Polycystic Ovary Syndrome Markers and Mechanisms

Erna Yovi Kurniawati[1], Noor Pramono[2], Syarief Thaufik Hidayat[2,] Endang Mahati[3]

[1]Ummi Khasanah Health Polytechnic
[2]Department Fertility and Endocrinology, Medical Faculty, Diponegoro University
[3]Department Pharmacology and Therapy, Medical Faculty, Diponegoro University

ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by hormonal imbalances, metabolic dysregulation, and reproductive abnormalities. This study aims to elucidate the significance of PCOS markers and their mechanisms while outlining the methodology employed. PCOS markers and mechanisms are essential to improve early diagnosis, effective clinical management, and the development of individually tailored therapies. A comprehensive literature review was conducted from 2020 to 2023 using PubMed, ScienceDirect, EMBASE, and Google Scholar databases. Key search terms included "pathophysiology," "pathogenesis," "PCOS," "marker," and "biomarker," aligned with the established inclusion and exclusion criteria to select suitable articles. Out of 50 research articles included in review. After removing duplicates, articles underwent a two-phase screening process based on predefined inclusion criteria. Additionally, a marker mechanism flowchart was created using the Biorender application. Results highlighted the pivotal role of various markers in understanding PCOS pathophysiology and guiding clinical management. Anthropometric, visual, metabolic, inflammatory, endocrine, and oxidative stress markers were analyzed for their diagnostic, prognostic, and therapeutic implications in PCOS. The study underscores the importance of marker interactions in personalized PCOS management. Limitations in marker interpretation warrant further research to refine diagnostic accuracy and optimize therapeutic interventions. Integrating marker mechanisms enhances understanding of PCOS heterogeneity and informs targeted treatment approaches tailored to individual phenotypic variations.
Keywords: biomarker, pathophysiology, polycystic ovary syndrome (PCOS).

Coresponding author: yovi.raharjanto@gmail.com

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder of both etiology and pathophysiology, characterized by hormonal imbalances, metabolic disorders, and reproductive abnormalities[1]. Understanding the pathophysiology of PCOS is essential to elucidate the underlying mechanisms and develop effective management strategies. PCOS poses significant challenges due to its heterogeneous nature and diverse clinical manifestations, ranging from menstrual irregularities and infertility to metabolic complications and cardiovascular risk[2,3]. One of the most important reasons to study the pathophysiology of PCOS is to unravel the complex interactions between hormonal dysregulation, metabolic disorders, and ovarian dysfunction[4]. This knowledge is critical in identifying key molecular pathways and targets for intervention, thus paving the way for more targeted and personalized treatment approaches tailored to individual phenotypic variations.

Understanding the importance of PCOS markers is crucial for accurate diagnosis, prognosis, and risk stratification[2]. Biomarkers associated with hormonal, metabolic, and inflammatory pathways provide valuable insights into disease progression, severity, and potential complications[5–7]. Utilizing these markers in clinical practice facilitates early detection, timely intervention, and better management of PCOS-related comorbidities. In addition, PCOS markers play an important role in guiding the development of new therapies and optimizing existing management strategies. By identifying specific molecular targets and pathways involved in the pathogenesis of PCOS, researchers can design targeted pharmacological interventions to restore hormonal balance, improve metabolic function, and enhance productive outcomes[8].

Investigating PCOS markers and understanding the underlying mechanisms is critical to advancing our knowledge of this complex disorder and improving clinical outcomes for affected individuals. By elucidating the pathophysiology, identifying diagnostic and prognostic markers, and developing targeted therapies, we can better manage PCOS and reduce the associated health risks, ultimately improving women's quality of life.

Methods

A thorough exploration was undertaken of scholarly articles released from 2020 to 2023, utilizing databases such as PubMed, ScienceDirect, EMBASE, and Google Scholar. The search terms encompassed key topics including "pathophysiology," "marker," "polycystic ovarian syndrome (PCOS)," "pathogenesis," and "biomarker". The quality assessment of the study follows the Joanna Briggs (JBI) Critical Assessment and PRISMA guidelines[9] (refer to figure 1). The retrieved literature was thoroughly examined to identify any instances of duplication. Subsequently, a two-stage screening process was conducted. Initially, the titles and abstracts were assessed to determine adherence to the predefined inclusion criteria. Literature that met these criteria proceeded to the second stage, where a detailed analysis was performed to ensure alignment between the journal content and the predetermined inclusion criteria (refer to Table 1). A flowchart illustrating the marker mechanism in PCOS was also using the Biorender application available at biorender.com[10].

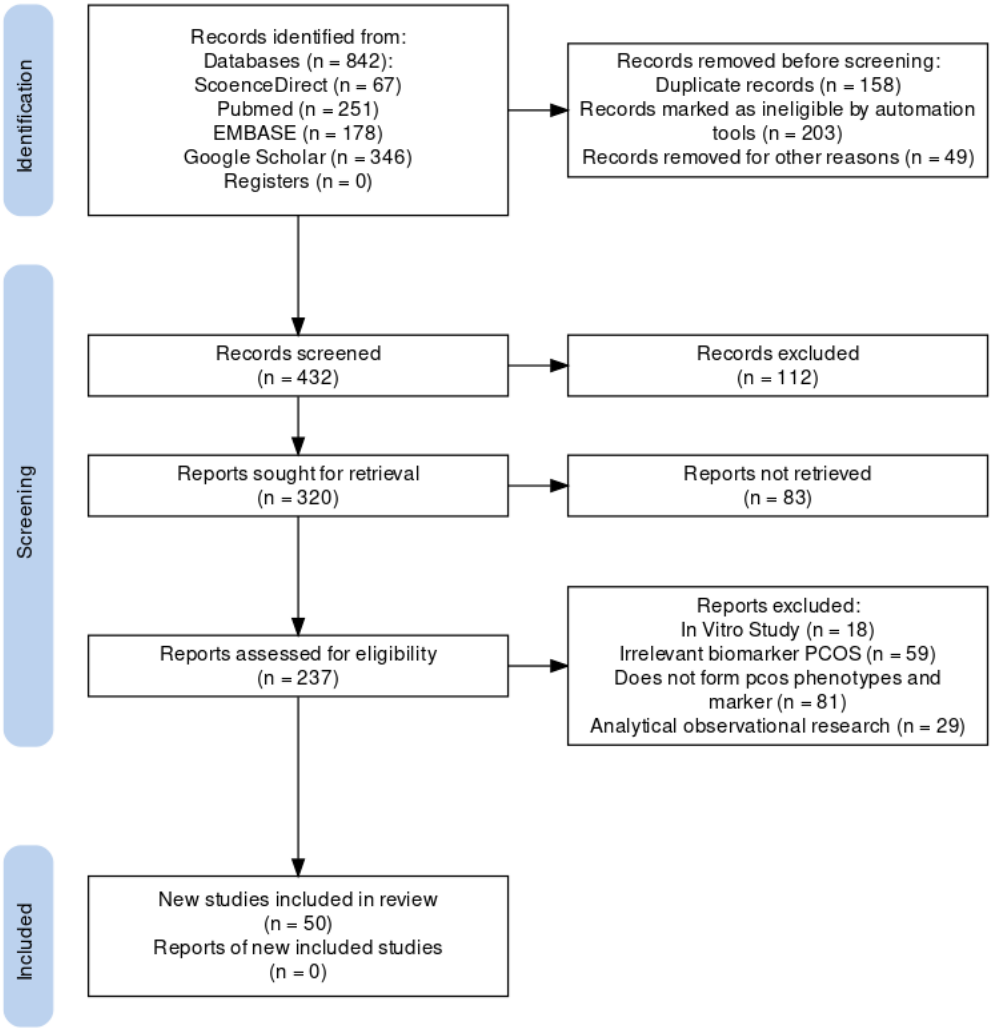

Figure 1. PRISMA Flow diagram of eligible studies

Table 1. Inclusion and Exclusion Criteria

Criteria	Inclusion	Exclusion
Population	PCOS Model, human	In vitro
Intervention	Studies that propose or test biomarkers as diagnostic or prognostic tools for PCOS.	Studies irrelevant to PCOS biomarkers.
Comparators	With and without a control group	-
Outcomes	Research shows PCOS marker and phenotype	Does not form PCOS phenotypes and marker
Time	Within the past five years	More than the past five years
Study design	Experimental research	Analytical observational research
Language	Indonesian, English	Besides Indonesian and English

Result

Fifty research articles were included studies. Table 2 summaries of PCOS markers. Markers such as hormonal, metabolic, and phenotypic provide deep insights into the pathophysiology of PCOS, aid in identifying symptoms and risk of complications and guide the development of targeted treatment strategies.

Table 2. PCOS Marker

Marker		PCOs Phenotype	Reference
Categoric	**Indicator**		
Anthropometric marker	Weight Body Mass Index (BMI) Waist-to-Height Rasio (WHtR) Waist circumference	Obesity	[65,69–73]
Visual/ histological marker	Antral Follicle Count (AFC)	ovarian polycystic	[22,74]
Metabolic marker	Lipid Accumulation Product (LAP) Visceral Adiposity Index (VAI) Triglyceride (TG) Fatty Acids (FA) Carnitines Phospholipids HDL-C ratio Fasting Plasma Glucose (FPG) Triglyceride to high-density lipoprotein cholesterol ratio (TG/HDL-C) Total cholesterol to high-density lipoprotein cholesterol ratio (TC/HDL-C)	Obesity Insulin resistance Dyslipidemia	[5,36,68,70–72,75]
metabolic and nutritional markers	25(OH)D/ calsidiol	disruption of hormone and metabolic balance	[22]
Metabolic and Inflammatory marker	Adipokine Leptin Resistin Adiponectin	Obesity Insulin resistance	[16]
	Advanced Glycation End Products (AGEs)	Inflammation Insulin resistance	[76,77]

Marker		PCOs Phenotype	Reference
Categoric	**Indicator**		
Endocrine biomarkers	Testosterone (T4) A/L Ratio: androstenedione (A)/ testosterone (L) 17OHP4 (17-α hydroxy progesterone) SHBG Androstenedione (A4) Dehydroepiandrosterone sulfate (DHEAS) TT:DHT Progesterone (P4) Luteinizing Hormone (LH) Follicle Stimulating Hormone (FSH) LH:FSH	Hyperandrogenism Ovulation disorders	[27,31,50,51,56,64,69,78–85]
	Anti-Müllerian Hormone (AMH)	polycystic ovary morphology (PCOM)	[66,67,74,86–94]
	Insulin-like Growth Factor 1 (IGF-1)	Hyperandrogenism Ovarium dysfunction Insulin resistance	[55]
	Cortisol	Hyperandrogenism Insulin resistance Stress oxidative	[85,95]
Inflammation markers	Tumor Necrosis Factor-alpha (TNF-α) Interleukin-6 (IL-6) Interleukin-8 (IL-8) Interleukin-10 (IL-10) Interleukin-17 (IL-17) Interleukin-18 (IL-18) Interleukin-33 (IL-33) Interleukin-1 alpha (IL-1α) Interleukin-1 beta (IL-1β)	Chronic low-grade inflammation	[14,96–98]
	White Blood Cell (WBC) Lymphocyte-to-Monocyte Ratio (LMR) Monocyte-to-HDL Ratio (MHR) Alpha-1 acid glycoprotein (AGP) C-reactive protein (CRP) Interferon-gamma (IFN-γ)	Chronic low-grade inflammation Insulin resistance	[5,6,64,68,99,100]
oxidative stress markers	Malonaldehyde (MDA)	Hyperandrogenism Insulin resistance	[5]
markers of nutritional status and oxidative stress	Copper (Cu) magnesium (Mg) total antioxidant capacity (TAC)	Inflammation Insulin resistance	[62]

Anthropometric markers, such as height, weight, body mass index (BMI), waist-to-hip ratio (WHtR), and waist circumference, serve as indicators of obesity, which is a common characteristic of polycystic ovary syndrome (PCOS)[11,12]. Obesity plays a pivotal role in the pathogenesis of PCOS, contributing to hormonal imbalances, insulin resistance, and inflammation, which are hallmark features of the condition[13,14]. Excess adipose tissue, particularly visceral fat, leads to increased secretion of adipokines and cytokines, promoting chronic low-

grade inflammation and disrupting metabolic homeostasis. Furthermore, adipose tissue dysfunction results in dysregulated production of sex hormones and adipokines, exacerbating hyperandrogenism and insulin resistance in PCOS[15–17]. The accumulation of visceral fat also leads to elevated levels of circulating free fatty acids, further impairs insulin sensitivity and exacerbates metabolic dysfunction. Consequently, the anthropometric markers of obesity serve as crucial indicators of the underlying metabolic disturbances and hormonal imbalances characteristic of PCOS phenotypes[18,19]. Additionally, individuals with PCOS who exhibit higher anthropometric measurements often present with more severe metabolic abnormalities and reproductive dysfunction, highlighting the importance of addressing obesity in the management of PCOS to mitigate its adverse health outcomes[20,21].

Visual marker, specifically the assessment of antral follicle count (AFC), serves as a crucial indicator for identifying polycystic ovaries, a hallmark feature of polycystic ovary syndrome (PCOS)[22,23]. An increased or abnormal AFC reflects disruptions in ovarian follicle development and maturation, which are central to the pathogenesis of PCOS. The excessive production of androgens in PCOS disrupts normal ovarian follicular development, accumulating immature follicles that fail to ovulate[24,25]. These immature follicles contribute to the characteristic appearance of polycystic ovaries observed via ultrasound imaging[22,26]. Furthermore, the dysregulation of hormonal signaling, particularly elevated levels of luteinizing hormone (LH) and androgens disrupts the delicate balance between follicular recruitment, growth, and atresia, further exacerbating the accumulation of antral follicles[27,28]. The AFC not only aids in the diagnosis of PCOS but also provides insights into the severity and phenotype of the condition. Individuals with PCOS presenting with a higher AFC often exhibit more severe hormonal disturbances and reproductive dysfunction, indicating the potential for increased metabolic and cardiovascular risks[29–31]. Therefore, the visual marker of AFC serves as a valuable tool for assessing ovarian morphology and guiding clinical management strategies tailored to the specific phenotypic manifestations of PCOS.

Metabolic markers, including Lipid Accumulation Product (LAP), Visceral Adiposity Index (VAI), triglycerides (TG), fatty acids (FA), carnitines, phospholipids, HDL-C ratio, and fasting plasma glucose (FPG), are indicative of the metabolic disturbances observed in polycystic ovary syndrome (PCOS)[18,19,32]. These biomarkers are elevated in individuals with PCOS. These metabolic biomarkers not only help in diagnosing and monitoring PCOS but also serve as prognostic indicators to assess the risk of metabolic complications and cardiovascular events. PCOS-specific metabolic phenotypes, which include varying degrees of insulin resistance, dyslipidemia, and obesity, influence the clinical presentation and severity of the syndrome. Insulin resistance and dyslipidemia are hallmarks of PCOS, often leading to metabolic complications such as type 2 diabetes and cardiovascular disease. Insulin resistance plays a central role in the pathophysiology of PCOS, contributing to hyperinsulinemia and compensatory hyperglycemia, which in turn stimulates androgen production by the ovaries and exacerbates metabolic dysregulation[6,28,33].

Dyslipidemia, characterized by elevated triglyceride levels and decreased HDL cholesterol levels, further compounds the metabolic abnormalities in PCOS, promoting a pro-inflammatory and pro-thrombotic state conducive to cardiovascular risk[34]. Additionally, altered lipid metabolism, evidenced by changes in fatty acid composition, carnitine levels, and phospholipid profiles, reflects disturbances in mitochondrial function, energy metabolism, and insulin signaling

pathways[35,36]. These metabolic markers not only aid in the diagnosis and monitoring of PCOS but also serve as prognostic indicators for assessing the risk of metabolic complications and cardiovascular events[37,38]. Furthermore, the specific metabolic phenotype of PCOS, characterized by varying degrees of insulin resistance, dyslipidemia, and obesity, influences the clinical presentation and severity of the syndrome, emphasizing the importance of individualized management strategies targeting metabolic abnormalities to mitigate long-term health risks in PCOS patients[32,39].

Metabolic and inflammatory markers, such as adipokines, advanced glycation end products (AGEs), and interleukins, reflect the chronic inflammation and insulin resistance that occur in polycystic ovary syndrome (PCOS)[7,34,40]. Chronic inflammation, characterized by elevated levels of pro-inflammatory cytokines and adipokines, contributes to cellular damage and tissue dysfunction, exacerbating PCOS symptoms and increasing the risk of metabolic complications[15,17,41]. Adipokines, including leptin, resistin, and adiponectin, play key roles in regulating inflammation, insulin sensitivity, and lipid metabolism[42]. Dysregulated adipokine secretion, particularly increased leptin and resistin levels and decreased adiponectin levels, promotes insulin resistance and adipose tissue dysfunction, further exacerbating the metabolic disturbances observed in PCOS[42,43]. Advanced glycation end products (AGEs), formed through non-enzymatic glycation and oxidation of proteins and lipids, accumulate in tissues under hyperglycemia and oxidative stress, contributing to chronic low-grade inflammation, endothelial dysfunction, and insulin resistance[44–46]. Interleukins, such as TNF-α, IL-6, IL-8, and IL-10, mediate inflammatory responses and immune cell activation, perpetuating the inflammatory cascade in PCOS. The interplay between metabolic dysfunction and chronic inflammation amplifies the pathophysiological mechanisms underlying PCOS, leading to impaired ovarian function, dysregulated hormone production, and disrupted folliculogenesis[40,44]. Furthermore, the specific metabolic and inflammatory phenotype of PCOS influences disease severity, clinical manifestations, and the risk of developing associated comorbidities, underscoring the importance of targeted interventions to mitigate inflammation and improve metabolic health in PCOS management[45].

Metabolic and nutritional markers, such as 25-hydroxyvitamin D (25(OH)D) or calcidiol, are crucial indicators of hormonal and metabolic imbalances implicated in polycystic ovary syndrome (PCOS)[47]. Deficiency in vitamin D levels disrupts endocrine function and metabolic homeostasis, contributing to insulin resistance, dyslipidemia, and hyperandrogenism characteristic of PCOS. Inadequate vitamin D levels exacerbate hormonal dysregulation, impair ovarian function, and promote adiposity, exacerbating PCOS symptoms and complications. Thus, addressing vitamin D deficiency through supplementation or lifestyle modifications may restore hormone and metabolic balance, ameliorating PCOS manifestations and improving overall health outcomes[48,49].

Endocrine biomarkers, including testosterone, androstenedione-to-testosterone ratio (A/L ratio), 17-α hydroxy progesterone (17OHP4), sex hormone-binding globulin (SHBG), androgen precursor dehydroepiandrosterone sulfate (DHEAS), progesterone (P4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), anti-Müllerian hormone (AMH), insulin-like growth factor 1 (IGF-1), and cortisol, reflect the hormonal dysregulation characteristic of polycystic ovary syndrome (PCOS)[18,50]. Hyperandrogenism, marked by elevated levels of testosterone, androgen precursors, and decreased SHBG levels, contribute to

follicular arrest, anovulation, and ovarian dysfunction observed in PCOS. Disruptions in the hypothalamic-pituitary-ovarian (HPO) axis, manifested by altered LH: FSH ratio and increased LH secretion relative to FSH, further exacerbate follicular development abnormalities and contribute to the pathogenesis of PCOS[51–53]. Anti-Müllerian hormone (AMH) levels, reflecting the ovarian reserve and follicular recruitment, are typically elevated in women with PCOS, indicating increased follicular activity and impaired follicle maturation. Insulin-like growth factor 1 (IGF-1) mediates the effects of insulin and growth hormone on ovarian function and steroidogenesis, contributing to hyperandrogenism and ovarian dysfunction in PCOS[54,55]. Dysregulated cortisol secretion, associated with chronic stress and adrenal dysfunction, may exacerbate hyperandrogenism and insulin resistance in PCOS. The intricate interplay between hormonal disturbances, particularly hyperandrogenism and ovarian dysfunction, underlies the pathophysiology of PCOS and contributes to the heterogeneity of PCOS phenotypes, including variations in clinical manifestations, reproductive outcomes, and metabolic profiles[56,57]. Understanding the role of endocrine biomarkers in PCOS pathogenesis is crucial for elucidating disease mechanisms and developing targeted therapeutic strategies to manage PCOS-associated hormonal imbalances and improve clinical outcomes.

Inflammation markers, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), IL-8, IL-10, IL-18, IL-33, IL-1α, IL-1β, and IL-17, reflect the presence of chronic inflammation in polycystic ovary syndrome (PCOS). Chronic inflammation plays a pivotal role in the pathogenesis of PCOS, contributing to various aspects of the disorder's pathophysiology[40,44]. Elevated levels of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8, promote insulin resistance, impair ovarian function, and disrupt follicular development in PCOS. These cytokines induce aberrant signaling pathways, leading to dysregulated steroidogenesis, follicular arrest, and impaired oocyte maturation[44]. Additionally, IL-10, an anti-inflammatory cytokine, may exhibit dysregulated expression in PCOS, contributing to chronic inflammation and metabolic dysfunction. IL-18 and IL-33 have been implicated in adipose tissue inflammation and insulin resistance[5,58], further exacerbating metabolic disturbances in PCOS. IL-1α and IL-1β mediate inflammatory responses and may contribute to ovarian dysfunction and follicular abnormalities in PCOS. IL-17, a pro-inflammatory cytokine primarily associated with autoimmune and inflammatory conditions, may also play a role in the pathogenesis of PCOS-associated inflammation[41,44]. Chronic low-grade inflammation in PCOS not only contributes to reproductive and metabolic dysfunction but also increases the risk of serious health complications, including cardiovascular disease, type 2 diabetes mellitus, and endometrial cancer[44,59]. Understanding the role of inflammation markers in PCOS pathophysiology is essential for elucidating disease mechanisms and developing targeted therapeutic interventions to mitigate inflammation, improve metabolic health, and reduce long-term health risks in women with PCOS.

Markers of oxidative stress, including malondialdehyde (MDA), copper (Cu), magnesium (Mg), and total antioxidant capacity (TAC), reflect an imbalance between free radical production and antioxidant defense mechanisms in the body, contributing to the pathogenesis of polycystic ovary syndrome (PCOS) and associated metabolic complications[5,60]. Elevated levels of MDA, a byproduct of lipid peroxidation, indicate increased oxidative damage to cell membranes and tissues in PCOS. Cu and Mg are essential cofactors for antioxidant enzymes, and their dysregulation may impair antioxidant

defense mechanisms, exacerbating oxidative stress in PCOS[44,61]. Conversely, alterations in TAC levels reflect changes in the overall antioxidant capacity of the body, which may be compromised in PCOS due to increased oxidative burden. Oxidative stress in PCOS disrupts cellular signaling pathways, impairs mitochondrial function, and induces inflammation and apoptosis in ovarian tissues, contributing to follicular dysfunction, anovulation, and infertility[6]. Furthermore, oxidative stress-mediated damage to pancreatic β-cells and insulin-sensitive tissues exacerbates insulin resistance and dyslipidemia in PCOS, promoting the development of metabolic syndrome and cardiovascular disease[34]. Understanding the role of oxidative stress markers in PCOS pathophysiology is crucial for identifying novel therapeutic targets to mitigate oxidative damage, restore antioxidant balance, and improve metabolic and reproductive outcomes in women with PCOS.

Markers of nutritional status and oxidative stress, such as copper (Cu), magnesium (Mg), and total antioxidant capacity (TAC), offer insights into metabolic health and oxidative conditions in polycystic ovary syndrome (PCOS). These markers reflect the body's micronutrient balance and antioxidant defense mechanisms, which are crucial in maintaining cellular homeostasis and combating oxidative damage[62]. Imbalances in Cu and Mg levels may disrupt antioxidant enzyme activity and exacerbate oxidative stress in PCOS, contributing to cellular dysfunction and inflammation[34,62]. Additionally, alterations in TAC levels indicate changes in the overall antioxidant capacity of the body, which may influence the severity of oxidative stress and metabolic disturbances in PCOS. Further research is needed to elucidate the specific mechanisms underlying the dysregulation of these markers in PCOS pathophysiology and to develop more effective treatment strategies targeting metabolic and oxidative abnormalities[63]. Understanding the interplay between nutritional status, oxidative stress, and PCOS pathogenesis holds promise for improving diagnostic accuracy, guiding therapeutic interventions, and ultimately optimizing health outcomes for individuals with PCOS.

Marker Mechanisms in PCOS (see Figure 2)

Obesity or being overweight is often a major risk factor associated with PCOS. Obesity causes changes in the body's metabolism, including increased insulin resistance and dyslipidemia. Obesity leads to increased adipose tissue, which in turn triggers the release of pro-inflammatory cytokines and adipose hormones[40]. This impairs insulin sensitivity in body tissues, leading to insulin resistance. Insulin resistance increases insulin production by the pancreas in response, increasing androgen release by the ovaries[64]. Insulin resistance also contributes to dyslipidemia, a lipid metabolism disorder characterized by increased triglycerides, decreased HDL cholesterol, and increased LDL fraction rich in triglycerides[36]. Adipocytes, or fat cells, in excess in the body of individuals with PCOS have impaired function. This includes increased release of pro-inflammatory adipokines such as leptin and resistin and decreased release of anti-inflammatory adiponectin[42,65].

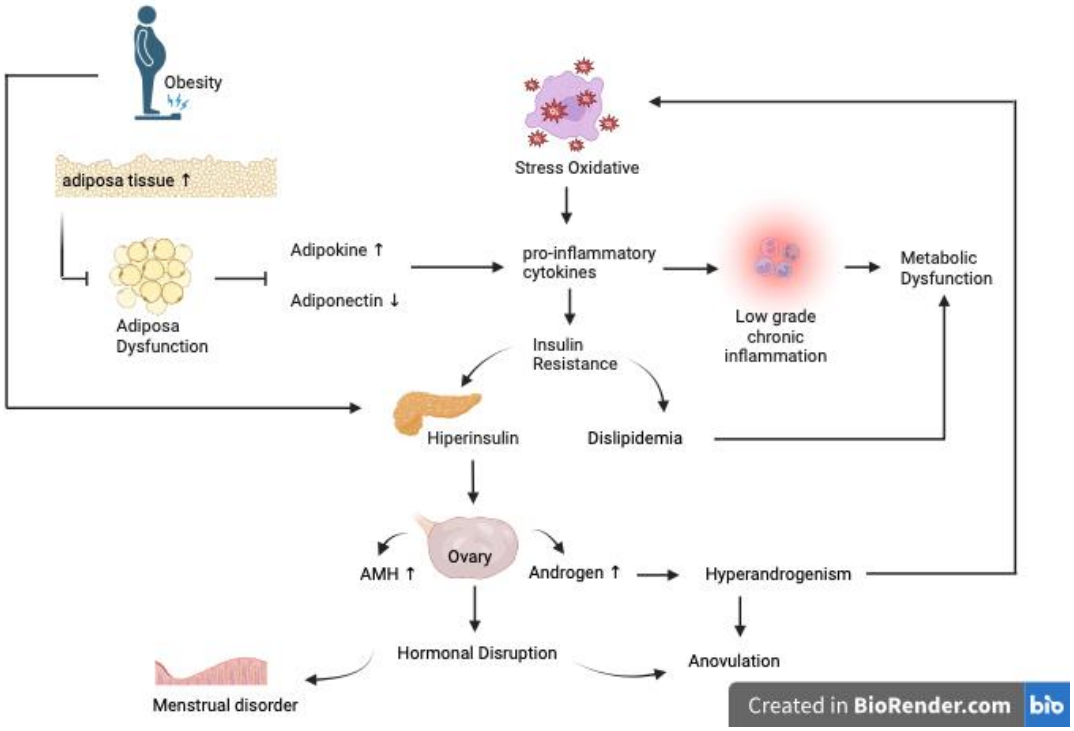

Figure 2. Marker Mechanisms in PCOS

Insulin resistance and obesity also lead to increased production of pro-inflammatory cytokines by adipose tissue. This chronic low-grade inflammation can lead to metabolic dysfunction and exacerbate insulin resistance and dyslipidemia[44,59]. Increased insulin levels in circulation stimulate ovarian cells to increase the production of androgens (male sex hormones) and anti-Mullerian hormone (AMH). This disrupts the normal hormonal balance in a woman's body, which can disrupt the menstrual cycle and ovulation[66,67].

Increased androgen production by the ovaries is one of the main characteristics of PCOS. Insulin resistance stimulates cells in the ovaries to produce more androgens. This can lead to hirsutism (abnormal hair growth in women) and other reproductive disorders[56]. Elevated levels of androgens and other hormones can interfere with the development and release of eggs from the ovaries. This can lead to anovulation (non-ovulation), one of the main features of PCOS[68]. Mitochondrial dysfunction associated with insulin resistance, dyslipidemia, and increased androgen hormone production can increase oxidative stress. This results in cellular and tissue damage and exacerbates the inflammation and metabolic dysfunction associated with PCOS[5,64].

Conclusions and Suggestion

Understanding PCOS markers is essential for diagnosis, monitoring, and management. These markers provide insights into pathophysiology, symptoms, and complications, guiding treatment strategies. However, there are limitations in marker interpretation, necessitating further research. The development of comprehensive PCOS therapy and management is essential to address obesity, insulin resistance, dyslipidemia, hormonal disruption, inflammation, adipose dysfunction, hyperandrogenism, ovarian dysfunction, and oxidative stress. Further investigation into marker interactions is needed to improve understanding and targeted interventions.

Acknowledgment

This academic paper provides initial investigations supported by the Ministry of

Education, Culture, Research, and Technology under the Indonesian Educational Scholarship Program for doctoral studies. The author bears full responsibility for its content. The author affirms the absence of any conflicts of interest that could influence the findings or interpretation presented in this manuscript.

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