REVIEW ARTICLE

The Association of Cardiovascular Disease Risk in Polycystic Ovarian Syndrome: A Qualitative Systematic Review

Priyanjali Sinha[1], Neema Acharya[2], Sourya Acharya[3], Sunil Kumar[4], Samarth Shukla[5], Shazia Mohammad[6]

Received on: 14 January 2023; *Accepted on:* 28 February 2023; *Published on:* 16 September 2023

Abstract

Polycystic ovarian syndrome (PCOS) is a complex hormonal imbalance with increased amounts of androgen, luteinizing hormone, and insulin. It shows various symptoms like acne, hirsutism, irregular menstruation, and obesity. Besides these, it is accompanied by hyperinsulinemia, hyperandrogenism, hyperlipidemia, anovulation, and insulin resistance. More recently PCOS has been increasingly linked with the development of cardiovascular and thrombotic risks compared to normal women of the same age. According to research so far, PCOS women experience a considerable increase in oxidative stress (OS), which causes many of the metabolic and cardiovascular abnormalities that characterize this condition. In this article, we address the risks associated with both established and emerging cardiovascular risk factors, as well as the various research that suggests women with PCOS may be more susceptible for developing thrombosis and cardiovascular disease (CVD).

Keywords: Anovulation, Hirsutism, Hyperandrogenism, Hyperinsulinemia, Hyperlipidemia, Polycystic ovarian syndrome.

Journal of South Asian Federation of Obstetrics and Gynaecology (2023): 10.5005/jp-journals-10006-2286

Introduction

Polycystic ovarian syndrome (PCOS) is a diverse disease that impacts women of childbearing age and is marked by anovulation, hyperandrogenism, and polycystic ovarian morphologic features.[1]

In the world, 5–10% of women of childbearing age suffer from PCOS.[2] This is the most common endocrine abnormality in premenopausal females. It is diagnosed by revised Rotterdam criteria that require the occurrence of any two of the following features: (A) anovulation/oligomenorrhea, (B) androgen abundance that is biochemical and/or clinical, and (C) polycystic-appearing ovaries on ultrasound.[3]

A condition with many clinical manifestations, PCOS is characterized by the presence of many cardiometabolic abnormalities including dyslipidemia, glucose intolerance, diabetes, and hypertension, these all being precursors for cardiovascular disease (CVD).

Numerous theories exist for the pathogenesis of PCOS, including ovarian overproduction of androgen, follicles that are resistant to rupture because of their thick shells, increased luteinizing hormone, excess anti-Mullerian hormone (a paracrine factor that blocks follicular development), and hypersecretion of insulin. These anomalies may manifest as a result of certain epigenetic changes, hormonal, metabolic, or even toxic variables that take place during the female gonad's early development or during the embryonic stage.[1]

Given that insulin resistance is an important pathology in evolution of both metabolic syndrome and PCOS, they both share similar metabolic and cardiovascular consequences, obesity, poor obstructive sleep apnea, connection with cancer, hypertension, glucose tolerance, type 2 diabetes mellitus, and coronary artery disease (CAD), and dermatological symptoms of hyperandrogenism are a few metabolic, cardiovascular, and clinical characteristics of PCOS.[4] In PCOS-affected individuals, hyperinsulinemia and insulin resistance are highly correlated with blood homocysteine levels.

It is known that hyperhomocysteinemia is a separate risk element for thromboembolic diseases and atherosclerotic disease. In women with PCOS, abnormalities in the enzymes involved in these processes, vitamin cofactor insufficiencies, increased insulin, or drugs that cause hyperhomocysteinemia can have cardiovascular problems at longer duration or reproductive problems at shorter duration.

We here discuss the danger of both traditional and novel CV risk factors in this article, as well as the evidence that suggests women with PCOS may be at higher risk for development of thrombosis and CVD in future life.

Methodology

Literature search includes database like PubMed, Scopus, Web of Science, Google Scholar, Cochrane Library between 2008 and October 2022 using the search terms "cardiovascular disease,"

[1,2,6]Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education & Research (DMIHER University), Wardha, Maharashtra, India

[3,4]Department of General Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education & Research (DMIHER University), Wardha, Maharashtra, India

[5]Department of Pathology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education & Research (DMIHER University), Wardha, Maharashtra, India

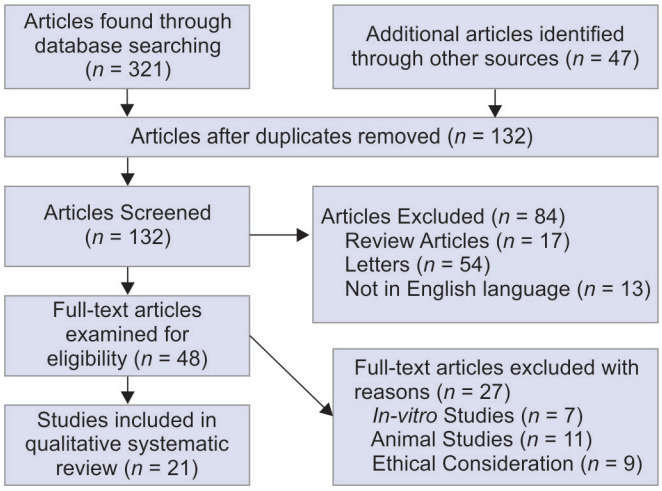
Corresponding Author: Priyanjali Sinha, Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education & Research (DMIHER University), Wardha, Maharashtra, India, Phone: +91 9599857372, e-mail: priyanjali.sinha333@gmail.com

How to cite this article: Sinha P, Acharya N, Acharya S, *et al*. The Association of Cardiovascular Disease Risk in Polycystic Ovarian Syndrome: A Qualitative Systematic Review. J South Asian Feder Obst Gynae 2023;15(4):497–500.

Source of support: Nil

Conflict of interest: None

Flowchart 1: The PRISMA flow diagram depicting the selection process



"oxidative stress," "thrombosis," "metabolic syndrome," and "polycystic ovarian syndrome," or "polycystic ovarian disease."

Additionally manual cross reference search after reading through these articles abstract and reference list were reviewed to identify additional manuscripts appropriate for review.

A total of 21 studies were identified after appropriate exclusions for the qualitative synthesis for this review. Flowchart 1 is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the selection process.

Review Discussion

Cardiovascular Risk Factors in Polycystic Ovarian Syndrome

Hypertension

Hypertension is a danger for PCOS-afflicted women. A study done by Wekker et al., compared 24-hour ambulatory blood pressure of 36 women with PCOS to 55 controls. After adjusting for body mass index, insulin resistance, and the distribution of body fat, it was observed that PCOS-affected women still had higher mean arterial blood pressure and daytime systolic pressures.[5]

Multiple variables, including hyperandrogenism, hyperactive sympathetic activity, obesity, and insulin resistance, contribute to the complex pathophysiology of hypertension in PCOS. According to meta-analysis, PCOS afflicted women are at higher risk to develop hypertension than those without the condition.[1]

The PCOS patients have an 80% higher prevalence of obesity and overweight status than non-PCOS women, with higher waist–hip ratio and body mass index (BMIs) over 30 kg/m^2 (obese) are more frequently seen in Caucasian women than Asian women.[1]

Atherosclerosis in Polycystic Ovarian Syndrome

Both obese and skinny PCOS women experience dyslipidemia, a metabolic disorder characterized by elevated triglycerides, low-density lipoprotein (LDL) cholesterol, and low high-density lipoprotein (HDL) cholesterol.[6] These females are predisposed to a subclinical vascular illness with carotid artery intimal-medial thickening, calcification of coronary artery, and endothelial dysfunction because of this imbalance, obesity, and insulin resistance.[7] These variations may aggravate the risk of stroke and fatal and nonfatal cardiac events in PCOS patients.

Vascular Diseases in Polycystic Ovarian Syndrome

Carotid intima-media wall thickness (cIMT) is a measurement of the arteries' tunica media and tunica intima. Myocardial infarction or stroke frequency is connected with this measurement, which is used to identify atherosclerosis and monitor its progression or regression. central obesity, hyperinsulinemia, dyslipidemia and elevated systolic blood pressure are known to be risk factors for PCOS and cIMT, respectively. Increased cIMT was observed in females under the age of 45, according to Talbott et al. They explained that since CVD have long incubation periods and metabolic changes that occur in adolescence may damage carotids in old age, it appears that aging and PCOS have a greater impact on cIMT than either factor acting alone.[7] Thereby increasing risk of vascular thrombotic events and eventually leading to CVD.

It is widely acknowledged that endothelial dysfunction and chronic inflammation are connected. In PCOS females, abnormal adipose tissue formation, disposition and function are linked with the production of cytokines, chemokines, and low-grade inflammatory process, which activate hypoxia-induced pathways and, as a result, reduce the synthesis of adiponectin.[8] Additionally, it is believed that androgens influence the metabolism of glucose, lipids, and oxidative stress (OS) in addition to mediating the conversion of preadipocytes into mature adipocytes.[9]

Oxidative Stress in Polycystic Ovarian Syndrome

The imbalance between antioxidant defense mechanisms and oxidants is defined as "oxidative stress." When the amount of oxidant surpasses the antioxidant capability, this disruption happens.[10] This imbalance causes a rise in reactive oxygen species (ROS), which harms proteins, lipids and DNA and prevents them from performing as they should.

Oxidants are chemical substances that have tendency to lose positive charge while gaining electrons. Both ROS and reactive nitrogen species (RNS), which are byproducts of nitric oxide metabolism, are examples of natural biological products that are included. Molecular oxygen is the source of ROS, which also includes free radicals (chemical substances with unpaired electrons), oxygen ions, and peroxides. At low concentrations, RNS and ROS play a variety of physiological activities, such as cellular signaling systems and defense against infectious pathogens. However, oxidants can damage DNA, cellular lipids, and proteins when they are present in excess and impede their capacity to operate normally.[10]

Lipid peroxidation is employed as a biosignature of OS in cells and tissues and is a recognized mechanism of cellular harm in humans. Research studies most frequently measure lipid peroxidation, and one of its by-products, isoprostanes (IsoP), has been accepted as the gold standard.[11] There are several studies that support the amount of IsoP as a credible indicator of endogenous lipid metabolism and consequently as a helpful marker for assessing OS and damage; due to this, it is regarded as the most accurate OS marker. IsoP are known to cause platelet aggregation and vasoconstriction. Additionally, conditions such as cardiovascular, neurological, and respiratory disorders have been linked to high levels of IsoP.[12]

Antioxidant defenses, physical defenses, and preventative and repair processes are all components of protective physiological mechanisms against oxidants. Antioxidants are chemicals that can

neutralize, scavenge, or stop oxidants from forming. They consist of both enzymes (such as glutathione peroxidase, catalase, and superoxide dismutase) and other non-enzymatic large molecules (ferritin and albumin) as well as small molecules (vitamin C, glutathione, and tocopherol).[10]

Nitric oxide and malondialdehyde, which are OS markers and are produced following lipid hydrolysis and oxidation through the breakdown of monounsaturated and polyunsaturated fatty acids, have been discovered at higher amounts in PCOS women as compared to control groups.[7]

Increasing number of studies show that obesity and metabolic syndrome causes OS in people. According to many studies, obesity has been linked to higher amounts of ROS. Potential builder to OS in obesity and metabolic syndrome entails hyperlipemia, hyperglycemia, increased muscular activity to support excess mass, chronic inflammation, hyperleptinemia, and low antioxidant protection. Furthermore, insulin resistance has been connected to the formation of reactive species and OS. Oxidative stress lowers insulin production from pancreatic β-cells. It also affects glucose absorption in muscle and adipose tissue.[10]

Polycystic ovarian syndrome has a complicated etiology, and its underlying cause is yet unknown. Local and systemic OS development could be impacted by a number of PCOS traits and relationships, such as hyperandrogenemia, visceral obesity, and insulin resistance, which may in turn aggravate these metabolic abnormalities.[13]

Cardiovascular Disease Markers in Polycystic Ovarian Syndrome

The plasma levels of PCOS patients have consistently been found to be higher for CRP and homocysteine, in spite of the absence of traditional CVD risk factors in women with PCOS. In addition, new techniques for miRNA analysis have made it possible to identify a number of miRNAs that are dysregulated in response to the metabolic alterations that are hallmark of this illness.

C-reactive Protein in Polycystic Ovarian Syndrome

Among the many circulating markers, C-reactive protein (CRP) is very popular indicator of inflammation in people. Recent studies have observed that CRP plays an initiating role in inflammation because it encourages complement system activation, triggers apoptosis, promotes phagocytosis, and releases proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNFα).[14]

Higher CRP laboratory values have been detected in women with PCOS, which suggests that chronic inflammation is likely involved in pathogenesis of the condition's elevated risk of CVD.[15]

Homocysteine in Polycystic Ovarian Syndrome

Homocysteine is a notable indicator of OS since it can increase the generation of ROS and, at high concentrations, cause endothelial cell damage.[16] In a large meta-analysis conducted in 2013, identification of circulating markers for PCOS and OS was compared between a group of 4,933 PCOS-positive women and 3,671 of control group women.[10] The results of this study exhibited that women with PCOS had a 23% increased mean homocysteine concentration, indicating that their levels of OS were greater.

Another study that examined the association between homocysteine and CAD involved monitoring and comparing the homocysteine serum levels of 70 patients with the presence of CAD using coronary angiography. Additionally, because it is associated with higher aortic stiffness and pulse pressure, homocysteine has been linked to the development of decreased arterial compliance.[17] Increased homocysteine levels has also been linked to a higher risk of venous thromboembolism. It has also been shown to play a role in platelet adherence to endothelial cells while also encouraging the development of prothrombotic substances like β-thromboglobulin and tissue plasminogen activator.[17]

Furthermore, according to many research, homocysteine increases intravascular thrombosis by causing platelet aggregation via the hydrogen sulfide pathway.[18] As a result, it is recognized and reported as a separate risk factor for atherosclerosis.

Micro-RNA in Polycystic Ovarian Syndrome

A class of non-coding RNAs called microRNAs (miRNA) is crucial for controlling the expression of genes, because they can identify target sequences in the messenger RNA's 3′-untranslated regions (3′-UTR), or third untranslated region (mRNA). The posttranscriptional expression of eukaryotic genes is regulated by miRNAs, and PCOS patients play a significant part in this process.

An elevated levels of miRNA-223 and miRNA-93 were detected in the group of women having PCOS. Recently, Sathyapaln et al. compared 25 PCOS women to 24 normal control women of the same age and weight. They demonstrated that miRNA-93 is a more accurate available biomarker for the identification of PCOS.[19] As opposed to that, miRNA-223, which attacks the glucose transporter type 4, has been discovered to have greatly increased in biopsies from the left ventricle in individuals with type 2 diabetes and left ventricular cardiac failure.[20] Deswal and Dang in 2020, published a meta-analysis comparing two novel miRNAs, miR-29a-5p, and miR-320, and suggested as potential diagnostic biomarkers for PCOS. Both of these molecules appears to be suppressed in women with PCOS.[21] Monitoring blood miRNAs to be utilized as markers for treatment response, prognosis, or diagnostic purposes is a promising area for future research.[1]

Conclusion

Polycystic ovarian syndrome is the most common endocrine abnormality typically in women of childbearing age and is also the most distinctive cause of infertility due to ovulatory dysfunction.

Insulin resistance and impaired glucose tolerance are two metabolic conditions linked to PCOS that start to manifest in adolescence. Other manifestations that become more pronounced with age include visceral obesity, dyslipidemia, hepatic steatosis, diabetes and an elevated risk of CVD like hypertension and myocardial infarction. The ROS levels and endothelial dysfunction are closely related and heavily dependent upon free radical damage in the body, is one of the many pathways that could increase the total CVD risk, particularly by generating hypertension and increasing risk to vascular thrombosis. Additionally, hyperhomocysteinemia contributes to atherosclerosis on its own by encouraging platelet aggregation and so boosting arterial thrombosis.

Overall, research to far indicates a definite rise in OS within PCOS women, leading to many cardiovascular and metabolic abnormalities that are a feature of this disease. The creation of preventative and therapeutic measures focused at reducing these patients' CVD risk would alter disease process but will also require further research about trimming of OS.

Orcid

Priyanjali Sinha https://orcid.org/0000-0001-5209-3411
Neema Acharya https://orcid.org/0000-0001-9899-8179
Sourya Acharya https://orcid.org/0000-0003-1969-0817
Sunil Kumar https://orcid.org/0000-0001-9905-4831
Samarth Shukla https://orcid.org/0000-0002-3289-7006
Shazia Mohammad https://orcid.org/0000-0001-8158-368X

References

1. Duică F, Dănilă CA, Boboc AE, et al. Impact of Increased Oxidative Stress on Cardiovascular Diseases in Women with Polycystic Ovary Syndrome. Front Endocrinol (Lausanne). 2021;12:614679. DOI: 10.3389/fendo.2021.614679.
2. Deligeoroglou E, Vrachnis N, Athanasopoulos N, et al. Mediators of chronic inflammation in polycystic ovarian syndrome. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol 2012;28(12):974–978. DOI: 10.3109/09513590.2012.683082.
3. Mak W, Dokras A. Polycystic ovarian syndrome and the risk of cardiovascular disease and thrombosis. Semin Thromb Hemost 2009;35(7):613–620. DOI: 10.1055/s-0029-1242715.
4. Kondapaneni V, Gutlapalli SD, Poudel S, et al. Significance of homocysteine levels in the management of polycystic ovarian syndrome: A literature review. Cureus 2020;12(10):e11110. DOI: 10.7759/cureus.11110.
5. Wekker V, van Dammen L, Koning A, et al. Long-term cardiometabolic disease risk in women with PCOS: A systematic review and meta-analysis. Hum Reprod Update 2020;26(6):942–960. DOI: 10.1093/humupd/dmaa029.
6. Diamanti–Kandarakis E, Kandaraki E, Christakou C, et al. The effect of pharmaceutical intervention on lipid profile in polycystic ovary syndrome. Obes Rev Off J Int Assoc Study Obes 2009;10(4):431–441. DOI: 10.1111/j.1467-789X.2009.00588.x.
7. Talbott EO, Zborowski J, Rager J, et al. Is there an independent effect of polycystic ovary syndrome (PCOS) and menopause on the prevalence of subclinical atherosclerosis in middle aged women? Vasc Health Risk Manag 2008;4(2):453–462. DOI: 10.2147/vhrm.s1452.
8. Pierard M, Tassin A, Conotte S, et al. Sustained intermittent hypoxemia induces adiponectin oligomers redistribution and a tissue-specific modulation of adiponectin receptor in mice. Front Physiol 2019;10:68. DOI: 10.3389/fphys.2019.00068.
9. Fauser BCJM, Tarlatzis BC, Rebar RW, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril 2012;97(1):28.e25–38.e25. DOI: 10.1016/j.fertnstert.2011.09.024.
10. Murri M, Luque–Ramírez M, Insenser M, et al. Circulating markers of oxidative stress and polycystic ovary syndrome (PCOS): A systematic review and meta-analysis. Hum Reprod Update 2013;19(3):268–288. DOI: 10.1093/humupd/dms059.
11. Milne GL, Dai Q, Roberts LJ II. The isoprostanes—25 years later. Biochim Biophys Acta 2015;1851(4):433–445. DOI: 10.1016/j.bbalip.2014.10.007.
12. Calzada M, López N, Noguera JA, et al. Elevation of isoprostanes in polycystic ovary syndrome and its relationship with cardiovascular risk factors. J Endocrinol Invest 2019;42(1):75–83. DOI: 10.1007/s40618-018-0888-y.
13. Liu S, Navarro G, Mauvais–Jarvis F. Androgen excess produces systemic oxidative stress and predisposes to beta-cell failure in female mice. PloS One 2010;5(6):e11302. DOI: 10.1371/journal.pone.0011302.
14. Spritzer PM, Lecke SB, Satler F, et al. Adipose tissue dysfunction, adipokines, and low-grade chronic inflammation in polycystic ovary syndrome. Reproduction 2015;149(5):R219–R227. DOI: 10.1530/REP-14-0435.
15. Garoufi A, Pagoni A, Papadaki M, et al. Cardiovascular risk factors and subclinical atherosclerosis in Greek adolescents with polycystic ovary syndrome: Its relationship with body mass index. Child Basel Switz 2021;9(1):4. DOI: 10.3390/children9010004.
16. Herman R, Jensterle M, Janež A, et al. Genetic variability in antioxidative and inflammatory pathways modifies the risk for PCOS and influences metabolic profile of the syndrome. Metabolites 2020;10(11):E439. DOI: 10.3390/metabo10110439.
17. Pang X, Liu J, Zhao J, et al. Homocysteine induces the expression of C-reactive protein via NMDAr-ROS-MAPK-NF-κB signal pathway in rat vascular smooth muscle cells. Atherosclerosis 2014;236(1):73–81. DOI: 10.1016/j.atherosclerosis.2014.06.021.
18. Shah H, Jan MU, Altaf A, et al. Correlation of hyper-homocysteinemia with coronary artery disease in absence of conventional risk factors among young adults. J Saudi Heart Assoc 2018;30(4):305–310. DOI: 10.1016/j.jsha.2018.04.002.
19. Sathyapalan T, David R, Gooderham NJ, et al. Increased expression of circulating miRNA-93 in women with polycystic ovary syndrome may represent a novel, non-invasive biomarker for diagnosis. Sci Rep 2015;5:16890. DOI: 10.1038/srep16890.
20. Lu H, Buchan RJ, Cook SA. MicroRNA-223 regulates Glut4 expression and cardiomyocyte glucose metabolism. Cardiovasc Res 2010;86(3):410–420. DOI: 10.1093/cvr/cvq010.
21. Deswal R, Dang AS. Dissecting the role of micro-RNAs as a diagnostic marker for polycystic ovary syndrome: A systematic review and meta-analysis. Fertil Steril 2020;113(3):661.e2–669.e2. DOI: 10.1016/j.fertnstert.2019.11.001.