Review Article

# Regulatory Roles of MicroRNAs in Female and Male Human Reproduction: A Narrative Review

Mohadeseh Khoshandam[1,2], PhD; Leila Naserpour[1,3], PhD; Mohammad Taghi Hedayati Goudarzi[4], MD; Hossein Soltaninejad[5], PhD; Hadi Zare-Zardini[6], PhD; Ashraf Alsadat Hoseiny[1], MSc; Neda Golpar Raboki[1], MSc; Elahe Sadat Mousavi[1], MSc; Mohammad Ali Salami[7], PhD

[1]Department of Reproductive Biology, Academic Center for Education, Culture, and Research (ACECR), Qom, Iran;
[2]National Institute of Genetic Engineering and Biotechnology (NIGEB), Tehran, Iran;
[3]Department of Tissue Engineering, Qom University of Medical Sciences, Qom, Iran;
[4]Department of Cardiology, School of Medicine, Babol University of Medical Sciences, Babol, Iran;
[5]Department of Stem Cells Technology and Tissue Regeneration, Faculty of Interdisciplinary Science and Technologies, Tarbiat Modares University, Tehran, Iran;
[6]Department of Biomedical Engineering, Meybod University, Meybod, Iran;
[7]Department of Biomaterials, Nanotechnology and Tissue Engineering, School of Advanced Technologies in Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

**Correspondence:**
Hossein Soltaninejad, PhD;
Tarbiat Modares University, Jalal Al Ahmad Hwy., Nasr Bridge, Postal code: 14117-13116, Tehran, Iran
**Email:** hosoltaninejad@gmail.com
hossein.soltani@modares.ac.ir

Received: 12 November 2024
Revised: 16 October 2024
Accepted: 23 December 2024

## What's Known

- The role of microRNAs (miRNAs) in human reproduction is an exciting area of research, and these regulatory molecules likely play an essential role in reproductive function. However, the current understanding of miRNAs' regulatory role in male and female reproduction remains unclear, with a considerable amount of conflicting and inconsistent data.

## What's New

- An extensive review of studies revealed a consistent relationship between aberrant miRNA expression and infertility. Therefore, measuring the expression of specific miRNAs identified in this review could serve as valuable biomarkers for male and female infertility and could lead to the development of novel and specialized treatments.

## Abstract

The role of microRNAs (miRNAs) in human reproduction represents an area of research, as these regulatory molecules appear to play essential roles in reproductive function. However, the current understanding of miRNAs' regulatory mechanisms in male and female reproduction remains incomplete, with considerable contradictory evidence in the literature. This targeted review aimed to analyze high-quality studies published to date on miRNA expression patterns in female and male reproduction to elucidate their biological roles and associations with infertility, thereby updating knowledge in this field. A comprehensive review of the literature was conducted using different electronic databases and search engines, including PubMed Central, MEDLINE, and Google Scholar from the earliest available records up to 2023. This search identified 18,100 articles related to miRNA expression in infertility, polycystic ovary syndrome (PCOS), endometriosis, and biomarkers, of which 72 met our criteria for further analysis. The findings of the present study revealed that specific, stable miRNA populations exist in different tissues and cells, potentially influencing spermatogenesis and oogenesis. The extensive review of studies suggested a consistent relationship between aberrant miRNA expression patterns and infertility. Consequently, the miRNAs identified in this review might serve as valuable biomarkers for both male and female infertility and could lead to the development of novel and specialized treatments.
This manuscript has been released as a preprint at Authorea: (https://doi.org/10.22541/au.169609839.97787658/v1).

Please cite this article as: Khoshandam M, Naserpour L, Hedayati Goudarzi MT, Soltaninejad H, Zare-Zardini H, Hoseiny AA, Golpar Raboki N, Mousavi ES, Salami MA. Regulatory Roles of MicroRNAs in Female and Male Human Reproduction: A Narrative Review. Iran J Med Sci. doi: 10.30476/ijms.2025.104375.3797.

**Keywords** ● Infertility ● MicroRNAs ● Spermatogenesis ● Polycystic ovary syndrome ● Endometriosis ● Biomarkers

## Introduction

MicroRNAs (miRNAs) are single-stranded RNA molecules approximately 22 nucleotides long.[1] These molecules play a significant and crucial role in gene expression through partial complementarity with the 3' untranslated region (3'UTR).[2] Several miRNAs have been identified in humans, and research has shown their importance in biological processes, including cell cycle regulation, differentiation, metabolism, proliferation, apoptosis, gametogenesis (both male and female), and embryo development.[3]

Over the past decade, studies have indicated the ubiquitous

presence of miRNAs across all human tissues, including the reproductive system.[4, 5] The identification of miRNAs in various reproductive organs and tissues, such as the testis, ovary, uterus, epididymis, spermatozoa, oocytes, seminal plasma, and extracellular vesicles, coupled with their known regulatory functions, suggested that miRNA dysregulation might impair spermatogenesis, disrupt oocyte maturation, and contribute to various types of infertility.[6]

This study aimed to systematically review high-quality published studies to investigate the association between miRNAs and reproductive functions in both sexes, with particular focus on their role in infertility. While the available studies demonstrated considerable heterogeneity, a comprehensive synthesis of this evidence could help consolidate findings, resolve existing inconsistencies, and provide guidance for future research.

The growing urgency for rapid infertility diagnostics and treatments highlighted the potential of innovative approaches, such as liquid biopsy, which offers faster and less invasive alternatives to conventional approaches. Given their established role in gene expression regulation and demonstrated associations with various infertility-related factors, miRNAs represent promising candidates for diagnostic biomarker development.

*The Role of MiRNAs in Epigenetics and Infertility*

Epigenetics refers to changes in gene activity that do not involve changes in the underlying DNA sequence. These changes can be modulated by various environmental factors, such as diet status, psychological stress, and exposure to environmental toxins. Importantly, such epigenetic changes can significantly influence the expression of genes involved in reproductive health, which can affect fertility.

Research indicated that epigenetic modifications could contribute to both male and female infertility. In men, abnormal DNA methylation patterns in spermatozoa could affect sperm quality and motility and lead to problems with conception. In women, epigenetic alterations in ovarian or endometrial tissues might disrupt folliculogenesis, hormonal regulation, and embryo implantation success.

In addition, epigenetic changes can also be passed from one generation to another, potentially affecting the offspring's fertility through mechanisms collectively termed transgenerational epigenetic inheritance.[7, 8] This phenomenon underscores the critical need to elucidate epigenetic contributions to infertility. Among epigenetic regulators, miRNAs are known to exert epigenetic effects, altering gene expression and production of specific proteins.[9] MiRNAs affect fertility by regulating various cellular processes, such as sperm production in men and the ovarian cycle in women.[10, 11] Consequently, changes in miRNA levels can affect these processes, potentially leading to infertility.

By studying the epigenetic mechanisms involved in infertility, researchers hope to develop novel diagnostic modalities and targeted therapeutic strategies to enhance fertility outcomes for couples trying to conceive. The identification and modulation of epigenetic contributors to infertility could enable more precise, personalized treatment approaches. In addition, improved understanding of epigenetic influences on fertility might also lead to lifestyle modifications to optimize outcomes in assisted reproductive technologies (ART).

*MicroRNAs in Female Infertility: Polycystic Ovary Syndrome (PCOS) and miRNAs*

Polycystic ovary syndrome (PCOS) affects approximately 5-10% of reproductive-aged women, representing one of the most prevalent endocrine disorders in this population.[12] The diagnostic triad of PCOS includes chronic anovulation, polycystic ovarian morphology, and clinical and/or biochemical hyperandrogenism.[13, 14] Importantly, PCOS demonstrates strong associations with metabolic disorders, such as type 2 diabetes (T2D), insulin resistance, and obesity.[13, 14] While the precise etiology of PCOS remains unclear, current research implicates multifactorial influences including genetic predisposition, environmental factors, and iatrogenic effects such as chemotherapy exposure.[15] Recent studies revealed distinct miRNA expression profiles in women with PCOS compared to healthy women, suggesting potential involvement of miRNAs in PCOS pathogenesis.[16] This section aimed to evaluate the research in this area and discuss probable associations between miRNA dysregulation in PCOS, with particular focus on establishing mechanistic links that may inform novel therapeutic strategies. According to a study, PCOS patients had significantly higher levels of miRNAs, including miR-21, miR-155, miR-103, and miR-27b, than healthy women (table 1),[17] which further supported the potential role of miRNAs in PCOS development and progression. Multiple studies demonstrated significant alterations in circulating miRNA profiles in women with PCOS. Specifically, serum levels of miR-16, miR-222, miR-106b, miR-19a, miR-146a, miR-30c, miR-186, and miR-24 were consistently increased in women with PCOS, while miR-320 was reduced compared to healthy

**Table 1:** Differential expressions of miRNAs in polycystic ovary syndrome and endometriosis

| Differential expressions | PCOS | Endometriosis |
|---|---|---|
| Increase | miR-21, miR-103, miR-155, miR-27b, miR-222, miR-106b, miR-19a, miR-146a, miR-16, miR-30c, miR-24, miR-5706, mir let-7i-3 pm, miR-4463, miR-638, miR-3665 | miR-145, miR-99a, miR-143, miR-126, miR-99b, miR100, miR-150, miR125-b , miR-125a, miR-194, miR-223, miR-365 , miR-1, miR-29c, miR-22-3p, miR-20a, miR-320a |
| Decrease | miR- 320, miR-128, miR-124-3p, miR let-7c, miR -29a-3p | miR-200a, miR-200b, miR-141, miR-424, miR-142-3p, miR-34c, miR-196b, miR-20a |

PCOS: Polycystic ovary syndrome

controls (table 1).[18, 19] Therefore, miR-146a and miR-30c exhibited particularly strong diagnostic potential for PCOS.[20] Increased expression of miR-222 was associated with type 2 diabetes and gestational diabetes pathogenesis.[21]

Additional studies revealed significant dysregulation of specific miRNAs in PCOS patients, with five miRNAs (let-7i-3 pm, miR-5706, miR-4463, miR-3665, and miR-638) showing increased expression and four miRNAs (miR-124-3p, miR-128, miR-29a-3p, and let-7c) demonstrating decreased expression compared to controls (table 1).[22] Bioinformatics analyses of these altered miRNAs suggested that they participate in multiple pathological mechanisms underlying PCOS, including metabolic dysfunction, inflammatory responses, programmed cell death (apoptosis), vascular development (angiogenesis), immune system function, cellular energy metabolism (ATP binding), MAPK signaling cascades, and p53 pathways.[16, 23] These consistent findings suggested that changes in miRNA levels might contribute to the PCOS development and progression.

Research has also explored the relationship between abnormal androgen production in PCOS and miRNA. In PCOS patients, free testosterone levels were strongly associated with miRNA levels, such as miR-21, miR-103, and miR-155, suggesting that aberrant miRNA expression might contribute to PCOS characteristics.[24]

While miRNA research has advanced considerably, the precise mechanisms by which miRNAs contribute to PCOS pathophysiology remain under investigation. Profiling miRNAs can provide new insights into these molecular changes, offering therapeutic and prognostic information.[25] However, considerable controversy persists regarding optimal clinical strategies for symptom management, fertility improvement, and prevention of long-term PCOS complications.[26] A better understanding of these relationships and underlying processes could ultimately lead to more effective interventions and improved outcomes for individuals with PCOS.

*Endometriosis and MiRNAs*

Endometriosis is a gynecological disorder characterized by the growth of endometrial tissue outside the uterine cavity. Emerging evidence suggested that miRNAs might serve as natural post-transcriptional regulators involved in the development of endometriotic lesions.[27] The current gold standard for definitive endometriosis diagnosis remains laparoscopic surgical evaluation, an invasive procedure with inherent patient risks.[28] Therefore, developing new non-invasive biomarkers to diagnose endometriosis in the early stages is an urgent need.[29] A previous study identified serum miRNAs as promising diagnostic biomarkers,[26] with 14 upregulted miRNAs (miR-145, miR-143, miR-99a, miR-99b, miR-126, miR100, miR125-b, miR-150, miR-125a, miR-223, miR-194, miR-365, miR-29c, and miR-1) and eight downregulated miRNAs (miR-200a, miR-141, miR-200b, miR-142-3p, miR-424, miR-34c, miR-20a, and miR-196b) identified (table 1).[30] In another study, researchers showed that in patients with endometriosis, the miR-9 and miR-34 families had abnormalities in the atopic endometrium.[31] For example, studies showed elevated miR-20a levels in endometriosis lesions.[32] The researchers suggested that dysregulation of these miRNAs and their target genes could contribute to the proliferative phenotype observed during the early secretory phase of the menstrual cycle in affected women.[33] As a result, many miRNAs have been identified as regulators of gene expression involved in inflammatory responses, local estrogen biosynthesis, progesterone resistance, cell invasion, extracellular matrix regeneration, and angiogenesis in endometriosis.[34] Six miRNAs (i.e., miR-134-5p, miR-197-5p, miR-22-3p, miR-320a, miR-494-3p, and miR-939-5p) were selected as biomarkers of endometriosis and validated using qRT-PCR (table 1).[35] Among these, miR-22-3p and miR-320a exhibited significantly increased expression in the serum exosomes of patients with endometriosis (table 1).[36] Considering that endometriosis diagnosis and treatment are frequently delayed due to nonspecific symptoms and the lack of reliable biomarkers, with laparoscopic surgery remaining the diagnostic gold standard, there remains a

**Table 2:** Differential expressions of miRNAs in male infertility

| Differential expressions | Expressions of miRNAs in male infertility |
|---|---|
| Increase | miR-145, miR-302a, miR-491-3p, miR-122-5p |
| Decrease | miR-122, miR-449a, miR-23b, miR-383, miR-520d-3p, miR-34b, miR-34c, miR-34c-5p, miR-122, miR-146b-5p, miR-181a, miR-374b, miR-509-5p, and miR-513a-5p |

critical need to identify effective non-invasive indicators for early stages of the disease.

*MicroRNAs in Male Infertility*

Male infertility represents a multifactorial reproductive disorder accounting for over 50% of couples' infertility cases.[37] This condition may arise from diverse etiologies, including genital tract infections, hormonal disorders, genitourinary tract infections, genetic mutations, and testicular hyperthermia. The latter may occur in clinical contexts such as varicocele or behavioral patterns including prolonged driving with a vehicle, or habitual laptop use on the lap, a documented risk factor for elevated scrotal temperature.[38] Currently, semen analysis serves as the standard diagnostic tool for male infertility. However, this method has some limitations and fails to identify the cause of infertility in approximately 40% of cases, highlighting the need for more effective diagnostic tools. Biomarkers represent one of the most promising emerging diagnostic tools. These molecules, detectable in body fluids, can indicate disease states such as infertility through abnormal expression patterns. Thus, miRNAs have emerged as potential biomarkers for different types of male infertility, including azoospermia, oligospermia, asthenospermia, and teratozoospermia.[38] In related research, scientists developed a transgenic mouse model in which the downregulation of miR-382-3p was prevented by overexpression in mature Sertoli cells (table 2).[39]

Azoospermia, the most serious type of male infertility, affects 15-20% of infertile men and is classified into two main types: obstructive azoospermia (OA) and non-obstructive azoospermia (NOA).[40] NOA, resulting from impaired spermatogenesis, represents approximately 60% of azoospermia cases. In contrast, OA accounts for the remaining 40% and occurs when normally produced sperm cannot reach the ejaculate due to genital tract obstructions.[41] NOA specifically refers to testicular failure to produce sperm and accounts for approximately 0.6% of all men, 10% of infertile men, and 60% of men with azoospermia.[41] In recent years, the misplaced expression of miRNAs has been shown to affect several biological processes and was associated with certain reproductive disorders in men, particularly those affecting spermatogenesis. Given the crucial role of miRNAs in all stages of spermatogenesis, their dysregulation logically contributes to numerous male infertility issues.[41] A study showed decreased levels of miR-383 and miR-520d-3p and increased expression of miR-302a and miR-491-3p in NOA patients. It also reported that the expression of miR-17-92 and miR-371 was regulated in the testes of NOA patients (table 1).[42] Another study found that decreased levels of miR-34b and miR-34c were associated with reduced male fertility, NOA, defective meiosis, impaired sperm maturation, and spermatogenesis disorders (table 2).[43]

A similar study showed that dysregulation of miR-449 was associated with male infertility characterized by impaired sperm motility.[44] Comparative analysis of seminal plasma from fertile and infertile men revealed significantly reduced levels of seven miRNAs, including miR-34c-5p, miR-122, miR-146b-5p, miR-181a, miR-374b, miR-509-5p, and miR-513a-5p in azoospermic patients (table 2).[45] Another study found that miR-122-5p was upregulated in OA patients compared to NOA patients.[46-48] These miRNAs could be used as diagnostic biomarkers for idiopathic male infertility and could inform the development of targeted therapies. Their irregularity could be the key to developing new and advanced diagnostic and prognostic approaches in male infertility. To take full advantage of their potential, further investigation is required to identify additional miRNAs involved in reproductive pathologies, the mechanism by which they work, and how their expression modulation might improve clinical outcomes. Collectively, these findings substantiate the regulatory role of miRNAs in male germ and somatic cells, where expression alterations could lead to reproductive disorders.

*MiRNAs as Potential Biomarkers in Infertility Diagnosis*

An ideal biomarker should be target-specific, stable, non-invasive, sensitive to detection, and easily accessible from accessible biological sources.[49] In clinical practice, serum proteins have conventionally served as biomarkers for disease detection and prognosis.[50] However, proteins as biomarkers have limitations, such

as reduced diagnostic value due to inadequate specificity and sensitivity. On the other hand, miRNAs emerge earlier in both intracellular and extracellular environments and can be detected with greater precision, enabling earlier disease identification. MiRNAs are typically expressed during specific biological phases.[50, 51] Additionally, miRNAs are often observed as homogeneous populations, while proteins often undergo post-translational modifications and create heterogeneous forms.[52]

Various diagnostic approaches have been developed for infertility assessment in both sexes, with biomarker-based methods representing the most recent advancement. Biomarkers can be utilized to detect diseases prior to clinical symptom manifestation. Among potential biomarkers, miRNAs are considered particularly promising due to their unique properties. Circulating (serum) miRNAs were initially employed as biomarkers for diagnosing B-cell lymphoma.[53] In another study, a decrease in miR-122, miR-181a, and miR-34c was observed in the serum of patients with oligoasthenospermia.[54, 55] Several studies published in recent years demonstrated that miRNAs could be suitable biomarkers for diagnostic purposes.[52, 56, 57]

Protein factors, DNA methylation, and non-coding RNAs are all present in the sperm and egg genomes.[58] During spermatogenesis and oogenesis in mammals, mRNAs undergo post-transcriptional and post-translational regulation in differentiated germ cells, enabling observation of miRNAs during both spermatogenesis and oocyte maturation.

*MiRNAs and Infertility Treatment*

The modification and manipulation of miRNA activity in the body is of great interest due to their abnormal expression and role in the pathogenesis of human diseases.[59] The use of anti-miRNA oligonucleotides to target disease-related miRNAs is the most widely used approach for understanding their *in vivo* function and shows promise for developing new miRNA-based therapies.[60, 61] In addition to their potential use as biomarkers, miRNAs can be considered for therapeutic purposes in a personalized medical field related to male and female infertility.[62] Researchers are exploring different methods to modulate miRNA levels for therapeutic purposes, including supplementation with microRNA mimics to either reduce or upregulate their expression, and using lab-engineered molecules called anti-miRNAs for conditions involving miRNA overexpression.[62]

The therapeutic potential of miRNAs, along with advances in nanomedicine, could lead to the development of novel fertility treatments for both male and female infertility.[63, 64] With advances in genomics, researchers demonstrated that these small non-coding RNA molecules are essential for mammalian ovarian function. The most recent microRNA-based therapeutic strategies for infertility focus on addressing gonadal damage through multi-pathway targeting agents. Given existing treatment limitations, an integrated approach combining preventive measures with microRNA therapy represents both a practical and desirable clinical option.

## Conclusion

Understanding the mechanisms that lead to infertility in both men and women is essential. Despite careful and expensive clinical examinations, including invasive techniques such as testicular biopsy, infertility sometimes remains undiagnosed. Current research has provided conclusive evidence on the role of miRNAs in regulating infertility. When combined with traditional diagnostic techniques, miRNAs have significantly improved infertility diagnosis. MiRNAs are affordable, readily available, and can be easily extracted from blood and semen, making them clinically practical. This diagnostic simplification may enable more effective treatment strategies after symptom and goal identification. To establish miRNAs as diagnostic biomarkers for various infertility types, developing standardized protocols and accurate diagnostic validation techniques would be essential.

## Authors' Contribution

M.Kh: Study concept, data gathering, and drafting, L.N: Data gathering and drafting; MT.HG: Study concept, data gathering, and drafting, H.S; Data gathering and drafting, H.ZZ: Data gathering and drafting; A:S: Data gathering and drafting; N.GR: Data gathering and drafting; E.M: Data gathering and drafting; MA.S: Data gathering and drafting; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

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