GENETIC AND EPIGENETIC FACTORS CONTRIBUTING TO THE DEVELOPMENT OF PCOD

[1]Ms. Rupali Jadhao, [2]Ms. Ashvini Nagare, [3]Dr. Vijaykumar Kale, [4]Dr Mahesh Thakhare, [5]Mr. Vaibhav Narvade.

[1]Student of Pharmacy, [2]Assistant Professor, [3]Principal of Pharmacy, [4]Associate Professor, [5]Assistant Professor
[1]Pharmacy, Kasturi College of Pharmacy.,
[1]Department of Pharmacy, Kasturi College of Pharmacy, Pune, India.

Abstract:

Polycystic Ovarian Disease (PCOD) is a common endocrine and metabolic disorder affecting women of reproductive age. It is characterized by chronic anovulation, hyperandrogenism, and polycystic ovarian morphology. The etiology of PCOD is complex and multifactorial, involving genetic predisposition, hormonal imbalance, insulin resistance, obesity, and environmental influences. Studies show that 40–70% of women with PCOD have a family history of metabolic or reproductive disorders, highlighting a strong genetic component. Epigenetic changes caused by lifestyle, diet, stress, and endocrine-disrupting chemicals may alter gene expression and contribute to disease progression. Understanding the interaction between genetic and environmental factors is essential for improving diagnosis and individualized treatment. This review summarizes the mechanisms, risk factors, clinical features, and current approaches for managing PCOD.

To review the genetic, epigenetic, hormonal, and environmental factors involved in the development of PCOD and summarize current trends in diagnosis and management.

Keyword

PCOD, PCOS, Hyperandrogenism, Insulin resistance, Ovarian dysfunction, Anovulation, Hormonal imbalance, Genetics, Epigenetics.

INTRODUCTION

Polycystic Ovarian Disease (PCOD) is one of the most frequent hormonal disorders in women of reproductive age and a leading cause of infertility. It presents with irregular menstruation, excess androgen levels, and multiple immature ovarian follicles. Research indicates that PCOD is primarily driven by dysfunction of the hypothalamic–pituitary–ovarian (HPO) axis, leading to excessive androgen production by ovarian theca cells. Insulin resistance further worsens hormonal imbalance by increasing ovarian androgen synthesis. Environmental changes, obesity, and stress also contribute significantly. PCOD affects 15–20% of women globally and 2–26% in India, emphasizing its public health relevance.

Polycystic Ovary Syndrome (PCOS) is one of the most common hormone-related problems in women of reproductive age. Women with PCOS often experience higher levels of depression and anxiety. Between 1989 and 1995, researchers suggested that PCOS happens mainly because of a problem in the way the body controls androgen (male hormone) production. This leads to a condition called functional ovarian hyperandrogenism (FOH), where the ovaries produce too many male hormones.
Later studies supported this idea. When PCOS is defined as "unexplained high male hormones and irregular or absent ovulation," about two-thirds of women with PCOS show this functional ovarian problem. FOH is seen through an increased level of 17-hydroxyprogesterone after gonadotropin stimulation, meaning the ovaries react abnormally.

PCOD is usually seen on ultrasound as enlarged ovaries with many small follicles (tiny fluid-filled sacs) and thickened ovarian tissue.
Sometimes, doctors wonder if the adrenal glands (which make some hormones) may also play a role in PCOD.
Women with PCOD often have symptoms such as excessive hair growth (hirsutism), acne,

irregular periods (oligomenorrhea), or difficulty getting pregnant.
Studies have shown that women with PCOD often have high insulin levels in their blood, even if they are not overweight. High insulin is linked to high levels of male hormones like testosterone and androstenedione. This suggests that insulin resistance (when the body doesn't respond properly to insulin) may contribute to high male hormones and related symptoms.
Some researchers believe a single molecular problem may cause both high male hormones and insulin resistance. In some cases, surgery called

ovarian wedge resection is done if medications like clomiphene citrate do not help with ovulation or pregnancy.

Obesity in women can worsen PCOD and increase the risk of problems such as irregular ovulation, high male hormone levels, menstrual problems, infertility, thickening of the uterine lining, and higher chances of endometrial or breast cancer. Some women with high male hormones also have high insulin and insulin resistance, and insulin levels are often linked to hormone levels in PCOD.

To review the genetic, epigenetic, hormonal, and environmental factors involved in the development of PCOD and summarize current trends in diagnosis and management.

Causes of PCOD

1. Genetic Factors

PCOD tends to run in families. Multiple genes involved in insulin signaling, androgen production, and follicle development contribute to susceptibility. Women with a family history of diabetes, obesity, or PCOD have a higher risk.

2. Insulin Resistance

A major contributor to PCOD. Excess insulin stimulates the ovaries to produce more androgens, reduces SHBG levels, and disrupts follicle maturation. This leads to anovulation and cyst formation.

3. Hormonal Imbalance

Increased LH:FSH ratio

Excess androgens

Disturbed estrogen–progesterone balances
These abnormalities impair ovulation and cause persistent follicular growth.

4. Obesity and Lifestyle

Obesity increases insulin resistance and inflammation, worsening symptoms. Sedentary lifestyle, high-calorie diets, and stress contribute significantly.

5. Inflammation and Environmental Factors

Low-grade inflammation promotes androgen excess. Exposure to plastics, pesticides, and hormone-disrupting chemicals can alter endocrine function.

Symptoms of PCOD

- Irregular or absent menstrual cycles
- Anovulation and infertility
- Hyperandrogenism: acne, hirsutism, scalp hair loss
- Polycystic ovarian morphology on ultrasound
- Insulin resistance symptoms (acanthosis nigricans, weight gain)
- Mood disturbances and sleep problems
- Increased risk of diabetes, hypertension, and metabolic syndrome

- Etiology of PCOD

PCOD arises from the interaction of genetic susceptibility and environmental influences. Key etiological factors include:

- **Genetic predisposition:** Multiple gene variants associated with insulin resistance and androgen production.
- **HPO-axis dysfunction:** Elevated LH stimulates excess androgen formation.
- **Metabolic disturbances:** Insulin resistance and obesity intensify hormonal imbalance.
- **Epigenetic modifications:** Diet, stress, and chemical exposure can change gene expression without altering DNA structure.
- **Inflammation:** Chronic inflammation affects ovarian function and contributes to metabolic syndrome.

These combined factors disrupt normal ovarian physiology, leading to chronic anovulation and hyperandrogenism.

Treatment of PCOD

1. Lifestyle Management

- Balanced diet, high in fiber, low in refined sugars
- Regular physical activity (30–45 minutes/day)
- Weight reduction improves ovulation and insulin sensitivity, Stress management and adequate sleep

2. Pharmacological Therapy

For irregular cycles**:** Combined oral contraceptives, progesterone

For ovulation induction**:** Clomiphene citrate, Letrozole, Metformin

For insulin resistance**:** Metformin

For acne/hirsutism**:** Anti-androgens

Citrate (CC) remains a first-line ovulation-inducing agent. It increases FSH and LH release by blocking estrogen receptors, leading to follicle maturation. Ovulation occurs in up to 80% of patients.

3. Cosmetic and Supportive Measures

Laser hair reduction, acne therapies, and lifestyle counseling.

4. Surgical Options (Rare)

Ovarian drilling for medication-resistant cases.

Artificial Intelligence in PCOD

AI supports earlier and more accurate diagnosis by analyzing ultrasound images, hormonal profiles, and symptom patterns. Machine-Learning models can predict PCOD risk, suggest treatment pathways, and improve clinical decision-making. AI-based tools also help in personalized therapy and long-term monitoring.

Conclusion: -

PCOD is a multi-factorial disorder resulting from the interplay of genetic, hormonal, metabolic, and environmental factors. Insulin resistance and hyperandrogenism remain central to its pathophysiology. Early diagnosis, lifestyle modification, and targeted drug therapy can significantly improve reproductive and metabolic outcomes. Continued research in genetics, epigenetics, and AI-driven diagnostics will support more individualized and effective management strategies for women with PCOD.

REFERENCE

1]Timur Giirgan, M.D.Hiisnii M.D. Hakan Yarali, M.D. Osman Develioglu, M.D. Hulusi Zeyneloglu, M.D. Tarik Aksu, M.D. Evaluation of adhesion formation after laparoscopic treatment of polycystic ovarian disease. Fertility and Sterility. December 1991; 56(6): 1176-1178.

2) Dana Hdaib, Noor Almajali, Hiam Alquran, Wan Azani Mustafa, Waleed Al-Azzawi, Ahmed Alkhayyat. Detection of Polycystic Ovary Syndrome (PCOS) Using Machine Learning Algorithms. 5th International Conference on Engineering Technology and its Applications 2022- (5thIICETA2022). September 2022; 532-536.

3) Soumya V, Venkatesh P and Sharfudeen. Polycystic Ovary Disease (PCOD)- An Insight into Rodent Models, Diagnosis and Treatments. Journal of Clinical and Medical Images. 06 July 2021; 5(11): 1-13.

4) Vincenzina Bruni1 & Anna Capozzi & Stefano Lello. The Role of Genetics, Epigenetics and Lifestyle in Polycystic Ovary Syndrome Development: the State of the Art. Reproductive Sciences. 11 March 2021.https://doi.org/10.1007/s43032-021-00515-4

5) Aparna Prathap, T. P. Subhalakshmi, P. Joseph Varghese. A Cross-sectional Study on the Proportion of Anxiety and Depression and Determinants of Quality of Life in Polycystic Ovarian Disease. Indian Journal of Psychological Medicine. May-June 2018; 40(3): 257-262.

6) Ahmed Abdel Gadir, Ph.D., Huda M. I. Alnaser, M.B.Ch.B., Rawof S. Mowafi, M.D., Robert W. Shaw, M.D.The response of patients with polycystic ovarian disease to human menopausal gonadotropin therapy after ovarian electrocautery or a luteinizing hormone-releasing hormone agonist. Fertility and Sterility.February 1992; 57(2): 309-313.

7) Fatma A. Aleem, M.D., Ph.D.t Tracy McIntosh, Ph.D. Elevated plasma levels ofendorphin in a group of women with polycystic ovarian disease. Fertility and Sterility. November 1984; 42(5): 686-689

8)Archana Shirsath, Neela Aundhakar , Prathmesh Kamble. Study of oxidative stress and antioxidant levels in polycystic ovarian disease. International J. of Healthcare and Biomedical Research. July 2015; 03(04): 16-24.

9) Fatma A. Aleem, M.D., Ph.D. Mladen Predanic, M.D., M.sc.Transvaginal color Doppler determination of the ovarian and uterine blood flow characteristics in polycystic ovary disease. Fertility and Sterility. March 1996; 65(3): 510-516.

10) Joseph W. Goldzieher, M.D., and Leonard R. Axelrod, ph.D. Clinical and biochemical features of Polycystic ovarian disease. Fertility and Sterility. 1963; 14(6): 631-653.

11) Fred Benjamin, M.D. t Stanley Deutsch, Ph.D. Hildy Saperstein, M.D. Vickie L. Seltzer, M.D. Prevalence of and markers for the attenuated form of congenital adrenal hyperplasia and hyperprolactinemia masquerading as polycystic ovarian disease. Fertility and Sterility. August 1986; 46(2): 215-221

12) Mitchell E. Geffner, M.D., Solomon A. Kaplan, M.D., Noelle Bersch, B.A., David W. Golde, M.D., Elliot M. Landaw, M.D., ph.D., R. Jeffrey Chang, M.D. Persistance of insulin resistance in Polycystic ovarian disease after inhibition ofovarian steroid secretion. Fertility and sterility. March 1986; 45(3): 327-333.15-221.

13) P.GCrosignani and A.E.Nicolosi. Polycystic ovarian disease: heritability and heterogeneity. European society of Human Reproduction and Embryology. 2001; 7(1): 3-7.

14) Chun Fu Wang, M.D., Carl Gemzell, M.D. The use of human gonadotropins for the induction of ovulation in women with polycystic ovarian disease. Fertility and Sterility. May 1980; 33(5): 479-486.

15) Halimovae'zozamirzohidovna. Obesity as a risk factor for recurrent polycystic ovary disease. Asian journal of Pharmaceutical and biological research. Sept-Dec 2021; 10(3): 96-114.

16) Leena Anttila, M.D., Ying-Qing Ding, M.B., Kristiina Ruutiainen, M.D., Risto Erkkola, M.D., Kerttu Irjala, M.D., Ilpo Huhtaniemi, M.D. Clinical features and circulating gonadotropin, insulin, and androgen interactions in women with polycystic ovarian disease. Fertility and Sterility. June 1991; 55(6): 1057- 1061.

17) Roy G. Smith, Ph.D., Palige K. Besch, Ph.D. Buena Dill, M.T. (A.S.C.P.) Veasy C. Buttram, Jr., M.D. Saliva as a Matrix for Measuring Free Androgens: Comparison with Serum Androgens in Polycystic Ovarian Disease. Fertility and Sterility. May 1979; 31(5): 513-517.

18) Sunandini Ghosh1,Shrinjana Dhar, Sandip Bhattacharjee, Pritha Bhattacharjee.Contribution of environmental, genetic and epigenetic factors to obesity-related metabolic syndrome. Nucleus. 11 April 2023; https://doi.org/10.1007/s13237-023-00420-y

19) Rashmi Wardhan. Polycystic Ovarian Cyst Disorder (PCOD): Causes and Control. International Journal of Biotechnology and Biomedical Sciences. January-June 2016; 2(1): 32-33. http://www.krishisanskriti.org.

20) PonJola Coney, M.D.Polycystic ovarian disease: current concepts of pathophysiology and therapy.Fertility and Sterility. November 1984; 42(5): 667-682.

21) Sharvi, Shweta Gupta , Umang. Etiology of Polycystic Ovarian Disease (PCOD): Systematic Review. International Journal of Toxicological and Pharmacological Research. 2025; 15(1): 82-87.t: https://www.researchgate.net/publication/388494657

22) Fredrika Pekonen, M.D., Timo Laatikainen, M.D., Richard Buyalos, M.D., Eeva-Marja Rutanen, M.D. Decreased 34K insulin-like growth factor binding protein in polycystic ovarian disease. Fertility and Sterility. June 1989; 51(6): 972-975.

23) Robert J Norman, Ruijin Wu and Marcin T Stankiewicz. Polycystic ovary syndrome. Medical