Sinaei *et al.*
Egyptian Journal of Medical Human Genetics (2023) 24:40
https://doi.org/10.1186/s43042-023-00419-9

Egyptian Journal of Medical Human Genetics

REVIEW

Open Access

The role of miRNAs in the diagnosis and treatment of male infertility: a review study

Roya Sinaei[1,4], Khosro Jamebozorgi[2,4], Hossein Mirshekarpour[3,4], Hossein Poormasoumi[2,4], Amirhossein Mahdizadeh[1,4], Zahra Akbari[4,5] and Eskandar Taghizadeh[1,4*]

Abstract

Infertility is a widespread issue that affects over five million couples globally. The cause of this condition can be related to women, men, or both. Male infertility, as a clinical disorder, can be caused by problems in spermatogenesis, testicular development, epididymal, and sperm maturation. Various methods have been proposed to diagnose and treat this disorder, but in some cases, it still remains idiopathic. Nowadays, the investigation of miRNAs is being discussed for the diagnosis and treatment of male infertility. miRNAs are small non-coding RNAs that regulate the expression of many genes after transcription. The aim of this review is to study miRNAs as noninvasive biomarkers for the diagnosis of infertility, as well as proposed treatment strategies and the challenges ahead in these avenues.

Keywords MiRNA, Biomarkers, Male infertility, Diagnosis, Therapeutics

Introduction

Infertility is a common disorder of the male or female reproductive system that is characterized by the inability to successful pregnancy after regular unprotected intercourse for a period of one year [1]. This problem is increasingly recognized as a worldwide public health concern. It is estimated that 48.5 million couples experience infertility, and about 9% of men and 10% of women aged 15 to 44 reported infertility problems in the United States. As both men and women can contribute to infertility, infertility is nearly as common in men as it is in women in the U.S [2, 3]. The main causes of infertility in men is due to abnormal functioning of the testicles, varicocele, difficulty in ejaculating semen, reduction or absence of sperm, and abnormalities in the morphology and movement of sperm. In addition, genetic diseases, environmental factors, and lifestyle can also affect the occurrence of infertility [4].

Generally, the inability to have a child affects the normal life of many women and men in the world [5]. The occurrence of psychological and physical problems can be one of the consequences of infertility in people [6]. Also, every person should be able to decide about having a child, the time of pregnancy, and the intervals between pregnancies [7]. Problems such as depression, anxiety, divorce, social stigma, and betrayal are among the social consequences of infertility [8]. Therefore, infertility is an issue that needs more attention [6]. The past years have seen increasingly rapid advances in the field of methods for the treatment of some cases of infertility were presented, such as in vitro fertilization (IVF) but diagnosis and prevention were more important to researchers [9].

Until today, different methods have been used to diagnose infertility in women and men.

Currently, some laboratory and genetic methods such as spermiogram, karyotyping, and evaluation of

*Correspondence:
Eskandar Taghizadeh
eskandar.taghizadeh@yahoo.com
[1] Department of Genetics, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
[2] Faculty of Medicine, Zabol University of Medical Sciences, Zabol, Iran
[3] Nuclear Medicine of Shafa Hospital, Kerman University of Medical Sciences, Kerman, Iran
[4] Department of Medical Genetics, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5] Department of Periodontics, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

y-chromosome microdeletions can help to diagnose male infertility [10].

In addition to the fact that these tests are not able to detect the exact cause of all cases of male infertility, high cost, time-consuming and uncertainty are other problems of these diagnostic methods. Today, one of the most significant current discussions is the use of non-coding RNAs such as microRNAs (miRNAs). MiRNAs play an important role in regulating gene expression. They usually interact with the 3′ untranslated regions (3′ UTR) of target mRNAs and cause gene silencing after transcription and translation suppression. Recent evidence suggests that miRNAs can be used as noninvasive biomarkers to diagnose infertility [11]. Examining the expression profile of miRNAs can be a potential diagnostic tool to identify male infertility. The purpose of this study is to review the role of miRNAs as noninvasive biomarkers for the diagnosis of male infertility and then we will review the therapeutic potential of these miRNAs.

The role of miRNAs in spermatogenesis

MiRNAs are small non-coding RNAs that act as post-transcriptional regulators of protein-coding genes. Over 2300 miRNAs have been identified in human cells, and their expression varies based on time and tissue patterns. MiRNA coding sequences are located in exons, introns of protein-coding genes, or intergenic regions [12]. The role of miRNAs is to downregulate gene expression by base-pairing with the 3′ untranslated regions (3′ UTRs) upon binding to the target mRNA [13].

MiRNAs biogenesis

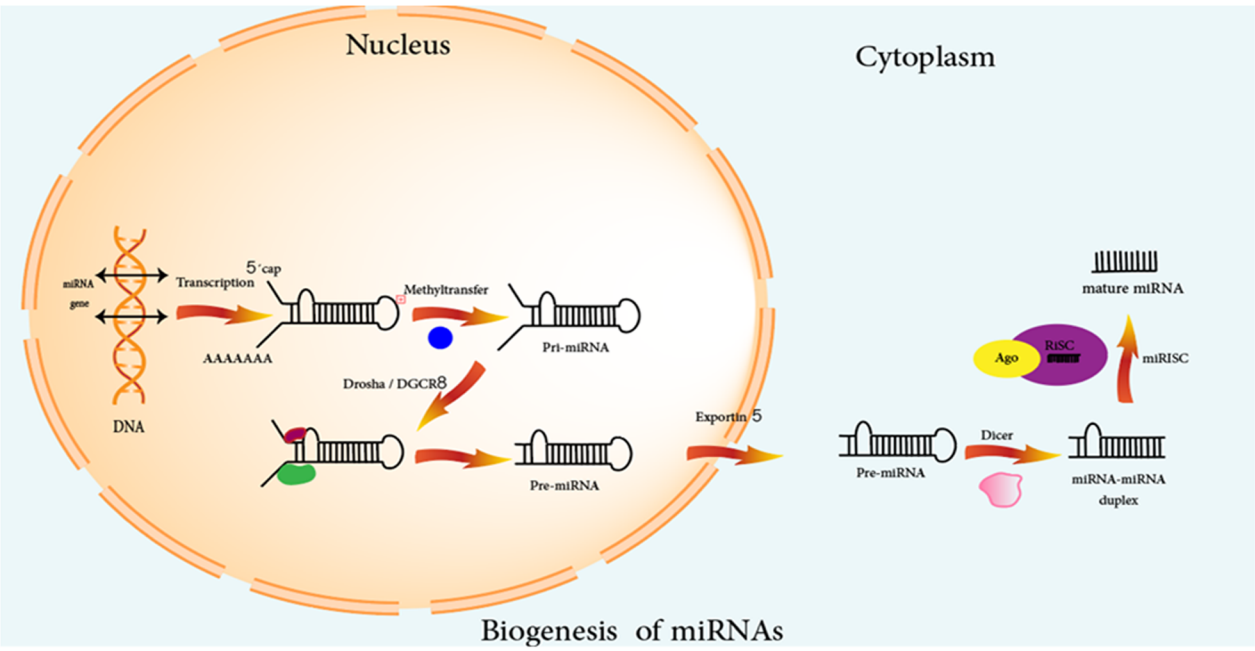
MiRNAs Biogenesis occurs in several steps. At first, it is transcribed from the miRNA gene and primary miRNA (Pri-miRNA) with a length between 100 and 1000 nucleotides is created. Then they are methylated by the methyltransferase like 3 (METTL3). In the next step, Pri-miRNAs are processed by drosha ribonuclease III (Drosha) and its cofactor DiGeorge syndrome critical region 8 (DGCR8) and Pre-miRNAs with a length of 70 nucleotides are created, then by exportin 5 (EXP5) together with Ran -GTP are transferred to the cytoplasm and then they are cleaved into double-stranded RNAs of 22 base pairs (bp) by Dicer. The dsRNAs are loaded on the Argonaute protein (AGO) and the miRNA-induced silencing complex (miRISC) where one strand of the 22 nucleotides duplex RNA remains in the AGO as a mature miRNA, and the other strand is degraded [14] (Fig. 1).

Spermatogenesis is a process that leads to sperm differentiation by self-renewing spermatogonia stem cells (SSCs) in the epithelia of seminiferous tubules and is accompanied by successive mitosis and meiosis, which finally transforms germ cells into mature male gametes [15, 16]. Many miRNAs play a role as post-transcriptional repressors in the regulation of different stages of spermatogenesis such as mitotic proliferation and formation of spermatogonia, SSC self-renewal and differentiation, and during meiosis and spermatogenesis of spermatocytes [17].

Roles of miRNAs in SSC self-renewal and differentiation

SSCs are the basis of the spermatogenesis process, and the important point for the continuous production of sperm is to maintain the balance between self-renewal and differentiation of SSCs [18]. There is a group of miRNAs that prefer to be expressed in an environment rich in SSCs. Therefore they play an important role in the maintenance of SSCs and causes their self-renewal [19].

In a study, He et al. [20] reported that miRNA-20 and miRNA-106a tend to be expressed in mouse SSCs and play a role in maintaining their homeostasis, and by targeting STAT3 and Ccnd1, they cause self-renewal at the post-transcriptional level. During their research, Niu et al. [21] observed that inhibition of miR-21 in SSC-enriched germ cell cultures increases the number of germ cell apoptosis and concluded that this miRNA plays a vital role in maintaining the SSC population. Song et al. [22] found that miRNA-554 regulates the self-renewal of SSCs in goats by targeting PLZF, which was the first identified transcription factor in SSCs self-renewal. Also, Moritoki et al. [23] identified an interaction between miR-135a and FoxO1 and suggested that miR-135a contributes to the maintenance of SSCs by modulating FoxO1 activity. In their study on male dairy goat germ cells, Li et al. observed that miR-34c increased apoptosis in mGSCs and decreased their proliferation. Furthermore, the expression of miR-34c was dependent on p53 [24]. These are a large number of studies about miRNAs' roles in regulating the fate of SSCs. In addition, miRNAs also play an effective role in the differentiation of SSCs. Retinoic acid (RA) is one of the factors that play a significant role in guiding the continuous spermatogonial differentiation and its entry into the meiosis cycle [25]. Studies showed that miR-let 7-family [26], miR-17-29, and miR-106b-25 [27] were downregulated during RA-induced differentiation. In a study conducted by Tong et al. [27], they observed that the deletion of miR-17-29 causes oligospermia in the epididymis of mice and the shrinking of the testes, and inversely causes an increase in the expression of the miR-106b-25 cluster. Also, Yang et al. [16], by examining the expression of miR-221/222, concluded that these miRNAs show a decrease in expression under RA and an increase in expression under GDNF, and their dysfunction is the cause of the loss of SSC differentiation ability. Huszar et al. [28], referring to the role of miR-146 in the regulation and control



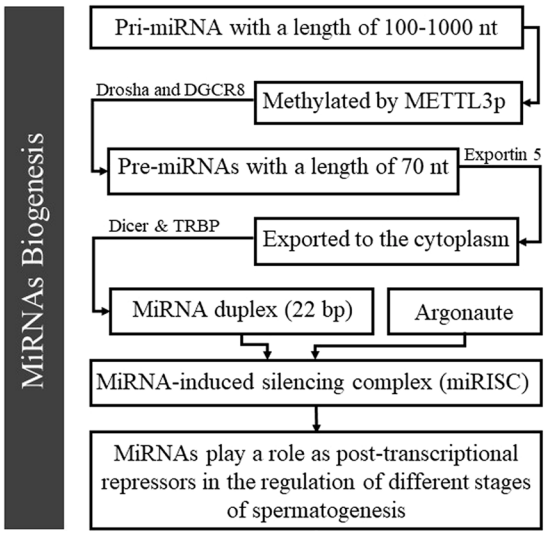


Fig. 1 Overview of MicroRNA biogenesis

of retinoic acid, found that the expression level of this miRNA is very high in undifferentiated cells. Generally, it can be concluded from the studies that miRNAs play a role in the post-transcriptional regulation of spermatogonial differentiation. The list of miRNAs and their role in spermatogenesis is summarized in Table 1.

The role of microRNAs as diagnostic biomarkers for male infertility

A useful biomarker should be unique, sensitive, noninvasive, and obtainable from an accessible source [29]. MiRNAs can be detected in body fluids such as semen, which are called circulating or extracellular miRNAs. Levels of these miRNAs are stable in body fluids and observing a change in the level of these can be considered a sign of pathophysiological processes [30]. MiRNAs in seminal plasma can be isolated and identified by noninvasive methods such as RT-qPCR and miRNA microarray, which are much better and simpler methods than the old methods like testicular biopsy. Therefore miRNAs can be used as noninvasive biomarkers to investigate infertility disorders [31]. Several studies

Table 1 miRNAs in SSC self-renewal and differentiation

miRNAs	Location	Action	Result	Refs.
miR-20 miR-106a	SSCs	Expressed in mouse SSCs, targeting STAT3 and Ccnd1	Help maintain and SSC homeostasis in mouse	[20]
miR-21	SSCs	Decreased apoptosis by increasing the expression of miR-21	Maintaining the SSC population	[21]
miRNA-554	SSCs	Targeting PLZF	Self-renewal of SSCs in goats	[22]
miR-135a	SSCs	Modulating FoxO1 activity	Help maintain SSCs	[23]
miR-34c	SSCs	Expression in goats	Increasing apoptosis of SSCs and reducing their proliferation dependent on P53	[24]
miR-let 7-family	SSCs	Down regulating	Differentiation of spermatogonia and entry into meiosis	[26]
miR-17-29 miR-106b-25	SSCs	Down regulating Up regulating	Shrinking of the testis and occurrence of oligospermia in mice	[27]
miR-221 miR-222	SSCs	Exposed to RA: down-regulating Exposed to GDNF: up regulating	Occurrence of disorder caused by the loss of differentiation ability	[17]
miR-146	SSCs	Regulation and control of retinoic acid	High expression level in differentiated cell	[28]

reported differential miRNA expression in infertile men compared to controls. For example, Joshi et al. [32] isolated miRNAs from sperm samples in individuals and then analyzed them with RT-PCR, and after comparing with the control group, they found that three miRNAs: hsa-miR-9-3p, hsa-miR-30b-5p, and hsa-miR-122-5p are strongly associated with infertility and have great potential as biomarkers of sperm quality. In another study, Dorostghoal et al. [33] investigated the sperm parameters and miR-26a-5p and PTEN transcript content in ejaculated spermatozoa in infertile and normozoospermic infertile men with RT-qPCR and observed changes in the expression level of this miRNA, so it was concluded that it has the potential to be used as a diagnostic biomarker for male infertility. Abu-Halima et al. analyzed a set of miRNAs in several patients with different forms of spermatogenic impairments (subfertile and nonobstructive azoospermia) and compared with the control group, observed changes in their expression levels, such that hsa-miR-34b*, hsa-miR-34b, hsa-miR-34c-5p, hsa-miR-122 causes down-regulating and has-miR-429 causes up-regulating. These findings showed that these five miRNAs have the potential as new noninvasive biomarkers for the diagnosis of infertility patients. Except for hsa-miR-429, the combination of these miRNAs with other conventional tests improves the diagnostic accuracy for the diagnosis of patients with different forms of NOA [34]. Also, Gholami et al. conducted a study to investigate the relationship between CRISP3 and four candidate miRNAs in teratozoospermia (TZ) infertile men. They isolated miRNAs from sperm samples and analyzed them by RT-PCR. Finally, up-regulation of miR-182-5p, miR-192-5p, and miR-493-5p was observed and these were introduced as possible biomarkers of TZ [35]. In the study that Llavanera et al. [36] conducted to identify the strongest molecular biomarker in sperm and seminal plasma to detect male infertility, miR-34c-5p was identified as the strongest and most specific biomarker by the RT-qPCR method. In addition to these studies, many other studies have been conducted that have led to important and acceptable results for the identification of miRNAs as biomarkers related to male infertility, these studies are briefly described in Table 2.

Role of microRNAs as therapeutic biomarkers for male infertility

Studies have shown that in addition to the diagnostic value of miRNAs, they can also be important in the field of therapy. There is increasing hope that therapeutic methods based on miRNAs can be effective in future for some diseases for therapy. There are some challenges in this area such as accurately delivering therapeutic agents to the target cells.

The researchers intend to create a balance in the level of miRs by injecting or using inhibitors, respectively, in cases where we are faced with a down-regulating or up-regulating in their expression and eliminate the effect of this disorder [37, 38].

Two miRNA-based therapeutic methods have been used to date, which include anti-miRs and miRNA mimics. Anti-miRs, miRNA Inhibitors are chemically modified, single-stranded nucleic acids designed to specifically bind to and inhibit miRNA molecules. These inhibitors can be introduced into cells by transfection and electroporation parameters [39]. miRNA mimics are chemically synthesized miRNAs that mimic naturally occurring miRNAs after transfection into the cell. miRNA inhibitors are single-stranded, modified RNAs that, after transfection, specifically inhibit miRNA function.

Table 2 MicroRNAs with biomarker capability for male infertility in previous studies

MirRNAs	Type of patients	Analysis method	Up/down-regulating	Sample type for RNA isolation	Refs.
has-miR-9-3p has-miR-30b-5p has-miR-122-5p	Infertile men	RT-PCR	–	Sperm	[32]
miR-26a-5p	Infertile men, normozoospermia	RT-qPCR	Down	Ejaculated sperm	[33]
miR-34/449 family	Infertile men	–	–	–	[37]
has-miR-34b* has-miR-34b has-miR-34c-5p has-miR-429 has-miR-122	Subfertile, nonobstructive azoospermia	RT-qPCR	Down Down Down Up Down	Semen	[34]
miR-20a-5p	Nonobstructive azoospermia, normozoospermia	RT-qPCR	Up	Blood plasma	[38]
miR-182-5p miR-192-5p miR493-5p	Teratozoospermia infertile men	RT-PCR	Up Up Up	Semen	[35]
miR-34c-5p	Infertile men	RT-qPCR	up	Seminal plasma	[36]
miR-383 miR-122 miR-15b	Infertile men: SOAT, MOAT, NOA, OA	Diff-Quick, RT-qPCR	Up Up Up	Sperm and testicular tissue	[39]
has-miR-942-5p/has-miR-1208 has-miR34b-3p/has-miR93-3p	Asthenozoospermia Teratozoospermia, Oligozoospermia, unexplained male infertility [UMI]	RT-qPCR	–	Semen	[40]
miR-210-3p	varicocele	RT-PCR	Up	Semen	[41]
miR-141 miR-429 miR-7–1-3p	Nonobstructive azoospermia	Tagman RT-qPCR assay	Up Up UP	Seminal plasma	[42]
miR-26b miR-374b	Normospermia	NGS	Down Down	Seminal plasma	[43]
miR-371a-3p	Oligozoospermia	qPCR	Down	Unprocessed ejaculate	[44]
miR-192a	Nonobstructive azoospermia and varicoceles	RT-qPCR	Down	Seminal plasma an d testicular tissue	
miR-155	Hypogonadal and eugonadal	RT-PCR	–	Cell-free serum	
miR-27a	Asthenotertozoo-spermia, normozoospermia	RT-qPCR Western blot	Up	Semen	

Until now, anti-miR therapy and miRNA mimics have been tested for various cancers and some other diseases [40]. Considering the different challenges (which are explained in the next paragraph), strategies for treating male infertility using these ways are also discussed [20]. It seems that miRNA-based therapies can be used in personalized medicine in future.

Challenges

Despite the potential benefits of miRNA-based therapies in diagnosing and treating diseases, there are several challenges that need to be addressed. One of the biggest challenges is identifying appropriate miRNA candidates and their targets for each disease. This process involves both computational algorithms and experimental methods, which can be difficult and time-consuming. Additionally, the complexity of the data and the sheer number of software available make it difficult to identify a single miRNA [41]. Another challenge is that one gene can be regulated by multiple miRNAs, or multiple genes can be regulated by a single miRNA. This suggests that a miRNA panel may be more effective in treating certain diseases. The delivery of therapeutic agents such as inhibitors or activators of miRNAs to target cells is another significant challenge. The amount of miRNA isolated from body fluids is often too small, and getting the therapeutic agents to the target cells can be difficult.

Furthermore, the cost of data analysis can be high, and there is a relatively limited range of variation in miRNA expression in infertility biomarkers. Despite these challenges, researchers are exploring the potential of miRNA-based therapies as a promising new approach to treating a wide range of diseases. As research continues, new insights will likely emerge that will help address these challenges and improve our understanding of how miRNAs can be used in personalized medicine [42, 43].

To date, miRNA-based therapies have been tested for various cancers and diseases However, there is still a lot of work to be done to fully realize their potential. One possible solution to some of the challenges facing miRNA-based therapies is to use a combination of different therapeutic methods, including anti-miRs, miRNA mimics, and gene therapy [44]. Another important area of research is the development of more efficient and effective methods for delivering therapeutic agents to target cells. Several approaches, such as the use of nanoparticles, liposomes, and viral vectors, are currently being investigated [32]. Finally, it is important to continue to develop new computational algorithms and experimental methods to identify and select the most effective miRNA candidates and their targets for each disease. By doing so, researchers can help to unlock the full potential of miRNA-based therapies and improve outcomes for patients with a wide range of diseases.

Conclusion and future perspective

The quest to unravel the mystery behind male infertility continues to be an arduous journey, fraught with numerous challenges. It is disheartening to note that a significant proportion of infertility cases in men remain inexplicable, despite the utilization of various expensive and invasive investigative techniques.

However, recent research has shone a glimmer of hope, with the discovery of miRNAs' potential role in male infertility. These tiny molecules, found in body fluids, offer a noninvasive avenue to investigate the underlying cause of male infertility. Their easy isolation and speedy investigation have provided a quicker route to diagnosis, complementing existing investigative techniques.

Moreover, researchers are currently exploring the therapeutic potential of miRNAs in treating male infertility. However, for this hope to translate into reality, there is a need to overcome the numerous obstacles impeding progress in this field. Achieving global standardization and overcoming the associated challenges would be a significant milestone in the quest for a reliable and effective treatment for male infertility.

Abbreviations

SSCs	Spermatogonia stem cells
mGSCs	Male germline stem cells
GDNF	Glial cell derived neurotrophic factor
RT-qPCR	Quantitative reverse transcription PCR
RT-PCR	Real time PCR
NOA	Notice of assessment
CRISP3	Cysteine rich secretory protein 3

Acknowledgments
Not applicable

Author contributions
RS, KJ, HM provided the primary draft; RS, HP and AM designed the figure and tables; ZA and ET revised the article along with English editing of the text.

Funding
This study was funded by Ahvaz University of Medical Sciences.

Availability of data and materials
Data are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors have no competing interests.

Received: 11 November 2022 Accepted: 12 June 2023
Published online: 24 June 2023

References

1. Rotimi DE, Elebiyo TC, Ojo OA (2023) Therapeutic potential of rutin in male infertility: a mini review. J Integr Med 21(2):130–135
2. Minhas S, Bettocchi C, Boeri L, Capogrosso P, Carvalho J, Cilesiz NC et al (2021) European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 update on male infertility. Eur Urol 80(5):603–620
3. Ombelet W (2011) Global access to infertility care in developing countries: a case of human rights, equity and social justice. Facts Views Vis Obgyn 3(4):66–257
4. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS et al (2015) EDC-2: The Endocrine Society's Second Scientific Statement on endocrine-disrupting chemicals. Endocr Rev 36(6):1–150
5. Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA (2012) National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. PLoS Med 9(12):e1001356
6. Zhang X, Guan Q, Yu Q, Xiao W, Chen Z, Dong C et al (2022) Estimating the effects of policies on infertility prevalence worldwide. BMC Public Health 22(1):1–11
7. Zegers-Hochschild F, Dickens BM, Dughman-Manzur S (2013) Human rights to in vitro fertilization. Int J Gynecol Obstet 123(1):86–89
8. Krueger RB, Reed GM, First MB, Marais A, Kismodi E, Briken P (2017) Proposals for paraphilic disorders in the international classification of diseases and related health problems, eleventh revision (ICD-11). Arch Sex Behav 46(5):1529–1545
9. Macaluso M, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A et al (2010) A public health focus on infertility prevention, detection, and management. Fertil Steril 93(1):16
10. Long J, Shvartsman K (2022) Infertility. In: Papadakis MA, McPhee SJ, Rabow MW, McQuaid KR (eds) Current medical diagnosis & treatment 2022. McGraw-Hill Education, New York
11. Forouhari S, Mahmoudi E, Safdarian E, Beygi Z, Gheibihayat SM (2021) MicroRNA: a potential diagnosis for male infertility. Mini Rev Med Chem 21(10):1226–1236
12. CarolineDiener A, Meese E (2022) Emerging concepts of miRNA therapeutics: from cells to clinic. Trends Genet 38:6
13. Gu S, Jin L, Zhang F, Sarnow P, Kay MA (2009) Biological basis for restriction of microRNA targets to the 3′ untranslated region in mammalian mRNAs. Nat Struct Mol Biol 16(2):144–150
14. Chen X, Li X, Guo J, Zhang P, Zeng W (2017) The roles of microRNAs in regulation of mammalian spermatogenesis. J Anim Sci Biotechnol 8(1):1–8

15. Kotaja N (2014) MicroRNAs and spermatogenesis. Fertil Steril 101(6):1552–1562
16. Yang Q-E, Racicot KE, Kaucher AV, Oatley MJ, Oatley JM (2013) MicroRNAs 221 and 222 regulate the undifferentiated state in mammalian male germ cells. Development 140(2):280–290
17. Papaioannou MD, Nef S (2010) microRNAs in the testis: building up male fertility. J Androl 31(1):26–33
18. Yang Q-E, Oatley JM (2014) Spermatogonial stem cell functions in physiological and pathological conditions. Curr Top Dev Biol 107:235–267
19. Sojoudi K, Azizi H, Skutella T (2023) A review of the potential of induced pluripotent stem cell-derived exosome as a novel treatment for male infertility. Biotechnol Genet Eng Rev 1–26
20. He Z, Jiang J, Kokkinaki M, Tang L, Zeng W, Gallicano I et al (2013) MiRNA-20 and mirna-106a regulate spermatogonial stem cell renewal at the post-transcriptional level via targeting STAT3 and Ccnd1. Stem cells 31(10):2205–2217
21. Niu Z, Goodyear SM, Rao S, Wu X, Tobias JW, Avarbock MR et al (2011) MicroRNA-21 regulates the self-renewal of mouse spermatogonial stem cells. Proc Natl Acad Sci 108(31):12740–12745
22. Song W, Mu H, Wu J, Liao M, Zhu H, Zheng L et al (2015) miR-544 regulates dairy goat male germline stem cell self-renewal via targeting PLZF. J Cell Biochem 116(10):2155–2165
23. Moritoki Y, Hayashi Y, Mizuno K, Kamisawa H, Nishio H, Kurokawa S et al (2014) Expression profiling of microRNA in cryptorchid testes: miR-135a contributes to the maintenance of spermatogonial stem cells by regulating FoxO1. J Urol 191(4):1174–1180
24. Li M, Yu M, Liu C, Zhu H, He X, Peng S et al (2013) miR-34c works downstream of p53 leading to dairy goat male germline stem-cell (mGSC s) apoptosis. Cell Prolif 46(2):223–231
25. Busada JT, Geyer CB (2016) The role of retinoic acid (RA) in spermatogonial differentiation. Biol Reproduct 94(1):10
26. Tong M-H, Mitchell D, Evanoff R, Griswold MD (2011) Expression of Mirlet7 family microRNAs in response to retinoic acid-induced spermatogonial differentiation in mice. Biol Reprod 85(1):189–197
27. Tong M-H, Mitchell DA, McGowan SD, Evanoff R, Griswold MD (2012) Two miRNA clusters, Mir-17–92 (Mirc1) and Mir-106b-25 (Mirc3), are involved in the regulation of spermatogonial differentiation in mice. Biol Reproduct 86(3):72
28. Huszar JM, Payne CJ (2013) MicroRNA 146 (Mir146) modulates spermatogonial differentiation by retinoic acid in mice. Biol Reproduct 88(1):15
29. Etheridge A, Lee I, Hood L, Galas D, Wang K (2011) Extracellular microRNA: a new source of biomarkers. Mutat Res Fundam Mol Mech Mutagen 717(1–2):85–90
30. Pratt S, Calcatera S (2017) Expression of microRNA in male reproductive tissues and their role in male fertility. Reprod Fertil Dev 29(1):24–31
31. Wang C, Yang C, Chen X, Yao B, Yang C, Zhu C et al (2011) Altered profile of seminal plasma microRNAs in the molecular diagnosis of male infertility. Clin Chem 57(12):1722–1731
32. Joshi M, Andrabi SW, Yadav RK, Sankhwar SN, Gupta G, Rajender S (2022) Qualitative and quantitative assessment of sperm miRNAs identifies hsa-miR-9-3p, hsa-miR-30b-5p and hsa-miR-122-5p as potential biomarkers of male infertility and sperm quality. Reprod Biol Endocrinol 20(1):122
33. Dorostghoal M, Galehdari H, Moramezi F, Danyari R (2020) Sperm miR-26a-5p and its target PTEN transcripts content in men with unexplained infertility. Andrology 8(5):1167–1173
34. Abu-Halima M, Hammadeh M, Backes C, Fischer U, Leidinger P, Lubbad AM et al (2014) Panel of five microRNAs as potential biomarkers for the diagnosis and assessment of male infertility. Fertil Steril 102(4):989–97.e1
35. Gholami D, Amirmahani F, Yazdi RS, Hasheminia T, Teimori H (2021) MiR-182-5p, MiR-192-5p, and MiR-493-5p constitute a regulatory network with CRISP3 in seminal plasma fluid of teratozoospermia patients. Reprod Sci 28(7):2060–2069
36. Llavanera M, Delgado-Bermúdez A, Ribas-Maynou J, Salas-Huetos A, Yeste M (2022) A systematic review identifying fertility biomarkers in semen: a clinical approach through Omics to diagnose male infertility. Fertil Steril 118(2):291–313
37. Chakraborty C, Sharma AR, Sharma G, Doss CGP, Lee S-S (2017) Therapeutic miRNA and siRNA: moving from bench to clinic as next generation medicine. Mol Therapy-Nucl Acids 8:132–143
38. Stenvang J, Petri A, Lindow M, Obad S, Kauppinen S (2012) Inhibition of microRNA function by antimiR oligonucleotides. Silence 3(1):1–17
39. Chavda VP, Pandya A, Kumar L, Raval N, Vora LK, Pulakkat S et al (2023) Exosome nanovesicles: a potential carrier for therapeutic delivery. Nano Today 49:101771
40. Nedaeinia R, Avan A, Ahmadian M, Nia SN, Ranjbar M, Sharifi M et al (2017) Current status and perspectives regarding LNA-Anti-miR oligonucleotides and microRNA miR-21 inhibitors as a potential therapeutic option in treatment of colorectal cancer. J Cell Biochem 118(12):4129–4140
41. Abu-Halima M, Becker LS, Al Smadi MA, Kunz LS, Gröger L, Meese E (2023) Expression of SPAG7 and its regulatory microRNAs in seminal plasma and seminal plasma-derived extracellular vesicles of patients with subfertility. Sci Rep 13(1):3645
42. Brunet Vega A, Pericay C, Moya I, Ferrer A, Dotor E, Pisa A et al (2013) microRNA expression profile in stage III colorectal cancer: circulating miR-18a and miR-29a as promising biomarkers. Oncol Rep 30(1):320–326
43. Witwer KW (2015) Circulating microRNA biomarker studies: pitfalls and potential solutions. Clin Chem 61(1):56–63
44. Glinge C, Clauss S, Boddum K, Jabbari R, Jabbari J, Risgaard B et al (2017) Stability of circulating blood-based microRNAs–pre-analytic methodological considerations. PLoS ONE 12(2):e0167969

Publisher's Note