268, 2018, doi: 10.1016/j.fertnstert.2018.05.004

[3] T. Zore, N.V. Joshi, D. Lizneva, and R. Azziz, "Polycystic Ovarian Syndrome: Long-Term Health Consequences," Semin. Reprod. Med. 35:271–281, 2017, doi: 10.1055/s-0037-1603096

[4] I.F. Stein and M.L. Leventhal, "Amenorrhea associated with bilateral polycystic ovaries. American Journal of Obstetrics and Gynecology," 29[2], 181-191, 1935, doi:10.1016/S0002-9378(15)30642-6

[5] F. Day, T. Karaderi, M.R. Jones, C. Meun, C. He, and V. Mooser, "Large-scale genome-wide meta-analysis of polycystic ovary syndrome suggests shared genetic architecture for different diagnosis criteria," PLoS genetics, 14[12], e1007813.2018, doi: 10.1371/journal.pgen.1007813

[6] M.J. Khan, A. Ullah, and S. Basit, "Genetic Basis of Polycystic Ovary Syndrome [PCOS]: Current Perspectives," Appl Clin Genet. Dec 24;12:249-260, 2019, doi: 10.2147/TACG.S200341

[7] C.K. Welt, "Genetics of Polycystic Ovary Syndrome: What is New," Endocrinol Metab Clin North Am. Mar;50[1]:71-82, 2021, doi: 10.1016/j.ecl.2020.10.006

[8] P.M. Visscher, N.R. Wray, and Q. Zhang, "10 Years of GWAS Discovery: Biology, Function, and Translation," American journal of human genetics. 101[1]:5–22, 2017, doi: 10.1016%2Fj.ajhg.2017.06.005

[9] International HapMap C, "The International HapMap Project," Nature. 426[6968]:789–796, 2003.

[10] Z. Shaaban, A. Khoradmehr, M.R. Jafarzadeh Shirazi, and A. Tamadon, "Pathophysiological mechanisms of gonadotropins- and steroid hormones-related genes in etiology of polycystic ovary syndrome," Iran J Basic Med Sci. Jan;22[1]:3-16, 2019, doi: 10.22038/ijbms.2018.31776.7646

[11] P. Fenichel, C. Rougier, S. Hieronimus, and N. Chevalier, "Which origin for polycystic ovaries syndrome: Genetic, environmental or both," Ann Endocrinol.78:176–185, 2017, 10.1016/j.ando.2017.04.024

[12] R.L. Rosenfield and D.A. Ehrmann, "The pathogenesis of polycystic ovary syndrome [PCOS]: the hypothesis of PCOS as functional ovarian hyperandrogenism revisited," Endocr Rev. 37:467–520, 2016, doi:10.1210/er.2015-1104

[13] A.V. Roland and S.M. Moenter, "Reproductive neuroendocrine dysfunction in polycystic ovary syndrome: insight from animal models," Front Neuroendocrinol. 35:494–511, 2014, doi: 10.1016/j.yfrne.2014.04.002

[14] M. Luque-Ramírez, J.L. San Millán, and H.F. Escobar-Morreale, "Genomic variants in polycystic ovary syndrome," Clin Chim Acta. 366:14–26, 2006, doi: 10.1016/j.cca.2005.10.017

[15] K. Unluhizarci, Z. Karaca, and F. Kelestimur, "Role of insulin and insulin resistance in androgen excess disorders," World J Diabetes. May 15;12[5]:616-629, 2021, doi: 10.4239/wjd.v12.i5.616

[16] H. Ding, J. Zhang, F. Zhang, S. Zhang, X. Chen, W. Liang, and Q. Xie. "Resistance to the Insulin and Elevated Level of Androgen: A Major Cause of Polycystic Ovary Syndrome," Front Endocrinol [Lausanne]. Oct 20;12:741764, 2021, doi: 10.3389/fendo.2021.741764

[17] E. Diamanti-Kandarakis and A. Dunaif, "Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications," Endocr Rev. 33[6]:981–1030, 2012, doi: 10.1210/er.2011-1034

[18] M.E. Lujan, D.R. Chizen, and R.A. Pierson, "Diagnostic criteria for polycystic ovary syndrome: Pitfalls and controversies," J. Obstet. Gynaecol. Can. 30:671–679, 2008, doi: 10.1016/S1701-2163(16)32915-2

[19] M.E. Lujan, A.K. Peppin, T.G. Bloski, D. Leswick, S. Kriegler, and R.A. Pierson, "Improving inter-observer variability in the evaluation of ultrasonographic features of polycystic ovaries," Proceedings of the 53rd Annual Meeting of the Canadian Fertility and Andrology Society; Halifax, Canada, 2007, doi: 10.1186/1477-7827-6-30

[20] J. Parker, C. O'Brien, J. Hawrelak, and F.L. Gersh, "Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment," Int J Environ Res Public Health. 19[3]:1336, 2022, doi: 10.3390/ijerph19031336

[21] J. Parker, "NEM: A New Paradigm for Understanding the Common Origins of the Chronic Disease Epidemic," ACNEM J. 37:6–11, 2018, doi: 10.5539/gjhs.v7n2p210

[22] H. Teede, M. Misso, M. Costello, *et al*., "International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome," National Health and Medical Research Council [NHMRC]; Canberra, Australia: pp. 1–198, 2018, doi: 10.1016/j.fertnstert.2018.05.004

[23] S.J. Glastras, D. Valvi, and A. Bansal, "Editorial: Developmental programming of metabolic diseases," Front. Endocrinol, 2021, doi: 10.3389/fendo.2021.781361

[24] A. Tsatsoulis, M.D. Mantzaris. B. Sofia, and M. Andrikoula. "Insulin resistance: An adaptive mechanism becomes maladaptive in the current environment—An evolutionary," perspective Metabolism. 62:622–633, 2013, doi: 10.1016/j.metabol.2012.11.004

[25] S. Abraham Gnanadass, Y. Divakar Prabhu, and A. Valsala Gopalakrishnan, "Association of metabolic and inflammatory markers with polycystic ovarian syndrome [PCOS]: an update," Arch Gynecol Obstet. 303[3]:631-643, 2021, doi: 10.1007/s00404-020-05951-2

[26] E. Rudnicka, K. Suchta, M. Grymowicz, A. Calik-Ksepka, K. Smolarczyk, A.M. Duszewska, R. Smolarczyk, and B. Meczekalski, "Chronic Low Grade Inflammation in Pathogenesis of PCOS," Int J Mol Sci. 22[7]:3789, 2021, doi: 10.3390/ijms22073789

[27] K. Ebejer, J. Calleja-Agius, "The role of cytokines in polycystic ovarian syndrome," Gynecol Endocrinol. 29[6]:536-40, 2013, doi: 10.3109/09513590.2012.760195

[28] M. Pawelczak, J. Rosenthal, S. Milla, Y.H. Liu, and B. Shah, "Evaluation of the pro-inflammatory cytokine tumor necrosis factor-α in adolescents with polycystic ovary syndrome," J Pediatr Adolesc Gynecol. 27[6]:356-9, 2014, doi: 10.1016/j.jpag.2014.01.104

[29] M.D. Kahsar-Miller, C. Nixon, L.R. Boots, R.C. Go, and R. Azziz, "Prevalence of polycystic ovary syndrome [PCOS] in first-degree relatives of patients with PCOS," Fertil Steril. 75[1]:53-8.2021, doi: https://doi.org/10.1016/s0015-0282(00)01662-9

[30] S. Colilla, N.J. Cox, and D.A. Ehrmann, "Heritability of insulin secretion and insulin action in women with polycystic ovary syndrome and their first-degree relatives," J Clin Endocrinol Metab. 86[5]:2027–31, 2001, doi: 10.1210/jcem.86.5.7518

[31] B.V. Lakkakula, M. Thangavelu, and U.R. Godla, "Genetic variants associated with insulin signaling and glucose homeostasis in the pathogenesis of insulin resistance in polycystic ovary syndrome: a systematic review," J Assist Reprod Genet. 30[7]:883-95, 2013, doi: 10.1007/s10815-013-0030-1

[32] X. Li, H. Xiao, Y. Ma, Z. Zhou, and D. Chen, "Identifying novel genetic loci associated with polycystic ovary syndrome based on its shared genetic architecture with type 2 diabetes," Front Genet. 13:905716, 2022, doi: 10.3389/fgene.2022.905716

[33] H.T. Lee, S. Oh, D.H. Ro, H. Yoo, and Y.W. Kwon, "The Key Role of DNA Methylation and Histone Acetylation in Epigenetics of Atherosclerosis," J Lipid Atheroscler. 9[3]:419-434, 2020, doi: 10.12997/jla.2020.9.3.419

[34] B. Prajna, K.S. Prasanna, M. Lakshmi, and P. Prakash, "Hormonal, genetic, epigenetic and environmental aspects of polycystic ovarian syndrome," Gene Reports, Volume 29, 101698, ISSN 2452-0144, 2022, doi: 10.1016/j.genrep.2022.101698

[35] M.A. Charifson and B.C. Trumble, "Evolutionary origins of polycystic ovary syndrome: An environmental mismatch disorder," Evol. Med. Public Health, 2019, doi: 10.1093/emph/eoz011

[36] J. Parker, J. Hawrelak, and F.L. Gersh, "Nutritional role of polyphenols as a component of a wholefood diet in the management of polycystic ovary syndrome," J. ACNEM. 40:6–12, 2021.

[37] F.F. He and Y.M. Li, "Role of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome: A review," J. Ovarian Res. 13:73, 2020, doi: 10.1186/s13048-020-00670-3

[38] N.E.H. Mimouni, I. Paiva, A.L. Barbotin, *et al*, "Polycystic ovary syndrome is transmitted via a transgenerational epigenetic process," Cell Metab. 33[3]:513-530.e8, 2021.

[39] R. Sanjiv, L. Congru, L. Qing, *et al*. "Transgenerational transmission of reproductive and metabolic dysfunction in the male progeny of polycystic ovary syndrome, Cell Reports Medicine," Volume 4, Issue 5, 101035, ISSN 2666-3791, 2023, doi: 10.1016/j.xcrm.2023.101035

[40] J.J. DiNicolantonio, H O'Keefe, "Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes". Open Heart.9(1):e001989, 2022, doi: 10.1136/openhrt-2022-001989

[41] Z. Saadia, "Follicle Stimulating Hormone [LH: FSH] Ratio in Polycystic Ovary Syndrome [PCOS] - Obese vs. Non-Obese Women," Med Arch. 74[4]:289-293, 2020, doi: 10.5455/medarh.2020.74.289-293

[42] F. González, "Inflammation in Polycystic Ovary Syndrome: underpinning of insulin resistance and ovarian dysfunction". Steroids.10;77(4):300-5, 2012, doi: 10.1016/j.steroids.2011.12.003

[43] C.N. di, C. Racine, and R.A. Re, "Anti-Müllerian Hormone and Polycystic Ovary Syndrome in Women and Its Male Equivalent," Biomedicines. 10[10]:2506, 2022, doi: 10.3390/biomedicines10102506

[44] C.A. Amisi, "Markers of insulin resistance in Polycystic ovary syndrome women; An update," World J Diabetes. 13[3]:129-149, 2022, doi: 10.4239/wjd.v13.i3.129

[45] S. Livadas, R. Paparodis, and P. Anagnostis, "Assessment of Type 2 Diabetes Risk in Young Women with Polycystic Ovary Syndrome," Diagnostics [Basel]. 13[12]:2067, 2023, doi: 10.3390/diagnostics13122067

[46] J.J. Kim and Y.M. Choi, "Dyslipidemia in women with polycystic ovary syndrome," Obstet Gynecol Sci. 56[3]:137-42, 2013, doi: 10.5468/ogs.2013.56.3.137

[47] K. Rami, A. Wesam, A. Fida, F. Al-Rshoud, and K. Maysa, "Inter-observer variability in the assessment of ultrasound features of polycystic ovaries," Middle East Fertility Society Journal, Volume 22, Issue 3, Pages 226-232, ISSN 1110-5690, 2017, doi: 10.1016/j.mefs.2017.03.005

[48] H.R. Harris, L.J. Titus, D.W. Cramer, and K.L. Terry, "Long and irregular menstrual cycles, polycystic ovary syndrome, and ovarian cancer risk in a population-based case-control study," Int J Cancer. 140[2]:285-291, 2017, doi: 10.1002/ijc.30441

[49] B. Yildiz, "Approach to the Patient: Contraception in Women With Polycystic Ovary Syndrome," The Journal of clinical endocrinology and metabolism. 100. 794-802. 10.1210/jc.2014-3196, 2015, doi: 10.1210/jc.2014-3196

[50] D. Lizneva, L. Gavrilova-Jordan, W. Walker, R. Azziz. "Androgen excess: investigations and management". Best Pract Res Clin Obstet Gynaecol. 37:98–118, 2016, DOI: 10.1016/j.bpobgyn.2016.05.003

[51] H. Lashen, "Role of metformin in the management of polycystic ovary syndrome," Ther Adv Endocrinol Metab. 1[3]:117-28, 2010, doi: 10.1177/2042018810380215

[52] S. Kar, "Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women; A prospective randomized trial," J Hum Reprod Sci. 5[3]:262-5, 2012, doi: 10.4103/0974-1208.106338

[53] A. MEED, M. MEDM, M,O, Taha, I. Abozeid. "The effect of laparoscopic ovarian drilling on anti-Müllerian hormone, LH/FSH ratio and inhibin B". *Evid Based Women's Health J.*10:37–45, 2020, https://doi.org/10.21608/ebwhj.2019.17817.1038

[54] I. Eskiyörük, R. Melekoğlu, C. Çetin, I.F. Ürünsak, M.T. Çetin, " Laparoscopic ovarian drilling: Is it a safe alternative of gonadotropin treatment for second-line therapy in patients with polycystic ovary syndrome resistant to clomiphene citrate". 25th European Congress of Obstetrics and Gynaecology and 15th Congress of Turkish Society of Obstetrics and Gynaecology; 17-21, 2018, DOI:10.24074/tjrms.2018-62975

[55] H.A. Hashim, "Management of women with clomifene citrate resistant polycystic ovary syndrome-an evidence based approach". *Polycystic Ovary Syndrome.* 7:1–22, 2012, DOI: 10.5772/27856

[56] S. Mitra, P.K. Nayak, S. Agrawal, "Laparoscopic ovarian drilling: An alternative but not the ultimate in the management of polycystic ovary syndrome". J Nat Sci Biol Med. 6:40–48, 2015, DOI: 10.4103/0976-9668.149076

[57] M. Eftekhar, R. Dehghani Firoozabadi, P. Khani, *et al.*, "Effect of laparoscopic ovarian drilling on outcomes of in vitro fertilization in clomiphene-resistant women with polycystic ovary syndrome". Int J Fertil Steril. 2016;10:42–47, 2016, DOI: 10.22074/ijfs.2016.4767

[58] Z. Moazami, H. Fallahzadeh, A. Aflatoonian, M. Mirzaei, "Laparoscopic ovarian electrocautery versus gonadotropin therapy in infertile women with clomiphene citrate-resistant polycystic ovary syndrome: A systematic review and meta-analysis". Iran J Reprod Med.12:531–539, 2014, PMCID: PMC4233311

[59] A. Moini, T. Esfidani, *et al*., "The effect of laparoscopic ovarian drilling on pregnancy outcomes in polycystic ovary syndrome women with more than 2 in-vitro fertilization cycle failures: A pilot RCT". Int J Reprod Biomed.19;21(11):901-908, 2023, doi: 10.18502/ijrm.v21i11.14653

[60] K.M. Seow, Y.W. Chang, K.H. Chen, *et al*., "Molecular Mechanisms of Laparoscopic Ovarian Drilling and Its Therapeutic Effects in Polycystic Ovary Syndrome," Int J Mol Sci. 21[21]:8147, 2020, doi: 10.3390/ijms21218147

[61] D. Dewani, P. Karwade, and K.S. Mahajan, "The Invisible Struggle: The Psychosocial Aspects of Polycystic Ovary Syndrome," Cureus. 15[12]:e51321, 2023, doi: 10.7759/cureus.51321

[62] G. D'Angelo, M. Ascione, I. Morra, *et al*., "What's new on the horizon for polycystic ovarian syndrome? Exploring emerging drugs in phase II," *Expert Opinion on Emerging Drugs*, *28*(3), 149–152, 2023, doi: 10.1080/14728214.2023.2260746

[63] J.R. Mellembakken, S.L. Berga, M. Kilen, T.G.Tanbo, T. Abyhol, and P. Fedorcsák, "Sustained fertility from 22 to 41 years of age in women with polycystic ovarian syndrome," Hum Reprod. 26[9]:2499-504, 2011, doi: 10.1093/humrep/der214

[64] Giampaolino P, Foreste V, Di Filippo C, *et al*., "Microbiome and PCOS: State-of-Art and Future Aspects". Int J Mol Sci. 2021 Feb 19;22(4):2048, 2021, doi: 10.3390/ijms22042048

[65] C. Stephanie, L. Siew , A. Chelsea, *et al*., "Lifestyle management in polycystic ovary syndrome – beyond diet and physical activity". BMC Endocrine Disorders. 23. 10.1186, 2023, DOI:10.1186/s12902-022-01208-y

متلازمة المبيض المتعدد الكيسات: رؤى حول المسببات والوراثة والتشخيص والعلاج والاتجاهات المستقبلية (مراجعة شاملة)

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المستخلص:

متلازمة المبيض المتعدد الكيسات (PCOS) هي اضطراب هرموني شائع يصيب النساء في سن الإنجاب. ويتميز بالاختلالات الهرمونية، وخلل التبويض، واضطرابات التمثيل الغذائي. تشير التقديرات إلى أن متلازمة تكيس المبايض تؤثر على 6-20% من النساء في جميع أنحاء العالم، مما يمثل تحديات للمتضررين ومقدمي الرعاية الصحية. هذا الاضطراب له مسببات معقدة، تشمل العوامل الوراثية والهرمونية والتمثيل الغذائي والبيئية. تشير الدراسات العائلية والتوائم إلى وجود عنصر وراثي قوي، حيث يلعب الاستعداد الوراثي دورًا مهمًا. حددت دراسات الارتباط على مستوى الجينوم مواقع وراثية متعددة مرتبطة بقابلية الإصابة بمتلازمة تكيس المبايض، مما يوفر نظرة ثاقبة لآلياتها الجزيئية. يمكن أن تختلف أعراض متلازمة تكيس المبايض بشكل كبير، بدءًا من عدم انتظام الدورة الشهرية وارتفاع مستويات الهرمونات الذكرية إلى العقم ومشاكل التمثيل الغذائي. يمكن أن تؤدي هذه المتلازمة إلى مشاكل صحية خطيرة مثل السمنة والسكري وأمراض القلب وسرطان بطانة الرحم، مما يؤكد أهمية أساليب العلاج الشاملة. يتضمن التشخيص تقييمًا شاملاً للأعراض ومستويات الهرمونات واختبارات التصوير وتاريخ الدورة الشهرية. يركز العلاج على إدارة الأعراض، وموازنة الهرمونات، وتقليل المخاطر طويلة المدى من خلال تغيير نمط الحياة، والأدوية، وعلاجات الخصوبة. على الرغم من التقدم المحرز في فهم متلازمة تكيس المبايض، لا تزال هناك فجوات في معرفتنا تؤكد ضرورة إجراء المزيد من الأبحاث لتوضيح الفيزيولوجيا المرضية المعقدة وتعزيز استراتيجيات العلاج لهذه الحالة السائدة والمعقدة. تقدم هذه المقالة ملخصًا لعلم الأوبئة والمسببات والتشخيص وخيارات العلاج والإجراءات الوقائية لمتلازمة تكيس المبايض، مع التركيز على التطورات الأخيرة والأبحاث القادمة.