Med Res Rep 2023;6(3):183-191
https://doi.org/10.55517/mrr.1324616

MEDICAL RESEARCH REPORTS

REVIEW

Abnormal Expression of miRNA in Women with Polycystic Ovary Syndrome (PCOS)

Sude TOPKARAOGLU[1], Gulam HEKIMOGLU[2]

[1] Department of Histology and Embryology, University of Health Sciences, Hamidiye Faculty of Medicine, Istanbul/Türkiye

[2] Department of Histology and Embryology, University of Health Sciences, Hamidiye International Faculty of Medicine, Istanbul/Türkiye

ÖZET

Polikistik over sendromu (PCOS), üreme çağındaki kadınların büyük bir kısmını etkileyen, zorlayıcı bir endokrin ve metabolik bozukluktur. Polikistik over görünümü, hiperandrojenizm, kronik anovulasyon, insülin direnci ve obezite gibi bir dizi belirtiyle kendini gösterir. Yıllar süren araştırmalara rağmen, PCOS'nin kesin nedeni hala belirsizdir, ancak son çalışmalar epigenetik mekanizmaların patogenezinde önemli bir rol oynayabileceğini öne sürmüştür. Özellikle mikroRNA'lar (miRNA'lar) ilgi çekicidir, DNA'dan transkript edilen ancak proteinlere çevrilmeyen kısa kodlamayan RNA'lardır. Son araştırmalar, miRNA'ların PCOS'da anormal ifadesinin bulunduğunu ve hastalığın gelişimine ve ilerlemesine katkıda bulunabileceğini göstermiştir. Bu derleme, PCOS'da anormal miRNA ifadesi ile ilgili mevcut bilginin ve zorlukların ayrıntılı bir analizini sunmayı amaçlamaktadır. Bu durumun hedefe yönelik tedavilere ve geliştirilmiş yönetim stratejilerine yönelik potansiyel bir yolunu aydınlatmaktadır. Derleme, miRNA'ların PCOS'daki rolünü araştıran çeşitli çalışmaların bulgularını özetlemektedir. PCOS'da disregüle olduğu bulunan belirli miRNA'ları ve hastalığın patofizyolojisine olan potansiyel etkilerini tartışmaktadır. Derleme ayrıca miRNA'ların incelenmesiyle ilişkili zorlukları vurgulamakta, bunların düzenlemesinin karmaşıklığını ve miRNA profilleme için standartlaştırılmış metodolojilere olan ihtiyacı ele almaktadır. Mevcut kanıtlara dayanarak, miRNA'ların anormal ifadesinin PCOS'nin gelişimine ve ilerlemesine önemli bir katkı sağladığı görülmektedir. Bu disregüle miRNA'ların hedef alınması, PCOS'nin yönetimi için yeni tedavi stratejileri sunabilir. miRNA ile ilişkili biyobelirteçler ve gen terapileri, PKOS tanı ve tedavisinin doğruluğunu ve etkinliğini artırabilir. Bununla birlikte, belirli miRNA'ların işlevsel rollerini ve tanısal veya terapötik hedef olarak potansiyellerini tam olarak anlamak için daha fazla araştırmaya ihtiyaç vardır. Sonuç olarak, bu derleme PCOS'daki miRNA'ların rolüne dair değerli içgörüler sunmakta ve gelecekteki araştırma ve tedavi yaklaşımları için umut verici bir yol belirlemektedir.

Anahtar kelimeler: Biyobelirteç, Epigenetik, Kısırlık, miRNA, PCOS

ABSTRACT

Polycystic ovary syndrome (PCOS) is a debilitating endocrine and metabolic disorder that affects a large proportion of women in their reproductive years. It differs by a range of symptoms including polycystic ovary appearance, hyperandrogenism, chronic anovulation, insulin resistance, and obesity. Despite years of research, the exact cause of PCOS remains elusive, but recent studies have suggested that epigenetic mechanisms may play a significant role in its pathogenesis. Of particular interest are micro-RNAs (miRNAs), short non-coding RNAs that are transcribed from DNA but not translated into protein. Recent research has demonstrated that abnormal expression of miRNAs is present in PCOS and may contribute to the development and progression of the disease. This review aims to provide an in-depth analysis of the current knowledge and challenges related to abnormal miRNA expression in PCOS, shedding light on a potential avenue for targeted therapies and improved management of this debilitating condition. The review summarizes the findings from various studies that have investigated the role of miRNAs in PCOS. It discusses the specific miRNAs that have been found to be dysregulated in PCOS and their potential impact on the pathophysiology of the disease. The review also highlights the challenges associated with studying miRNAs, including the complexity of their regulation and the need for standardized methodologies for miRNA profiling. Based on the available evidence, abnormal expression of miRNAs appears to be a significant contributor to the development and progression of PCOS. Targeting these dysregulated miRNAs could offer new therapeutic strategies for the management of PCOS. Biomarkers and gene therapies associated with miRNA may improve the accuracy and effectiveness of PCOS diagnosis and treatment. However, further research is needed to fully understand the functional roles of specific miRNAs and their potential as diagnostic or therapeutic targets.

Keywords: Biomarker, Epigenetic, Infertility, miRNA, PCOS

Cite this article as: Topkaraoglu S, Hekimoglu G. Abnormal Expression of miRNA in Women with Polycystic Ovary Syndrome (PCOS). Medical Research Reports 2023; 6(3):183-191

Corresponding Author: Gulam Hekimogluoglu **Correspondence Adress:** Sağlik Bilimleri Üniversitesi, Hamidiye Uluslararasi Tip Fakültesi, İstanbul/Türkiye Mail: gulam.hekimoglu@sbu.edu.tr

Received: 08.07.2023; Accepted: 01.09.2023

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a condition observed in women of reproductive age and advances with indications like failure to ovulate, masculinization, excessive androgen levels, and corpulence (1,2). The frequency of PCOS in females between puberty and menopause ranges from 5-20% (3). The etiology of this gynecological ailment is not accurately known, but recent research proposes that PCOS could be an epigenetic and polygenic disorder. The disorder entails pathophysiological mechanisms like hyperandrogenism, insulin resistance, and hyperlipidemia which occur during and after puberty until premenopause (4,5). Menstrual irregularities, long-term ovulatory dysfunction, an increase in male hormone production, and the typical sonographic appearance of the ovaries are the primary characteristics of PCOS.

MicroRNAs (miRNAs) are endogenously generated RNA molecules that are short in length (21-25 nucleotides) and act as cellular regulators without encoding proteins (6). MiRNAs bind to the 3'untranslated region (UTR) of target genes in a precise manner. This binding plays a crucial role in regulating genes post-transcriptionally by repressing gene translation and promoting gene destabilization. The expression of miRNAs varies across different tissues. Besides the intracellular environment, miRNAs are present in several tissue settings such as follicular fluid, plasma/serum, saliva, urine, and semen (7). The aberrant regulation of miRNAs has been linked to numerous disorders, including PCOS.

This assessment aims to aid in the dissemination of the latest information and challenges related to anomalous miRNA expression in PCOS, presenting a probable foundation for focused treatments.

Background on PCOS

PCOS is believed to be a multifaceted interplay of lifestyle, genetic, and environmental factors. Numerous studies have identified specific genes that are affiliated with PCOS, including those involved in hormone modulation and insulin signaling pathways (8). In addition, exposure to endocrine disruptors in the environment has also been linked to PCOS (9).

PCOS is defined by a combination of indications, including menstrual irregularities, polycystic ovaries, and hyperandrogenism. High levels of insulin and luteinizing hormone (LH) in females with PCOS can trigger an excess in androgen synthesis in the ovaries, leading to hirsutism, acne, and male-pattern baldness (10). Insulin resistance, a common trait in PCOS, is linked to an elevated risk of type 2 diabetes and cardiovascular diseases (11). The assessment of PCOS is established on clinical and laboratory criteria, encompassing the Rotterdam criteria. The latter mandates at least two out of three symptoms of hyperandrogenism, anovulation, and polycystic ovaries on ultrasound (12). Nevertheless, the fitting diagnostic criteria for PCOS are still being debated.

PCOS can have significant repercussions on emotional and physical well-being, leading to a decreased quality of life, depression, anxiety, and infertility. The treatment for PCOS is designed to address fundamental hormonal and metabolic imbalances. Lifestyle adjustments, such as physical exercise and weight loss, can improve insulin resistance and alleviate symptoms (12).

Ongoing research on PCOS is revealing novel information on the genetic and environmental elements that drive the disorder. Further, advancements in the area of imaging technology and the detection of biomarkers are opening up new prospects for diagnosis and therapy (13). By improving the comprehension and treatment of PCOS, women with this condition can enhance their well-being and lead more contented lives.

Overview of miRNA in PCOS

Several research studies have detected numerous miRNAs that exhibit differential expression in women with PCOS in comparison to healthy individuals. These miRNAs are involved in various pathways such as insulin signaling, inflammation, and ovarian function. For instance, miR-21 (14), miR-27a (15), and miR-103 (16) may contribute to hyperandrogenism and insulin resistance. On the other hand, miR-29a (17), miR-132 (18), and miR-let-7b (19) may be associated with inflammation and ovarian dysfunction in women with PCOS. Various miRNAs have also been found in follicular fluid, from women with PCOS (7, 20). A study by Chen et al. investigated the role of LINC00173, an RNA gene, in PCOS. This study utilized PCOS follicular cells and KGN (a human granulosa cell line) cells in vitro and in vivo rat models. The authors suggested that LINC00173 might regulate the miR-124-3p/JAG1 cascade and drive the progression of PCOS (21) (Figure 1).

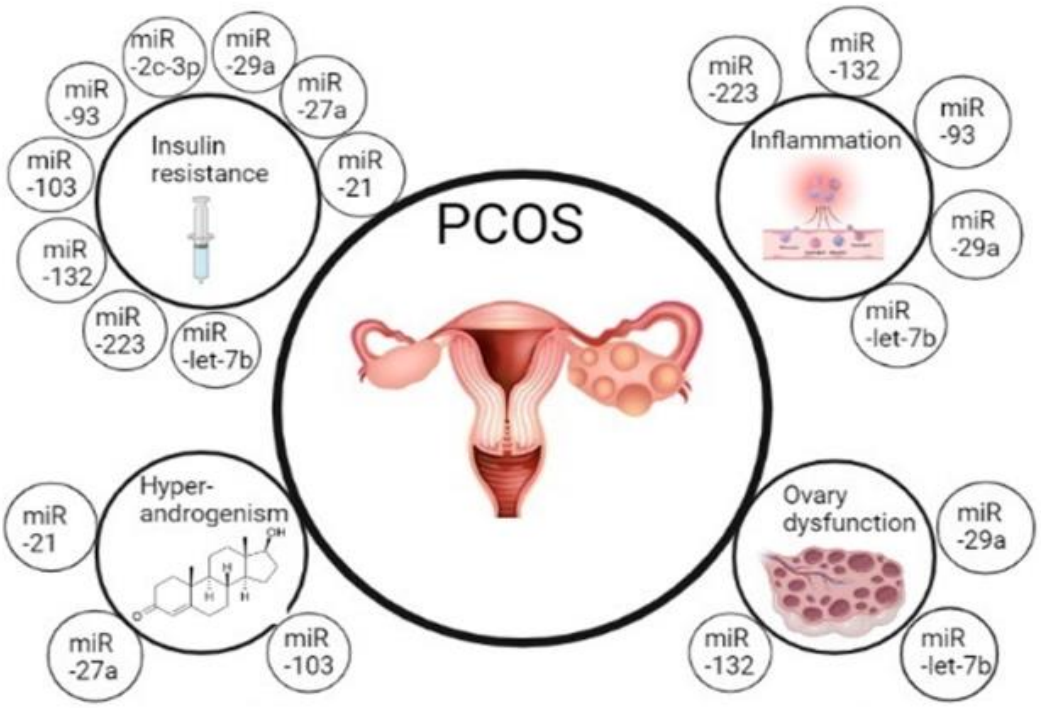

Figure 1. MiRNAs are associated with insulin resistance, inflammation, hyperandrogenism, and ovarian dysfunction in women with PCOS. For example, miR-21, miR-27a, miR-29a, miR-2c-3p, miR-93, miR-103, miR-132, miR-223 and miR-let-7b contribute to insulin resistance. MiR-223, miR-132, miR-93, miR-29a, and miR-let-7b are involved in inflammation. In addition, miR-21, miR-27a, miR-103, miR-29a, miR-132, and miR-let-7b contribute to hyperandrogenism and ovary dysfunction, respectively.

Another study identified miRNA-18b-5p in ovarian follicular cells in PCOS. The association between miRNA-18b-5p and chromosome 10 (PTEN) has not been fully clarified. Zhou et al. co-cultured KGN cells with a PTEN-related vector and injected rats with miR-18b-5p-modified exosomes. They concluded that blood miR-18b-5p levels could influence the development of PCOS complications in experimental PCOS rats (22). Ongoing research in this field is providing new insights into the molecular mechanisms underlying PCOS, which can ultimately lead to improved diagnosis and treatment.

Role of miRNA in PCOS

MiRNAs are key players in the regulation of gene expression and have been implicated in the development of PCOS. Abnormal miRNA expression is linked to several features of PCOS, including insulin resistance, hyperandrogenism, and ovarian dysfunction (23). Further studies have identified additional miRNAs that are differentially expressed in PCOS, such as miR-93, miR-122, and miR-223 (24). MiRNAs are highly susceptible to RNase activity. Recent research has demonstrated that miRNAs play vital roles in proliferation, apoptosis, differentiation, and metabolism (25). Moreover, miRNAs may have potential as biomarkers for the diagnosis and prognosis of PCOS. For instance, recent studies revealed that miRNAs, such as miR-132 (18), miR-424-5p (26), miR-142-5p (27), and miR-15a (28) had high diagnostic accuracy for PCOS.

Targeting specific miRNAs may offer a potential therapeutic approach for the management of PCOS. miRNA-93 is overexpressed in PCOS patients and women with insulin resistance (29). Other studies have also identified miRNAs that could predict the response to treatment or the risk of complications, including cardiovascular disease (30) (Figure 1).

MiRNAs could be employed as promising biomarkers for the diagnosis and prognosis of PCOS. For instance, a recent study found that miR-93 and miR-122 were significantly elevated in women with PCOS, suggesting their potential as diagnostic markers (24). Despite increasing evidence regarding miRNA involvement in PCOS, more research is necessary to comprehensively understand their role in the disorder and to investigate their potential for therapeutic targeting.

Abnormal expression of miRNAs in PCOS

Aberrant expression of miRNAs has been detected in diverse tissues of women with PCOS, such as the ovaries, plasma (31), serum (32), and follicular fluid (33). Within the ovaries of PCOS women, a number of miRNAs are dysregulated. For instance, miR-93 (24), miR-223 (29), and miR-29a (17) are overexpressed, while miR-132 (18) and miR-let-7b (19) are underexpressed in PCOS. These miRNAs are implicated in various pathways related to insulin resistance, ovarian steroidogenesis, and inflammation, all of which are linked to the development of PCOS. Xu et al. evaluated the expression of let-7i in granulosa-luteal cells obtained from women with PCOS, using KGN in their experiment. Their findings revealed that let-7i was downregulated in granulosa-luteal cells of PCOS (34) (Figure 1).

In addition, aberrant expression of miRNAs has been observed in peripheral blood mononuclear cells (PBMCs) of women with PCOS. A study indicated that miR-223 was overexpressed in PBMCs of PCOS patients, which may contribute to the inflammatory state observed in PCOS. Dysregulation of miRNAs in PCOS may contribute to the pathogenesis of the disorder and its associated features, such as insulin resistance, hyperandrogenism, and ovarian dysfunction. Qu et al. conducted research on the role of miR-144-3p in PCOS patients and a PCOS rat model. They found that miR-144-3p was downregulated in PCOS and HSP-70 was upregulated. This study suggests that miR-144-3p may be a potential target for treating PCOS by targeting HSP-70 (35).

Additionally, Zhao et al. reported that translocated miR-143-3p caused granulosa cell apoptosis in PCOS patients (36). Another study was conducted on a PCOS mouse model, which showed that miRNA-98-3p downregulated YY1 (Yin Yang 1) expression (37). YY1 affects the proliferation and apoptosis of ovarian follicular cells in PCOS.

Insulin resistance is a known feature of PCOS. Chen et al. conducted a study on PCOS patients, KGN cell lines, and experimental PCOS rats to investigate the role of miR-29c-3p in regulating insulin function through targeting Forkhead box O3 (Foxo3). Their findings indicate that miR-29c-3p expression is reduced, while Foxo3 is upregulated in PCOS. The study suggests that miRNA-29c-3p plays a role in improving insulin function and ameliorating PCOS by targeting Foxo3 (38) (Figure 1).

In vivo and in vitro investigations have been conducted on PTEN. Liu et al. observed upregulation of PVT1 and PTEN and downregulation of miR-17-5p in the ovarian granulosa cells and follicular fluid of PCOS patients (39). He et al. also reported on PTEN, showing that miR-200b and miR-200c suppress KGN cell proliferation by targeting PTEN (19). Butler et al. found that miRNAs in follicular fluid differ in PCOS patients, correlating with age, inflammation, and AMH levels. Additionally, according to Ingenuity Pathway Analysis, miRNAs correlated with BMI, insulin resistance, fertilization rate, and inflammation (19). Yu et al. investigated microRNA-21's role in regulating granulosa cell apoptosis and proliferation in PCOS through its targeting of toll-like receptor 8 (TLR-8) (14). Nanda et al. observed differential expression of miRNAs in the serum of PCOS patients, and the serum miR-24 analysis could serve as a biomarker for PCOS (17). Dehghan et al. found that miR-155 overexpression had a positive impact on embryo development, but negatively affected nuclear and cytoplasmic maturation in follicular cells of PCOS patients (40). Lin L et al. reported that miR-92a and miR-92b significantly downregulated and were potentially involved in PCOS pathogenesis (8). Finally, Roth et al. reported high levels of miR-9, miR-32, and miR-135a in PCOS follicular fluid (41).

Polycystic ovary syndrome (PCOS) disrupts fertility by causing alterations in ovarian miRNAs, as evidenced in multiple studies. For instance, miR-221, miR-222, let-7d, and miR-26b, were modified in the ovarian tissue of a rat PCOS model (42). Additionally, miR-141-3p targets Death-associated protein kinase (DAPK1) and inhibits apoptosis in rat ovarian granulosa cells (43).

Other research has suggested that the diminished expression of miR-145 in the granulosa cells of women with PCOS may promote granulosa cell proliferation by activating the MAPK/ERK signaling pathways (44). Similarly, it is believed that the decline of miR-483 expression in PCOS ovaries can enhance ovarian cell proliferation and survival (45). Interestingly, Overexpression of miRNA-509-3p in cumulus cells of women with PCOS was associated with increased estradiol secretion by granulosa cells (46). The reduced expression of miRNAs has also been associated with decreased insulin resistance in the cumulus cells (47).

Additionally, investigations have demonstrated that PCOS causes modifications in miRNA expression in the follicular cells, which can impact insulin resistance and various signaling pathways, including the Wnt and MAPK pathways, as well as progesterone-mediated oocyte maturation (44, 48).

Potential biomarkers for PCOS

Timely detection and control of PCOS are indispensable to prevent long-term health complications and enhance the standard of living of affected women. Recognition of dependable indicators can assist in the prompt diagnosis and control of PCOS. Numerous probable biomarkers have been detected in recent investigations.

One encouraging type of biomarker is miRNAs, which are tiny non-coding RNAs that regulate gene expression at the post-transcriptional stage. Irregular expression of miRNAs has been stated in PCOS, with certain miRNAs perceived as possible indicators for the disease. For instance, miR-93 and miR-223 are noticeably increased in the serum of women with PCOS in comparison to healthy individuals and may function as potential indicators for the disease. Similarly, miR-29c and miR-30d have been uncovered to be reduced in the serum of women with PCOS, and their amounts have been suggested to correlate with the gravity of the disease.

Recognition of dependable biomarkers for PCOS is vital for the early diagnosis and control of the disease. Although numerous potential biomarkers have been identified, additional research is required to validate their effectiveness in clinical practice.

Advantages of new biomarkers and possible new gene therapies in PCOS

New biomarkers may allow for earlier and more precise PCOS diagnosis, allowing medical professionals to start treatment strategies that are specifically tailored to each patient's needs. This may result in improved patient outcomes and better management of the illness (49). Advanced biomarkers may provide more accuracy in differentiating PCOS from other illnesses that are similar, lowering the risk of misdiagnosis and ensuring that patients receive the right care sooner (50). Novel biomarkers may offer information on the development of PCOS, allowing for improved monitoring of the condition's progression and permitting modifications to treatment plans over time (51).

Gene therapy can specifically address the underlying genetic factors causing PCOS, in contrast to present medications that largely treat symptoms, thereby offering more effective and long-lasting therapeutic options (52). By treating the underlying causes of PCOS, gene therapy has the potential to alter the disease's course, potentially resulting in long-lasting benefits and lowering the requirement for ongoing medication (53). To increase the effectiveness of current medications, gene therapies can be utilized in concert with them, perhaps providing a synergistic strategy that enhances patient outcomes (54).

CONCLUSION

To conclude, miRNAs have a vital function in the pathogenesis of PCOS, and their irregular expression has related to the emergence of the syndrome. Atypical expression of miRNAs can lead to the deregulation of target genes engaged in crucial pathways linked to follicular development, insulin signaling, and inflammation, all of which are involved in the pathogenesis of PCOS. These miRNAs have the potential to operate as biomarkers for the diagnosis and prediction of PCOS, as well as therapeutic objectives for the control of the syndrome. The combination of biomarkers and gene therapies may offer a great deal of optimism for persons with PCOS in the realm of recent medical advancements. These new concepts may improve the accuracy and effectiveness of PCOS diagnosis and treatment. Further investigation is necessary to completely comprehend the mechanisms underlying the deregulation of miRNAs in PCOS and to formulate focused treatments for this prevalent and intricate endocrine disorder.

Conflict of interest: None

Author’s contribution

ST: Conceived the idea, designed, and conducted the project, and wrote the manuscript.

GH: Conceived the idea, supervised the project and critically reviewed the manuscript for intellectual content.

Acknowledgment: The figure was “created with BioRender.com.” The authors thank BioRender for their contributions.

REFERENCES

1. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample was assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25(2):544–551.
2. Meier RK. Polycystic Ovary Syndrome. Nurs Clin North Am. 2018;53(3):407–420.
3. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016;106 (1):6–15.
4. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr Rev. 2016;37(5):467–520.
5. Escobar-Morreale HF. Polycystic ovary syndrome: definition, etiology, diagnosis, and treatment. Nat Rev Endocrinol. 2018;14(5):270–284.
6. He L, Hannon GJ. MicroRNAs: small RNAs with a big role in gene regulation. Nat Rev Genet. 2004;5(7):522–531.
7. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, Galas DJ, Wang K. The microRNA spectrum in 12 body fluids. Clin Chem. 2010;56(11):1733–1741.
8. Lin L, Du T, Huang J, Huang LL, Yang DZ. Identification of differentially expressed microRNAs in the ovary of polycystic ovary syndrome with hyperandrogenism and insulin resistance. Chin Med J (Engl). 2015;128(2):169–174.
9. Diamanti-Kandarakis E, Christakou CD, Kandarakis SA. Polycystic ovary syndrome: pathophysiology, molecular aspects, and clinical implications. Expert Rev Mol Med. 2008;10:e3.
10. Ndefo UA, Eaton A, Green MR. Polycystic ovary syndrome: a review of treatment options with a focus on pharmacological approaches. P T. 2013;38(6):336–355.
11. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev. 2012;33(6):981-1030.
12. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(12):4565-4592.
13. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2018;33(9):1602-1618.
14. Yu Y, Li G, He X, Lin Y, Chen Z, Lin X, Xu H. MicroRNA-21 regulates the cell apoptosis and cell proliferation of polycystic ovary syndrome (PCOS) granulosa cells through target toll-like receptor TLR8. Bioengineered. 2021;12(1):5789-5796.
15. Sang Q, Yao Z, Wang H, Feng R, Wang H, Zhao X, et al. Identification of microRNAs in human follicular fluid: characterization of microRNAs that govern steroidogenesis in vitro and are associated with polycystic ovary syndrome in vivo. J Clin Endocrinol Metab. 2013;98(7):3068-3079.
16. Mu J, Yu P, Li Q. microRNA-103 Contributes to Progression of Polycystic Ovary Syndrome Through Modulating the IRS1/PI3K/AKT Signal Axis. Arch Med Res. 2021;52(5):494-504.
17. Nanda D, Chandrasekaran SP, Ramachandran V, Kalaivanan K, Carani Venkatraman A. Evaluation of Serum miRNA-24, miRNA-29a, and miRNA-502-3p Expression in PCOS Subjects: Correlation with Biochemical Parameters Related to PCOS and Insulin Resistance. Indian J Clin Biochem. 2020;35(2):169-178.
18. Sang Q, Yao Z, Wang H, Feng R, Wang H, Zhao X, et al. Identification of MicroRNAs in Human Follicular Fluid: Characterization of MicroRNAs That Govern Steroidogenesis in Vitro and Are Associated With Polycystic Ovary Syndrome in Vivo. J Clin Endocrinol Metab. 2013;98(7):3068-3079.
19. Butler AE, Ramachandran V, Hayat S, Dargham SR, Cunningham TK, Benurwar M, et al. Expression of microRNA in follicular fluid in women with and without PCOS. Sci Rep. 2019;9(1):16306.
20. Chen B, Xu P, Wang J, Zhang C. The role of miRNA in polycystic ovary syndrome (PCOS). Gene. 2019; 706:91-96.
21. Chen L, Kong C. LINC00173 regulates polycystic ovarian syndrome progression by promoting apoptosis and repressing proliferation in ovarian granulosa cells via the microRNA-124-3p (miR-124-3p)/jagged canonical Notch ligand 1 (JAG1) pathway. Bioengineered. 2022;13(4):10373-10385.
22. Zhou Z, Tu Z, Zhang J, Tan C, Shen X, Wan B, et al. Follicular Fluid-Derived Exosomal MicroRNA-18b-5p Regulates PTEN-Mediated PI3K/Akt/mTOR Signaling Pathway to Inhibit Polycystic Ovary Syndrome Development. Mol Neurobiol. 2022;59(4):2520-2531.
23. Li H, Yu B, Li J, et al. Identification of differentially expressed microRNAs in the ovary of polycystic ovary syndrome with hyperandrogenism and insulin resistance. Mol Med Rep. 2017;16(1):940-946.

24. Li W, Zhang X, Chen Y, et al. MiR-93-5p and miR-122 as diagnostic biomarkers for polycystic ovary syndrome. Reprod Biol Endocrinol. 2019;17(1):65.
25. Sirotkin AV, Lauková M, Ovcharenko D, Brenaut P, Mlyncek M. Identification of microRNAs controlling human ovarian cell proliferation and apoptosis. J Cell Physiol. 2010;223(1):49-56.
26. Yuan D, Luo J, Sun Y, Hao L, Zheng J, Yang Z. PCOS follicular fluid derived exosomal miR-424-5p induces granulosa cells senescence by targeting CDCA4 expression. Cell Signal. 2021; 85:110030.
27. Li Y, Xiang Y, Song Y, Wan L, Yu G, Tan L. Dysregulated miR-142, -33b and -423 in granulosa cells target TGFBR1 and SMAD7: a possible role in polycystic ovary syndrome. Mol Hum Reprod. 2019;25(10):638-646.
28. Naji M, Nekoonam S, Aleyasin A, Arefian E, Mahdian R, Azizi E, et al. Expression of miR-15a, miR-145, and miR-182 in granulosa-lutein cells, follicular fluid, and serum of women with polycystic ovary syndrome (PCOS). Arch Gynecol Obstet. 2018;297:221-231.
29. Chen YH, Heneidi S, Lee JM, Layman LC, Stepp DW, Gamboa GM, et al. miRNA-93 inhibits GLUT4 and is overexpressed in adipose tissue of polycystic ovary syndrome patients and women with insulin resistance. Diabetes. 2013;62(7):2278-2286.
30. Sørensen AE, Udesen PB, Wissing ML, Englund ALM, Dalgaard LT. MicroRNAs related to androgen metabolism and polycystic ovary syndrome. Chem Biol Interact. 2016.
31. Sathyapalan T, David R, Gooderham NJ, Atkin SL. 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.
32. Eisenberg I, Nahmias N, Novoselsky Persky M, Greenfield C, Goldman-Wohl D, Hurwitz A, et al. Elevated circulating micro-ribonucleic acid (miRNA)-200b and miRNA-429 levels in anovulatory women. Fertil Steril. 2017;107:269-275.
33. Sørensen AE, Wissing ML, Englund ALM, Dalgaard LT. MicroRNA species in follicular fluid associating with polycystic ovary syndrome and related intermediary phenotypes. J Clin Endocrinol Metab. 2016;101:1579-1589.
34. Xu X, Shen HR, Yu M, Du MR, Li XL. MicroRNA let-7i inhibits granulosa-luteal cell proliferation and oestradiol biosynthesis by directly targeting IMP2. Reprod Biomed Online. 2022;44(5):803-816.
35. Qu B, Zhao Q, Ma Q, Yang T, Li X, Chen Y, et al. Overexpression of miR-144-3p alleviates polycystic ovaries syndrome by targeting expression of HSP-70. Gene Ther. 2022;29(5):217-226.
36. Zhao Y, Pan S, Li Y, Wu X. Exosomal miR-143-3p derived from follicular fluid promotes granulosa cell apoptosis by targeting BMPR1A in polycystic ovary syndrome. Sci Rep. 2022;12(1):4359.
37. Hu M, Gao T, Du Y. MiR-98-3p regulates ovarian granulosa cell proliferation and apoptosis in polycystic ovary syndrome by targeting YY1. Med Mol Morphol. 2022;55(1):47-59.
38. Chen H, Fu Y, Guo Z, Zhou X. MicroRNA-29c-3p participates in insulin function to modulate polycystic ovary syndrome via targeting Forkhead box O 3. Bioengineered. 2022;13(2):4361-4371.
39. Liu G, Liu S, Xing G, Wang F. lncRNA PVT1/MicroRNA-17-5p/PTEN Axis Regulates Secretion of E2 and P4, Proliferation, and Apoptosis of Ovarian Granulosa Cells in PCOS. Mol Ther Nucleic Acids. 2020; 20:205-216.
40. Dehghan Z, Mohammadi-Yeganeh S, Salehi M. MiRNA-155 regulates cumulus cell function, oocyte maturation, and blastocyst formation. Biol Reprod. 2020;103(3):548-559.
41. Roth LW, McCallie B, Alvero R, Schoolcraft WB, Minjarez D, Katz-Jaffe MG. Altered MicroRNA and Gene Expression in the Follicular Fluid of Women with Polycystic Ovary Syndrome. J Assist Reprod Genet. 2014;31(3):355-362.
42. Hossain MM, Cao M, Wang Q, Kim JY, Schellander K, Tesfaye D, Tsang BK. Altered expression of miRNAs in a dihydrotestosterone-induced rat PCOS model. J Ovarian Res. 2013; 6:36.
43. Li D, Xu D, Xu Y, Chen L, Li C, Dai X, et al. MicroRNA-141-3p targets dapk1 and inhibits apoptosis in rat ovarian granulosa cells. Cell Biochem Funct. 2017;35(4):197-201.
44. Cai G, Ma X, Chen B, Huang Y, Liu S, Yang H, Zou W. MicroRNA-145 negatively regulates cell proliferation through targeting IRS1 in isolated ovarian granulosa cells from patients with polycystic ovary syndrome. Reprod Sci. 2017; 24:902-910.
45. Xiang Y, Song Y, Li Y, Zhao D, Ma L, Tan L. miR-483 is down-regulated in polycystic ovarian syndrome and inhibits KGN cell proliferation via Targeting Insulin-Like Growth Factor 1 (IGF1). Med Sci Monit. 2016; 22:3383-3393.
46. Huang X, Liu C, Hao C, Tang Q, Liu R, Lin S, et al. Identification of altered microRNAs and mRNAs in the cumulus cells of PCOS patients: miRNA-509-3p promotes estradiol secretion by targeting MAP3K8. Reproduction. 2016; 151:643-655.
47. Shi L, Liu S, Zhao W, Shi J. miR-483-5p and miR-486-5p are down-regulated in cumulus cells of metaphase II oocytes from women with polycystic ovary syndrome. Reprod Biomed Online. 2015; 31:565-572.

48. Liu X, Ma L, Rao Q, Mao Y, Xin Y, Xu H, et al. MiR-1271 inhibits ovarian cancer growth by targeting cyclin G1. Med Sci Monit. 2015; 21:3152-3158.
49. Karakas SE. New biomarkers for diagnosis and management of polycystic ovary syndrome, Clinica Chimica Acta. 2017; 471: 248-253.
50. Cassar S, Teede HJ, Harrison CL, Joham AE, Moran LJ, Stepto NK. Biomarkers and insulin sensitivity in women with Polycystic Ovary Syndrome: Characteristics and predictive capacity. Clinical endocrinology. 2015; 83(1): 50-58.
51. Jing T, Wu Y, Wan A, Ge C, Chen ZJ, Du Y. Circular RNA as a Novel Regulator and Promising Biomarker in Polycystic Ovary Syndrome. Biomolecules. 2023; 13(7): 1101.
52. Sikiru AB, Adeniran MA, Akinola K, Behera H, Kalaignazhal G, Egena SSA. Unraveling the complexity of the molecular pathways associated with polycystic ovary syndrome (PCOS) and identifying molecular targets for therapeutic development: a review of literature. Middle East Fertility Society Journal. 2023; 28(1): 16.
53. Li PF, Wang F, Kong HJ, Zhao F, Bai AH, Chen XM, Sun YP. Establishment of polycystic ovary syndrome-derived human embryonic stem cell lines. Gynecological Endocrinology. 2012; 28(1): 25-28.
54. Islam H, Masud J, Islam YN, Haque FKM. An update on polycystic ovary syndrome: A review of the current state of knowledge in diagnosis, genetic etiology, and emerging treatment options. Women's Health. 2022; 18: 17455057221117966.