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INTEGRATION OF ULTRASOUND BIOMARKERS AND GENETIC PROFILING FOR EARLY DETECTION OF POLYCYSTIC OVARY SYNDROME: MOLECULAR AND PRECISION MEDICINE PERSPECTIVES

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine and metabolic disorder with a strong genetic and molecular basis, affecting women of reproductive age and contributing to significant reproductive and metabolic complications.

Objective: This review aims to summarize current advances in the integration of ultrasound biomarkers and genetic profiling for early detection of PCOS within the framework of precision medicine.

Materials and Methods: A systematic analysis of recent literature was conducted using major international databases, including PubMed, Web of Science, Scopus, and MEDLINE. Studies focusing on ultrasound diagnostics, molecular genetics, and integrative approaches in PCOS were included.

Results: Advances in ultrasound technologies, including three-dimensional imaging and automated follicular assessment, have improved the sensitivity and reproducibility of morphological evaluation. At the molecular level, genetic variations in insulin signaling pathways (IRS-1, PI3K, AKT), steroidogenesis-related genes, mitochondrial dysfunction, and epigenetic modifications play a key role in the pathogenesis and phenotypic heterogeneity of PCOS. The integration of imaging biomarkers with genomic and transcriptomic data enables the development of predictive models for early diagnosis, risk stratification, and identification of subclinical disease forms.

Conclusion: The combination of ultrasound biomarkers and genetic profiling represents a promising strategy for improving early detection of PCOS. Integrative multi-omics approaches enhance diagnostic accuracy and support the transition toward personalized and precision medicine in reproductive endocrinology.

KEYWORDS: polycystic ovary syndrome; genetic profiling; molecular mechanisms; ultrasound biomarkers; insulin signaling pathway; mitochondrial dysfunction; epigenetics; precision medicine

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders in women of reproductive age, manifested by a combination of ovulatory dysfunction, hyperandrogenism, and characteristic morphological changes in the ovaries (Kravchenko et al., 2023; Ziganshin et al., 2019; Abashova et al., 2019; Beglova and Elgina, 2019). Despite the almost century-long history of the study of this pathology, starting with the classic description by Stein and Leventhal in 1935, the etiology and pathogenesis of PCOS remain the subject of intense scientific debate, which emphasizes the complexity and multifactorial nature of this syndrome (Goodarzi et al., 2011; Azziz et al., 2016; Rosenfield and Ehrmann, 2016).

According to epidemiological studies, the prevalence of PCOS in the global population varies from 6.5 to 8% when using clinical and laboratory criteria and reaches 20–25% when ultrasound signs of polycystic ovarian morphology are included (Gus et al., 2002; Beglova et al., 2019; Chen et al., 2008). In the Russian Federation, the incidence rate is estimated at 8–12%, but the actual rates are probably higher due to diagnostic heterogeneity, variability in data interpretation approaches, and the lack of unified examination standards (Sukhonosova, 2015). In recent years, there has been a steady trend toward an increase in the number of PCOS cases, which is associated not only with lifestyle changes and the growing prevalence of metabolic disorders, but also with the expanded use of highly sensitive ultrasound technologies (Artymuk and Tachkova, 2021; Nardo and Gelbaya, 2008; Christ and Cedars, 2023).

In this regard, the combination of ultrasound and genetic approaches is becoming a key direction in the modern diagnosis of PCOS. This integrative approach makes it possible not only to improve diagnostic accuracy but also to identify

preclinical forms of the disease when classical hormonal abnormalities are not yet clearly expressed (Nandi et al., 2025; Joham et al., 2022; Kobayashi et al., 2025). This is especially important for young women, since early detection and correction of pathological changes may prevent the development of infertility, metabolic syndrome, type 2 diabetes mellitus, and cardiovascular complications (Hoeger et al., 2021; Wekker et al., 2020; Zhu et al., 2021).

Despite significant progress in PCOS research, key issues remain unresolved regarding the standardization of ultrasound criteria, determination of biomarker thresholds, and clinical significance of detected genetic variations (Christ and Cedars, 2023; Legro et al., 2013; Teede et al., 2018). The lack of comprehensive models combining morphological, metabolic, and genetic data still limits the possibilities of early detection and risk stratification in patients with suspected PCOS (Day et al., 2018; Dapas et al., 2020; Chen et al., 2011; Ghaderzadeh et al., 2025).

Thus, the relevance of this topic is determined by the high prevalence of PCOS, its impact on women's reproductive health and metabolic status, and the need to improve diagnostic algorithms. The modern paradigm of precision medicine requires a transition from descriptive diagnostic criteria to quantitative and analytical models based on the combination of ultrasound biomarkers and genetic profiling. This approach may make it possible to identify individual risks of disease development and optimize preventive and therapeutic strategies (Escobar-Morreale, 2018; Diamanti-Kandarakis and Dunaif, 2012; Teede et al., 2018).

Recent studies indicate that PCOS is not only an endocrine disorder but also a genetically determined condition with complex molecular mechanisms involving metabolic and reproductive pathways (Goodarzi et al., 2011; Azziz et al., 2016; Day et al., 2018; Dapas et al., 2020; Kobayashi et al., 2025).

The purpose of this review is to systematize current data on the use of ultrasound biomarkers and genetic profiling in the early diagnosis of polycystic ovary syndrome, as well as to analyze their potential for the formation of integrative models of personalized diagnosis and prognosis.

METHODOLOGY

A systematic search of scientific publications was conducted in the electronic databases eLibrary, CyberLeninka, PubMed, Web of Science, MEDLINE and Cochrane Library. Keywords and their English counterparts were used for the search: "polycystic ovary syndrome", "PCOS", "ultrasound biomarkers", "genetic profiling", "anti-muller hormone (AMH)", "ultrasound diagnostics", "reproductive health", "endocrine and metabolic disorders".

The review includes publications in Russian and English for the period from 2002 to 2025, covering the results of original research, systematic reviews and meta-analyses on the diagnostic capabilities of ultrasound methods and genetic markers in polycystic ovary syndrome.

Studies focused exclusively on pharmacotherapy, surgical treatment, or experimental models without clinical validation were excluded from consideration. Thus, the final review included 40 publications selected according to the criteria of scientific reliability, relevance and relevance to the stated research topic.

RESULTS AND DISCUSSION

This section reviews current data on the use of ultrasound biomarkers and genetic profiling for the early detection of polycystic ovary syndrome (PCOS), including their diagnostic significance and relationship with the pathogenetic mechanisms of the disease. Special attention is paid to the integration of morphological and molecular indicators that determine diagnostic accuracy and clinical informativeness. Key ultrasound parameters, genetic variations, and the prospects for combining them within personalized approaches to PCOS assessment and prediction are discussed below.

Ultrasound biomarkers in the diagnosis of PCOS

Since the first description of polycystic ovary syndrome, the understanding of its ultrasound morphology has undergone significant changes. While early diagnosis was based on laparoscopic visualization of the ovaries, the development of ultrasound technologies made it possible to perform non-invasive assessment of ovarian structure and function, turning sonographic signs into one of the key biomarkers of the disease (Nardo and Gelbaya, 2008; Joham et al., 2022). The transition from transabdominal to transvaginal ultrasound significantly improved the accuracy of follicle count and ovarian volume assessment, which later became the basis for the Rotterdam diagnostic criteria (Beglova et al., 2019; Legro et al., 2013; Teede et al., 2018).

Modern ultrasound criteria include the presence of ≥12 antral follicles measuring 2–9 mm in diameter and/or ovarian volume >10 cm^3; however, recent studies suggest revising these thresholds to 20–25 follicles due to the use of high-frequency ultrasound probes and improved imaging resolution (Wekker et al., 2020; Christ and Cedars, 2023; Teede et al., 2018). According to Beglova and Elgina, refinement of ultrasound parameters, including stromal echogenicity and follicle distribution, may increase diagnostic sensitivity and allow earlier detection of morphological signs of PCOS (Beglova and Elgina, 2019).

Several authors note that follicle number and ovarian volume are closely correlated with anti-Müllerian hormone levels, which emphasizes their complementary diagnostic value (Beglova et al., 2019; Fruzzetti et al., 2020). Nardo and Gelbaya demonstrated that increasing the follicle threshold to ≥20 may improve diagnostic specificity and reduce the risk of overdiagnosis (Nardo and Gelbaya, 2008).

Nevertheless, the interpretation of ultrasound biomarkers remains dependent on the operator and the technical characteristics of the equipment, which requires standardization of the examination methodology (Kravchenko et al., 2023; Christ and Cedars, 2023). The use of three-dimensional ultrasound and automated follicle assessment is considered a promising direction that may reduce subjectivity and improve reproducibility of diagnostic results (Joham et al., 2022; Liang et al., 2021).

Thus, the development of ultrasound technologies has made it possible to transform the morphological features of PCOS — follicle number, ovarian volume, and ovarian structure — into reliable biomarkers of the disease. However, for a more complete understanding of the syndrome, it is necessary to consider not only morphological but also molecular-genetic determinants underlying endocrine and metabolic disorders, which determines the transition to genetic profiling of PCOS (Paris et al., 2020; Besenek and Gurlek, 2021; Tian et al., 2021).
Recent advances in biomarker research indicate that ultrasound findings should be interpreted in combination with biochemical and molecular parameters, including lipidomic, proteomic, and genetic profiles, to improve diagnostic accuracy (Nandi et al., 2025; Kobayashi et al., 2025; Ghaderzadeh et al., 2025).

Genetic profiling and molecular mechanisms of PCOS

PCOS is increasingly recognized as a polygenic and multifactorial disorder, with genome-wide association studies identifying multiple susceptibility loci associated with metabolic and reproductive dysfunction (Day et al., 2018; Dapas et al., 2020; Chen et al., 2011). Modern research shows that genetic profiling allows PCOS to be considered not as an isolated endocrine disorder but as a polyetiological syndrome with a pronounced molecular component, in which defects in insulin signaling pathways and metabolic regulation play a key role (Joham et al., 2022; Christ and Cedars, 2023; Matevossian and Carpinello, 2021).
At the molecular level, mutations and polymorphisms of genes involved in insulin signaling, including IRS-1, PI3K, and AKT-related pathways, may disrupt metabolic flexibility and reduce tissue sensitivity to glucose, contributing to insulin resistance in PCOS (Joham et al., 2022; Hoeger et al., 2021). These alterations are supported by molecular studies demonstrating that insulin resistance in PCOS is mediated by defects in intracellular signaling cascades, particularly those involving PI3K/AKT pathways (Diamanti-Kandarakis and Dunaif, 2012; Moran et al., 2010; Dunaif, 1997).
Of particular interest is the role of mitochondrial dysfunction and epigenetic modifications. These mechanisms may alter the expression of genes controlling oxidative phosphorylation and energy metabolism, thereby contributing to genetic predisposition to insulin resistance and hyperandrogenism (Nandi et al., 2025; Zhu et al., 2021; Kobayashi et al., 2025). The combination of transcriptomic and DNA methylation data indicates that genetic and epigenetic factors may act synergistically, affecting receptors, enzymes, and transporter proteins in metabolically active tissues, including skeletal muscle and ovarian tissue (Christ and Cedars, 2023; Matevossian and Carpinello, 2021; Xu et al., 2011; Luo et al., 2021). These mechanisms are summarized in Table 1, which presents the key molecular and genetic mechanisms associated with the development of PCOS.

Table 1: Genetic and molecular mechanisms of PCOS

Group of genes / mechanism	Main effects	Diagnostic value	Key authors / studies
Insulin signaling pathway (IRS-1, PI3K, AKT)	Impaired metabolic flexibility and decreased tissue sensitivity to glucose	Detection of insulin resistance in PCOS	Joham et al., 2022; Hoeger et al., 2021
Mitochondrial dysfunction	Decreased expression of oxidative phosphorylation genes, impaired energy metabolism	Assessment of energy status and mitochondrial activity	Nandi et al., 2025; Zhu et al., 2021
Epigenetic modifications (DNA methylation, transcriptome)	Synergistic effect on the regulation of receptors, enzymes, and transport proteins	Prediction of predisposition to hyperandrogenism and metabolic disorders	Nandi et al., 2025; Matevossian & Carpinello, 2021
Androgen receptor genes and the TGF-β signaling cascade	Imbalance of interaction between endocrine and metabolic systems, phenotypic variability	Differentiation of PCOS phenotypes by severity and type of disorders	Tian et al., 2021; Matevossian & Carpinello, 2021
Genomic associative loci of PCOS	Regulation of energy exchange, lipid transport and reproductive functions	Creation of genetic panels for personalized diagnostics	Ganie et al., 2019; Christ & Cedars, 2023

In addition, recent evidence highlights the role of mitochondrial dysfunction, oxidative stress, and epigenetic modifications, including DNA methylation and microRNA regulation, in the pathogenesis of PCOS (Palomba et al., 2015; Xu et al., 2011; Luo et al., 2021).
Furthermore, studies by Tian et al. and Matevossian and Carpinello demonstrate that variations in androgen receptor genes and components of the TGF-β signaling pathway may disrupt the interaction between endocrine and metabolic systems, thereby contributing to the phenotypic heterogeneity of PCOS and variability in disease severity (Tian et al., 2021; Matevossian and Carpinello, 2021).

These findings are supported by genome-wide association studies that have identified PCOS-specific susceptibility loci linked to genes regulating energy metabolism, lipid transport, and reproductive function (Ganie et al., 2019; Christ and Cedars, 2023).
Collectively, these data support the concept that PCOS represents a systemic molecular disorder that requires integrative genomic and multi-omics approaches for accurate characterization and diagnosis (Legro et al., 2013; Teede et al., 2018).
The accumulation of knowledge on genetic and molecular mechanisms provides the foundation for the development of a new diagnostic paradigm that integrates morphological, biochemical, and genetic data, thereby enabling the transition toward personalized diagnostic strategies in PCOS.

Integration of ultrasound and genetic markers: prospects for personalized diagnostics

The integration of ultrasound and genetic markers represents an emerging direction in the personalized diagnosis of polycystic ovary syndrome, providing a more comprehensive understanding of its etiopathogenesis at both molecular and morphological levels (Valdimarsdottir et al., 2021; Rodgers et al., 2019; Heshmati et al., 2021; Krul-Poel et al., 2018; Trummer et al., 2019).
Modern approaches combine high-resolution ultrasound mapping of follicular architecture with the analysis of genetic variations involved in steroidogenesis and insulin metabolism, allowing the development of individualized diagnostic profiles for patients (Ostadmohammadi et al., 2019).
In contrast to traditional diagnostic methods based solely on morphological or hormonal assessment, multimodal data integration significantly improves risk stratification and facilitates the identification of latent or subclinical forms of PCOS at early stages (Gupta et al., 2020).
The application of artificial intelligence and machine learning enables the integration of imaging and genomic datasets, significantly improving early detection and classification of PCOS phenotypes (Ghaderzadeh et al., 2025; Lim et al., 2023).
Artificial intelligence and deep learning techniques play a key role in analyzing heterogeneous datasets by identifying complex correlations between morphological patterns and genetic variations that are not detectable through conventional analytical methods (Ghaderzadeh et al., 2025).
Such integrative approaches not only improve diagnostic accuracy but also form the basis for personalized therapeutic strategies aimed at correcting metabolic and reproductive dysfunctions in individual patients.
In the future, the integration of ultrasound imaging with genomic and epigenetic profiles may become a powerful tool for predicting reproductive outcomes, enabling precise identification of PCOS subtypes with different etiologies and responses to treatment (Valdimarsdottir et al., 2021; Rodgers et al., 2019).
Thus, the synergy between ultrasound biomarkers and genetic profiling forms the foundation of a new paradigm in precision medicine, where the diagnosis and management of PCOS become more targeted, objective, and clinically adaptable.

CONCLUSION

This review demonstrates that PCOS should be considered a multifactorial disorder with a strong genetic and molecular basis rather than solely a clinical or morphological condition. The integration of ultrasound biomarkers with genetic and epigenetic profiling provides a more comprehensive understanding of the disease pathogenesis and improves early detection, particularly in subclinical cases. Molecular insights into insulin signaling pathways, mitochondrial function, and gene regulation highlight the heterogeneity of PCOS and support the development of stratified diagnostic models.
The combination of imaging and genomic data represents a key step toward precision medicine, enabling individualized risk assessment and targeted therapeutic strategies. Future research should focus on validating integrative diagnostic algorithms and identifying robust genetic markers for routine clinical application.

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