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Advancements In Diagnostic Approaches For Polycystic Ovary Syndrome (PCOS): A Comprehensive Review

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder affecting reproductive-aged women, characterized by metabolic and reproductive abnormalities. PCOS has become increasingly common in recent years and is recognized as a multifaceted condition. Accurate diagnosis of PCOS is essential for effective management and prevention of long-term complications. This comprehensive review critically examines the advancements in diagnostic approaches for PCOS and explores future directions. The importance of accurate diagnosis for both clinical care and research is emphasized. Traditional diagnostic criteria, such as the Rotterdam criteria, have limitations, leading to diagnostic heterogeneity. Recent research has focused on refining the criteria by incorporating additional parameters such as ovarian reserve testing, anti-Müllerian hormone (AMH) levels, and metabolic markers. Imaging techniques have provided insights into PCOS pathophysiology. By incorporating molecular techniques into diagnostic cytogenetics, clinicians and researchers can gain a deeper understanding of the underlying genetic and epigenetic factors contributing to PCOS. This knowledge can aid in accurate diagnosis, stratification of patients based on risk, and the development of targeted therapeutic approaches. However, it is important to note that the utility of these molecular techniques in PCOS diagnosis and management is still evolving, and further research is needed to validate their clinical utility and establish standardized protocols. Future directions involve integrating multiple diagnostic modalities and utilizing machine learning algorithms for robust tools and risk prediction models. These advancements have the potential to revolutionize PCOS diagnosis and management, ultimately improving patient outcomes.

KEYWORDS

Polycystic ovary syndrome (PCOS), PCOS Diagnostic approaches, Rotterdam criteria, Anti-Müllerian hormone (AMH), ovarian reserve testing, metabolic markers, imaging techniques, transvaginal ultrasound, MRI, PCOS pathophysiology, PCOS subtypes, phenotypic classifications, molecular classifications.

INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a prevalent and complex endocrine disorder that affects reproductive-aged women (Azziz et al., 2016). It is characterized by a range of metabolic and reproductive abnormalities, including hyperandrogenism, menstrual irregularities, and polycystic ovaries. PCOS has gained increasing recognition in recent years due to its rising prevalence and significant impact on women's health and quality of life (Conway et al., 2014). Accurate and timely diagnosis of PCOS is crucial for effective management and prevention of long-term complications.

Polycystic ovary syndrome (PCOS) not only impacts fertility but also increases the risk of various health problems, including obesity, diabetes, cardiovascular diseases, psychological disorders, and more. Despite its prevalence, the precise causes and mechanisms of PCOS remain unclear, making it challenging to diagnose and treat effectively (Che et al., 2023). Advanced-level studies aimed at detecting new biomarkers can pave the way for improvements in the management of PCOS in the future.

The unclear understanding of the underlying causes and mechanisms of PCOS, there are many ongoing debates surrounding the diagnosis of PCOS in adolescents, and the limited number of studies focusing specifically on PCOS in this age group can be particularly challenging to manage polycystic ovary syndrome (PCOS) in adolescent patients (Meczekalski et al., 2023).

The diagnostic criteria for PCOS have evolved, with the Rotterdam criteria being widely used. However, these criteria have limitations, leading to diagnostic heterogeneity and challenges in providing personalized care. To address these limitations and improve diagnostic accuracy, researchers have made significant advancements in diagnostic approaches for PCOS. These advancements involve the incorporation of additional parameters, such as anti-Müllerian hormone (AMH) levels, ovarian reserve testing, and metabolic markers, to supplement the existing diagnostic criteria. Furthermore, imaging techniques, including transvaginal ultrasound and MRI, have provided valuable insights into the pathophysiology of PCOS and its associated metabolic alterations (Conway et al., 2014; Teede et al., 2018)

As per the article of Bharali *et al.,* (2022), the prevalence of polycystic ovary syndrome (PCOS) varies depending on the diagnostic criteria used. Rotterdam's criteria and AES criteria yielded a pooled prevalence close to 10%, while the NIH criteria resulted in a prevalence of 5.8%. These findings underscore the necessity for standardized and universally accepted diagnostic criteria to screen for PCOS. Although physicians play a crucial role in identifying PCOS and educating the public about the condition, the potential additional costs and time required for diagnosis and treatment may discourage some young women from seeking help. Healthcare professionals need to convey this information with cultural sensitivity. Establishing guidelines for PCOS management and awareness in India should involve the collaboration of policy-makers, government organizations, and healthcare providers, taking into account the evidence provided by studies in this field (Bharali et al., 2022).

By critically evaluating these advancements, this review aims to provide a comprehensive overview of the current state of PCOS diagnostics and shed light on the potential for improved management and patient outcomes.

Ovarian Reserve Tests

Ovarian reserve, the number of remaining oocytes in the ovary, impacts reproductive potential and aging. Evaluating ovarian reserve is important for understanding fertility and preventing early menopause. Current evaluation methods have limitations due to the lack of specific diagnostic criteria for ovarian reserve and individualized assessment. Clinical indicators like biochemical tests and ultrasound imaging are currently used. Anti-Müllerian hormone (AMH) is considered the most reliable marker as well as combining Machine learning, with its ability to analyze large medical datasets and incorporate new data, offers advantages in this context (Ding et al., 2023)

Ovarian reserve is a complex clinical phenomenon influenced by various factors such as age, genetics, and environment. The ideal ovarian reserve test should be convenient, reproducible, and have low variability, and high specificity to accurately diagnose diminished ovarian reserve and identify those at risk of ovarian hyperstimulation before fertility treatment. Additionally, it can assist in diagnosing polycystic ovary syndrome and determining its severity. While there is currently no perfect ovarian reserve test, antral follicular count and antimullerian hormone have shown the good predictive value and are superior to follicle-stimulating hormones. The convenience of untimed sampling, age-specific values, an automated platform, and potential standardization of antimullerian hormone assay make it the preferred biomarker for evaluating ovarian reserve in women (La Marca et al., 2009; Tal & Seifer, 2017)

Anti-Müllerian Hormone (AMH):

Anti-Müllerian Hormone (AMH) has emerged as a valuable diagnostic tool for the evaluation of Polycystic Ovary Syndrome (PCOS). AMH is a glycoprotein secreted by the granulosa cells of developing ovarian follicles and has been implicated in the pathophysiology of PCOS. Elevated AMH levels are commonly observed in women with PCOS, reflecting the increased number of small antral follicles characteristic of the syndrome (Conway et al., 2014; Nelson et al., 2015)

Saxena *et al.,* 2018, has conducted a prospective case-control study at Dr RML Hospital in New Delhi aimed to evaluate the diagnostic potential of Anti-Müllerian Hormone (AMH) in women with Polycystic Ovary Syndrome (PCOS). The study included 45 women diagnosed with PCOS based on the Rotterdam criteria, along with 45 control subjects. The results demonstrated that women with PCOS had significantly higher median AMH levels compared to the control group (4.32 ng/ml vs. 2.32 ng/ml, p = 0.001). The study explored different diagnostic approaches using AMH in combination with the Rotterdam criteria and found that the inclusion of AMH as a fourth parameter (OA+HA+PCOM+AMH) resulted in a sensitivity of 80% for PCOS diagnosis. Moreover, when AMH was used as a substitute for polycystic ovarian morphology (PCOM) in the Rotterdam criteria, combinations such as OA+HA+AMH (any two out of three) or OA/HA+AMH yielded sensitivities of 86.67% and 71.11%, respectively. The study concluded that AMH levels were significantly higher in women with PCOS and highlighted the potential of AMH as an adjunctive diagnostic marker in conjunction with the Rotterdam criteria for improved PCOS diagnosis (Saxena et al., 2018).

AMH is highly predictive in evaluating ovarian reserve, leading to improved efficiency in IVF procedures. Additionally, AMH shows promise as a diagnostic marker for ovarian diseases, including ovarian cancers, and could potentially be used as a treatment tool for certain cancers, preventing oocyte loss due to chemo or radiotherapy. Despite the lack of international standardization for AMH, there is a growing interest in its research and its potential to revolutionize reproductive medicine. Overall, finding out the importance of AMH in women's reproductive health and its multifaceted role as a biomarker in clinical practice can improve the diagnostic and management strategy of PCOS (Bedenk et al., 2020).

AMH may be leaning towards becoming the gold-standard biomarker due to its objectivity, potential standardization, and convenience of testing throughout the menstrual cycle. However, it is important to note that a perfect ovarian reserve measure has not yet been discovered. The variability in oocyte reserve and the number of developing follicles makes it necessary to find more reliable indicators of ovarian response for personalized treatment in assisted reproduction (Fleming et al., 2015).

Youssef & Marei (2019) investigated the relationship between Anti-Müllerian hormone (AMH), antral follicle count (AFC), ovarian volume (OV), and various biochemical parameters in women with polycystic ovary syndrome (PCOS). Results showed significantly higher levels of AMH, increased AFC, and larger OV in PCOS patients compared to the control group. There were strong positive correlations between AMH, AFC, OV, and other parameters. This study confirms the association between AMH and ovarian function in PCOS. Relation between anti-mullerian hormone with antral follicle count and ovarian volume in polycystic ovary syndrome (Youssef & Marei, 2019).

Ovarian Imaging:

Techniques such as transvaginal ultrasound or other imaging methods are employed to assess the size, structure, and overall health of the ovaries. These imaging evaluations provide additional information about the ovarian reserve. Ultrasound imaging plays a crucial role in diagnosing polycystic ovary syndrome (PCOS) due to its affordability, portability, and effectiveness. Medical practitioners freeze-frame ultrasound images to measure follicle size and count, manually assessing whether PCOS characteristics are present. However, to enhance the accuracy and efficiency of PCOS diagnosis, researchers are exploring medical image processing techniques that can automate and improve the measurement process. These advancements aim to streamline PCOS diagnosis and improve patient care (Nazarudin et al., 2023).

Machine Learning Framework for the Detection of Polycystic Ovary Syndrome

Deep learning models are achieving significant improvements in PCOS detection accuracy. Alamoudi *et al.,* (2023) proposed a PCOS diagnosis and analysis model for computer-aided diagnosis (CAD) systems using ultrasound images and clinical data. The study emphasizes the relevance of clinical features in PCOS diagnosis and suggests that combining image and clinical data enhances diagnostic performance. Overall, the proposed model shows promise in assisting physicians and reducing the risks associated with delayed PCOS diagnosis. They developed a fusion deep learning model combining ultrasound images and clinical features to diagnose PCOS. The model achieved 82.46% accuracy and outperformed other metrics (Alamoudi et al., 2023).

Multiple studies have proposed machine learning models for screening polycystic ovary syndrome (PCOS) using different datasets. However, the study of Khanna *et al.,* (2023) presented a novel approach utilizing a customized multi-level stack ML classifier, with a meta-learner based on random forest (RF), for PCOS diagnosis. The proposed pipeline outperforms existing architectures, achieving high accuracy, precision, and recall. The study emphasizes the importance

of interpretability and transparency in healthcare AI, utilizing tools like SHAP, LIME, and feature importance. The future scope includes building a user interface for real-time PCOS screening and scaling the framework for a larger population. However, further validation and rigorous testing are needed before deploying the framework in medical facilities (Khanna et al., 2023)

Molecular Diagnosis

PCOS is a complex syndrome influenced by various factors including genetic predisposition, clinical subtypes, age, BMI, epigenetics, and the environment. The precise causes and mechanisms that lead to the development of PCOS are still not completely understood. Therefore, conducting further research to explore the interaction between genetic and environmental factors holds significant potential for improving the diagnosis and management of PCOS (Daniele et al., 2023).

The expression of polycystic ovary syndrome (PCOS) presents itself in diverse ways, with chronic anovulation and/or hyperandrogenism being the most prominent manifestations. Due to the varied clinical nature of this disorder, several diagnostic criteria have been suggested to encompass the key characteristics of its phenotype. Thathapudi *et al.*, (2014) identified TNF α, an inflammatory cytokine, plays a significant role in the clinical and biochemical features of PCOS. Additionally, they mentioned that the association between the -C850T TNF α gene polymorphism and PCOS suggests its potential as a relevant molecular marker for identifying individuals at risk of developing PCOS (Thathapudi et al., 2014).

Recent studies in genomics and transcriptomics have aimed to identify genes involved in PCOS development. While pre-genome-wide association studies (GWAS) have provided some insights, most associations are for genetic regions rather than specific functional variants. Larger-scale GWAS efforts have successfully identified numerous novel loci associated with PCOS, many of which are also implicated in other diseases or traits related to metabolism, inflammation, insulin signaling, and cancer. Identifying susceptibility genes for early PCOS diagnosis could potentially help prevent long-term risks such as obesity, cardiovascular disease, and type 2 diabetes. Advances in techniques like GWAS and next-generation sequencing offer promising avenues for further molecular analysis of PCOS (Rani & Chandna, 2023)

Romero et al. (2021) developed a molecular diagnostic tool for polycystic ovary syndrome (PCOS) using targeted miRNA profiling of plasma samples. The study analyzed a cohort of 170 women categorized into different groups and utilized high-throughput miRNA analysis and targeted qPCR validation. Ten differentially expressed miRNAs were identified as biomarkers and decision-tree models were created to effectively differentiate PCOS from non-PCOS, considering both obese and non-obese women. This research provides a reliable method to accurately classify PCOS and distinguish it from obesity, which could lead to improved diagnosis and personalized treatment approaches (Romero-Ruiz et al., 2021).

Summary

In conclusion, significant advancements have been made in the diagnostic approaches for polycystic ovary syndrome (PCOS). Recent research has refined the diagnostic criteria by incorporating additional parameters such as anti-Müllerian hormone (AMH) levels, ovarian reserve testing, metabolic markers, and molecular markers. These advancements aim to improve the accuracy and personalized management of PCOS, providing healthcare professionals with more robust tools for diagnosis and risk prediction. Imaging techniques, including transvaginal ultrasound and MRI, have offered valuable insights into the pathophysiology of PCOS and its associated metabolic alterations, facilitating better understanding and targeted interventions. Machine learning algorithms show promise in PCOS diagnosis, enabling automated and efficient screening processes using ultrasound images and clinical data. Molecular diagnostic tools and genetic studies have expanded our understanding of the genetic factors and molecular mechanisms underlying PCOS, offering opportunities for early detection and personalized treatment approaches. The integration of these advancements has the potential to revolutionize PCOS diagnosis and management, ultimately leading to improved patient outcomes and quality of life. Moreover, the exploration of PCOS subtypes through phenotypic and molecular classifications holds promise for improving diagnosis and treatment strategies. Future directions in PCOS diagnosis involve integrating multiple diagnostic modalities and employing machine learning algorithms by understanding phenotypic subtypes of PCOS.

Abbreviations:

PCOS - Polycystic ovary syndrome

AMH - Anti-Müllerian hormone

MRI - Magnetic resonance imaging

BMI - Body mass index

GWAS - Genome-wide association studies

TNF – Tumour necrosis factor

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