

# Long Non-Coding RNAs in Male Infertility: Molecular Mechanisms, Biomarker Potential, and Perspectives for Non-Invasive Diagnosis

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**Abstract**—Male infertility affects approximately 7% of men of reproductive age and remains idiopathic in a substantial proportion of cases, reflecting the incomplete understanding of its molecular basis. Long non-coding RNAs (lncRNAs), defined as transcripts longer than 200 nucleotides with limited or no protein-coding potential, have emerged as important regulators of gene expression in the male reproductive system. Increasing evidence indicates that aberrant lncRNA expression contributes to impaired spermatogenesis, sperm maturation, oxidative stress, apoptosis, endocrine dysfunction, and disruption of the blood–testis barrier. This review summarizes current knowledge of lncRNA-mediated regulatory mechanisms in male infertility and evaluates their potential diagnostic and therapeutic relevance. lncRNAs act at multiple molecular levels, including epigenetic regulation of chromatin structure, transcriptional control, modulation of alternative splicing, direct interaction with RNA-binding proteins, and competitive endogenous RNA (ceRNA) activity through sequestration of microRNAs. Functionally important lncRNAs, including TUG1, MALAT1, H19, NLC1-C, HOTAIR, Gm2044, LINC00966, and LINC00893, have been associated with non-obstructive azoospermia, oligozoospermia, asthenozoospermia, oligo-astheno-teratozoospermia, and testicular injury. Their dysregulation affects key pathways involved in meiosis, germ-cell proliferation, apoptosis, steroidogenesis, mitochondrial homeostasis, cGMP signaling, oxidative stress, and intercellular junction integrity. Particular attention is given to the translational potential of lncRNAs detected in seminal plasma, serum, extracellular vesicles, and exosomes. Several candidates, notably TUG1, H19, MALAT1, CDKN2B-AS1, and Linc-ROR, have demonstrated promising diagnostic performance and may contribute to the prediction of testicular sperm retrieval outcomes in men with non-obstructive azoospermia. However, substantial barriers remain, including heterogeneity of patient cohorts, inconsistent infertility phenotyping, non-standardized sample processing, variable RNA isolation and normalization strategies, and limited external validation. Overall, lncRNAs represent a complex regulatory layer in male reproductive biology and a promising source of biomarkers for precision diagnostics. Future large-scale, multicenter, and functionally validated studies are required to establish clinically reliable lncRNA-based panels and to clarify whether selected lncRNAs may serve as actionable therapeutic targets in male infertility.

**Keywords**— long non-coding RNAs; male infertility; spermatogenesis; non-obstructive azoospermia; oligozoospermia; asthenozoospermia; sperm motility.

## I. INTRODUCTION

Male infertility remains one of the most pressing issues in reproductive medicine, affecting, according to various estimates, around 7 per cent of men of reproductive age, whilst the molecular mechanisms underlying a significant proportion of idiopathic cases remain unknown. In recent years, the rapid development of high-throughput sequencing technologies has enabled a fresh perspective on the regulatory potential of the non-coding portion of the transcriptome, with researchers paying particular attention to long non-coding RNAs (lncRNAs) — transcripts longer than 200 nucleotides that do not encode proteins but are involved in transcriptional, post-transcriptional and epigenetic regulation of gene expression [1]. A systematic review by Kyrgiafini and colleagues summarised, for the first time, data on the differential expression of lncRNAs in various forms of male infertility, identifying eight molecules (SPATA42, LINC00710, RUSC1-AS1, LINC00905, COX10-AS1, HOTAIR, LINC01091, LINC01359), the dysregulation of which is observed in several subtypes of pathospermia. It has been shown that many lncRNAs act as competitive endogenous RNAs (ceRNAs), ‘sponges’ for microRNAs, and also interact with DNA-binding proteins, modulating pathways critical for spermatogenesis [2].

The accumulated data suggest that dysregulation of specific lncRNAs is associated with particular clinical phenotypes of infertility. For example, hypomethylation of the imprinted region of the H19 gene is linked to reduced sperm motility and concentration in cases of oligo- and asthenozoospermia, and the H19

methylation profile has been proposed as a potential epigenetic biomarker of spermatogenesis defects [1]. In non-obstructive azoospermia, a reduction in the cytoplasmic form and an accumulation of the nuclear form of the lncRNA NLC1-C (LINC00162) have been described in spermatogonia and primary spermatocytes at the stage of mixed arrest of germ cell maturation. Recent studies have also shown that the lncRNA LINC00966 suppresses PDE2A expression, disrupting cGMP signalling and increasing oxidative stress, which leads to reduced viability and motility of spermatogenic cells in asthenozoospermia [3].

Functional studies in model organisms confirm the physiological significance of testis-specific lncRNAs. In particular, lncRNA Gm2044 regulates SYCP1 expression via a ceRNA mechanism in mouse spermatocytes and acts as a parental gene for miR-202, influencing the progression of meiosis and contributing to the pathogenesis of non-obstructive azoospermia. Knockout of the testis-specific lncRNA 1700052I22Rik in mice leads to reduced sperm count, subfertility and impaired chromatin condensation in spermatids, whilst deletion of the lncRNA CIRBIL in Leydig cells reduces testosterone levels and impairs the integrity of the sperm head and tail due to disrupted steroidogenesis. A large-scale transcriptomic analysis of approximately 600–700 lncRNAs in *Drosophila* testis tissues demonstrated that the expression levels of lncRNAs in developing germ cells can exceed those of coding genes, suggesting that these molecules play a significantly more important role in male reproduction than previously thought [4].

The advent of whole-genome sequencing methods has also made it possible to identify structural variants within the lncRNA genes themselves. A 2025 study based on WGS and RNA-seq identified 258 differentially expressed lncRNAs in men with asthenozoospermia, amongst which variants were prioritised that disrupt the structure of lncRNAs and their interaction with microRNAs in the Wnt signalling and cell proliferation pathways. A comprehensive review by Borji et al. examines lncRNAs within the broader context of non-coding RNA regulators of oogenesis and spermatogenesis, highlighting their potential as non-invasive diagnostic biomarkers and therapeutic targets in azoospermia and oligo-astheno-teratozoospermia [5]. Thus, the data accumulated in recent years convincingly demonstrates that lncRNAs are key regulators of spermatogenesis, sperm maturation and functional integrity, and that their dysregulation contributes to the development of various forms of male infertility. At the same time, questions remain unresolved regarding the standardisation of detection methods, the validation of causal relationships in clinical cohorts, and the translation of the knowledge gained into diagnostic and therapeutic approaches; these issues define the aim and objectives of the present study.

## II. MOLECULAR MECHANISMS OF ACTION OF LNCRNAs IN MALE INFERTILITY

Long non-coding RNAs are involved in a multi-level regulatory system — ranging from the control of transcription and epigenetic chromatin remodelling to post-transcriptional interactions with microRNAs, mRNAs and proteins — and are implicated in virtually all stages of spermatogenesis. The classification of lncRNA functions traditionally comprises three main levels: transcriptional regulation via interaction with methylation and deacetylation complexes, post-transcriptional regulation via competitive binding to microRNAs, and modulation of alternative splicing.

## III. EPIGENETIC AND TRANSCRIPTIONAL REGULATION

At the transcriptional level, dsRNA directs chromatin-modifying enzymes, including histone modifiers and DNA methyltransferases, to specific genomic loci, thereby determining the patterns of methylation and acetylation, which are critical for the differentiation of spermatogonial stem cells (SSCs). Some dRNAs facilitate the binding of the transcriptional apparatus to gene promoters, thereby activating transcription, whilst others block this binding, acting as repressors. A prime example is the imprinted H19 locus: disruption of its methylation is associated with reduced sperm motility and concentration, whilst H19 RNA itself, in a model of ischaemic-reperfusion injury to the testes, promotes apoptosis and inflammation via the PI3K/AKT/ZO-1 pathway, thereby disrupting the integrity of the haematotesticular barrier [6].

#### IV. THE MOLECULAR SPONGE MECHANISM FOR MICRORNAs

The most thoroughly studied mechanism is the function of dRNA as competitive endogenous RNA (ceRNA) — ‘sponges’ that bind specific microRNAs via shared binding sites, thereby lifting the repression of their target mRNAs. In male germ cells, the Gm2044 dRNA acts as a sponge for miR-335-3p, regulating SYCP1 protein expression and the proliferation of GC-2 line spermatocytes, and also serves as the host genome for miR-202, which controls entry into meiosis via regulation of the RBFOX2 protein [7]. Similarly, the dRNA AK015322, which is highly expressed in testicular SSCs, binds miR-19b-3p and stimulates stem cell proliferation, whilst the dsRNA NLC1-C, which accumulates in the nuclei of spermatogonia and primary spermatocytes in cases of non-obstructive azoospermia, binds to nucleolin and suppresses miR-320a and miR-383, leading to hyperactive proliferation and an imbalance in germ cell apoptosis [2]. Suppression of HOTAIR dsRNA reduces Nrf2 expression and enhances oxidative stress, which contributes to apoptosis and impaired sperm motility and viability. In asthenozoospermia, the opposite mechanism has been described: overexpressed LINC00966 dsRNA suppresses the PDE2A gene, disrupting cGMP signalling and inducing oxidative stress in spermatogenic cells.

#### V. REGULATION OF APOPTOSIS AND CELL VIABILITY

A significant proportion of the pathogenic effects of dsRNA in male infertility are mediated through the modulation of the balance between proliferation and apoptosis in germ and somatic cells of the testis. A review by Yu et al. [8] systematises evidence that dsRNA and circular RNAs act as ceRNA in the apoptotic pathways of germ cells, Sertoli cells and Leydig cells, by interacting with the key PI3K/AKT, NOTCH, Wnt/ $\beta$ -catenin and mTOR signalling cascades. In particular, the MIR22HG dsRNA promotes apoptosis in Leydig cells by binding to miR-125a -5p and re-activating the NDRG2 gene, thereby reducing testosterone synthesis, whilst FENDRR dsRNA enhances apoptosis in the same cells by accelerating the degradation of the Nrf2 transcription factor. In testicular ischaemia-reperfusion, increased expression of MALAT1 siRNA in testicular tissues and GC-1 cell line cells correlates positively with apoptosis and negatively with germ cell proliferation. HOTTIP dsRNA, in turn, regulates the  $\gamma$ -H2AX and p53 signalling pathways during UV-induced cell cycle arrest of spermatogonia in the G2/M phase and early apoptosis.

#### VI. MODULATION OF INTERCELLULAR JUNCTIONS AND THE HAEMATOTESTICULAR BARRIER

A distinct mechanism of action of dsRNA is linked to the regulation of the integrity of the intercellular junctions that form the haematotesticular barrier, which is critical for isolating developing germ cells from the immune system. Knockdown of dRNA5251 in mice enhances the expression of the intercellular contact genes JAM1, VCAM1, CX37, OCLN and CADM2, whilst its overexpression reduces sperm quality, indicating a modulatory role for this dRNA in maintaining the structural integrity of the barrier [9]. H19 deficiency in an oxidative-glucose deprivation model preserves barrier integrity by stabilising AKT phosphorylation and restoring the expression of the tight junction protein ZO-1.

#### VII. INTERACTION WITH PROTEINS AND REGULATION OF SPLICING

In addition to interacting with microRNAs, dNAs are capable of directly binding to RNA-binding proteins (RBPs), forming regulatory RNA-protein complexes that determine the fate of gene expression in male germ cells at several levels — from the processing and stability of transcripts to their translation. Such interactions can also direct alternative splicing of target mRNAs by binding to spliceosomal factors and influencing exon selection, thereby extending the functional repertoire of dRNA far beyond that of a simple microRNA trap. Taken together, these mechanisms — epigenetic, ceRNA-mediated, apoptotic and structural — form a multi-level regulatory network governing spermatogenesis, disruption of any link in which can lead to the development of various forms of male infertility [10].

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## IX. KEY MIRNAS ASSOCIATED WITH MALE INFERTILITY

To date, dozens of miRNAs have been identified that are differentially expressed in testicular tissues, spermatozoa and seminal plasma from men with various forms of infertility; however, the functional role of only a limited number of these molecules has been experimentally confirmed in cellular and animal models. The most extensively studied and clinically significant members of this group are discussed below [11].

### TUG1 (Taurine Upregulated Gene 1)

The TUG1 rRNA is one of the most conserved and functionally characterised loci critical for male fertility: knockout of the Tug1 locus in mice leads to completely penetrant sterility due to a reduction in sperm count and impaired sperm morphology [12]. Molecular analysis has shown that the Tug1 locus contains at least three distinct regulatory functions: a cis-acting DNA repressor of neighbouring genes, a trans-acting dsRNA, and a conserved open reading frame, which is translated into a peptide that influences mitochondrial membrane potential. TUG1 also maintains the integrity of tight junctions in Sertoli cells and the structure of the haematotesticular barrier, whilst its deficiency disrupts this barrier function. In clinical studies conducted in 2025, serum and seminal TUG1 levels were found to be significantly lower in patients with non-obstructive azoospermia and oligozoospermia compared with healthy men, making this molecule a promising non-invasive biomarker [13,14].

### MALAT1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1)

The MALAT1 cDNA is expressed in the nuclei of spermatozoa and in the interstitial cells of the testis, where it plays a role in the maturation of germ cells; it functions primarily via the ceRNA mechanism, binding to miR-483-3p and miR-141-3p. In testicular ischaemia-reperfusion, increased MALAT1 expression correlates positively with apoptosis and negatively with the proliferation of GC-1 germ cells. Clinical data are contradictory: serum levels of MALAT1 are elevated in patients with non-obstructive azoospermia, whilst they are reduced in those with secretory oligozoospermia, indicating subtype-specific regulation of this dsRNA [13].

Imprinted H19 RNA is linked to several phenotypes of male infertility: abnormal methylation of this locus is associated with reduced sperm motility and concentration in cases of oligo- and asthenozoospermia [15]. In a model of testicular torsion and ischaemia-reperfusion, H19 knockout in mice attenuated testicular tissue damage and preserved the integrity of the blood-testis barrier by stabilising AKT phosphorylation and restoring the tight junction protein ZO-1, whereas H19 overexpression exacerbated apoptosis and inflammation via the PI3K/AKT/ZO-1 pathway [1,6].

### The Gm2044

mRNA is highly expressed at specific stages of meiosis in male and female germ cells and acts as a molecular sponge for several microRNAs simultaneously: by binding to miR-335-3p, it regulates SYCP1 expression and spermatocyte proliferation, whilst, as the host gene for miR-202, it controls the entry of cells into meiosis via the RBFOX2 protein. Dysregulation of Gm2044 is involved in the pathogenesis of non-obstructive azoospermia and is considered a potential therapeutic target [7].

### NLC1-C (LINC00162) and HOTAIR

The NLC1-C DNRNA accumulates in the nuclei of spermatogonia and primary spermatocytes in patients with non-obstructive azoospermia at the stage of mixed arrest of germ cell maturation; it binds to nucleolin and suppresses miR-320a and miR-383, thereby stimulating proliferation and disrupting the apoptotic balance. When silenced, HOTAIR dsRNA reduces the expression of the Nrf2 transcription factor, which exacerbates oxidative stress and contributes to apoptosis and a reduction in sperm motility and viability [2].

### LINC00966 and LINC00893

Overexpressed LINC00966 dsRNA suppresses the PDE2A gene, disrupting cGMP signalling and inducing oxidative stress, which leads to reduced viability and motility of spermatogenic cells in asthenozoospermia. In contrast, LINC00893 dRNA is significantly reduced in patients with asthenozoospermia against a background of elevated levels of its m6A methylation; the constructed LINC00893/miR-125a-5p/COQ9 ceRNA network demonstrates that a reduction in LINC00893 derepresses miR-125a-5p, which suppresses the COQ9 gene, critical for autophagy and the sperm cell cycle [16, 17].

### Other testis-specific dsRNAs

A number of less well-studied but functionally significant dsRNAs have been described in recent studies: RNA 1700052I22Rik is dynamically expressed at different stages of spermatogenesis, and its knockout in mice results in reduced sperm count, subfertility and impaired chromatin condensation in spermatids. The 1700009J07Rik rRNA, which is highly expressed in spermatogenic cells, is not strictly essential for spermatogenesis, but it finely regulates sperm motility and influences libido via an indirect effect on testosterone metabolism [18]. The CIRBIL lncRNA, expressed in Leydig cells, reduces testosterone levels upon deletion and disrupts the integrity of the sperm head and tail through dysregulation of steroidogenesis. The panel of lncRNAs lnc32058, lnc09522 and lnc98487 shows specifically high expression in immotile spermatozoa compared with normally motile ones, making them candidate markers for asthenozoospermia. Finally, whole-transcriptome analysis using the WGCNA method and the construction of an mRNA-miRNA-lncRNA network in the sperm of patients with non-obstructive azoospermia identified a number of lncRNA regulators and hub genes associated with the pathogenesis of the disease [19, 20].

Taken together, these data demonstrate that the key dnRNAs — TUG1, MALAT1, H19, Gm2044, NLC1-C, HOTAIR, LINC00966 and LINC00893 — form a functionally diverse yet interconnected regulatory network, an imbalance in which is observed in the majority of clinical forms of male infertility.

## X.RNA IN BIOLOGICAL FLUIDS: PROSPECTS FOR NON-INVASIVE DIAGNOSIS

The limitations of invasive methods for diagnosing male infertility, particularly testicular biopsy in cases of non-obstructive azoospermia (NOA), are driving an active search for molecular markers in readily available biological fluids — seminal plasma, blood serum, urine and extracellular vesicles. lncRNAs are regarded as a particularly promising class of such markers due to their high stability in the extracellular space, tissue-specific expression and protection from degradation by RNases through packaging into exosomes or binding to protein complexes [21, 22].

### Seminal plasma as a source of diagnostic dRNA

Seminal plasma represents an optimal non-invasive matrix for assessing the status of spermatogenesis, as it contains extracellular RNA, microvesicles and proteins that directly reflect gonadal activity, in contrast to systemic blood serum. A large-scale study from 2026 [23] analysed a panel of seven miRNAs in the seminal plasma of patients with NAO and showed that six of them—CDKN2B-AS1, H19, lincROR, MALAT1, MIAT and TUG1 — differed significantly in expression from that of healthy men, with TUG1 (AUC 0.94), CDKN2B-AS1 (AUC 0.90) and H19 (AUC 0.90) demonstrating the highest diagnostic accuracy. The same miRNA panel demonstrated prognostic value with regard to the outcome of

TESE (surgical extraction of sperm from testicular tissue): Linc-ROR, TUG1, CDKN2B-AS1 and H19 enabled the prediction of success.

Whole-transcriptome analysis of seminal plasma from patients with oligoasthenozoospermia and NMA identified hundreds of differentially expressed circular and long non-coding RNAs; following qPCR validation and ROC analysis, several of these molecules demonstrated diagnostic accuracy comparable to established biomarkers [24, 25].

#### Extracellular vesicles and exosomal dnRNA

Extracellular vesicles (EVs) in seminal plasma, including exosomes and prostasomes, are regarded as natural ‘capsules’ that protect the non-coding RNAs they contain from enzymatic degradation and facilitate intercellular communication within the male reproductive tract. A 2026 review highlights the diagnostic potential of exosomal non-coding RNAs in seminal fluid, including dRNA, for assessing reproductive health and identifying the causes of male infertility, noting that a panel of exosomal dNAs has been proposed as a tool for predicting the presence of testicular spermatozoa in secretory azoospermia prior to surgical intervention [22, 25, 26].

This approach is particularly significant for patients with the secretory form of azoospermia, as it allows the likelihood of successful sperm retrieval to be assessed in advance and the approach to assisted reproductive technologies to be adjusted accordingly.

### XI. CLINICAL AND DIAGNOSTIC INTEGRATION AND LIMITATIONS

A systematic review of the clinical applicability of non-coding RNA biomarkers in male infertility introduces the concept of a test’s ‘clinical utility’—its ability to influence a specific clinical decision through analytical reliability, clinical validity and practical feasibility — and concludes that, despite promising data, no non-coding RNA-based assay is yet ready for routine clinical use. The main barriers include a lack of standardisation in pre-analytical protocols (collection, storage, RNA extraction), heterogeneity in quantification methods, and small sample sizes in most studies, which limit the reproducibility of results between laboratories. Nevertheless, by analogy with oncology—where circulating dRNA is already used as a marker for early diagnosis and prognosis due to its stability in plasma and serum—the accumulated data on TUG1, H19, MALAT1 and Linc-ROR in seminal plasma form the basis for the development of multi-marker, non-invasive panels capable of supplementing or partially replacing traditional semen analysis and hormonal profiling in the diagnosis and prognosis of treatment outcomes for male infertility.

### XII. CONCLUSION

Long non-coding RNAs have become increasingly recognized as essential regulators of male reproductive function rather than transcriptional by-products. Available evidence indicates that lncRNAs participate in virtually all major processes required for normal spermatogenesis, including spermatogonial stem-cell maintenance, meiotic progression, germ-cell differentiation, chromatin condensation, sperm motility, Leydig-cell steroidogenesis, oxidative-stress responses, apoptosis, and preservation of the blood–testis barrier. Their regulatory activity is mediated through epigenetic mechanisms, interactions with transcriptional and RNA-binding proteins, modulation of mRNA stability and splicing, and ceRNA networks involving microRNAs.

The altered expression of lncRNAs such as TUG1, H19, MALAT1, NLC1-C, HOTAIR, LINC00966, LINC00893, and Gm2044 has been linked to clinically relevant infertility phenotypes, including non-obstructive azoospermia, oligozoospermia, and asthenozoospermia. These molecules may therefore help explain part of the molecular heterogeneity observed in idiopathic male infertility. Importantly, lncRNAs in seminal plasma and extracellular vesicles offer an attractive opportunity for non-invasive assessment of spermatogenic impairment and may improve the prediction of sperm retrieval success before invasive procedures such as testicular sperm extraction.

Despite these promising findings, lncRNA research in male infertility is still primarily exploratory. The clinical translation of candidate biomarkers is limited by small study populations, inconsistent diagnostic criteria, methodological variability, insufficient mechanistic validation, and the lack of prospective multicenter studies. Future research should prioritize standardized pre-analytical and analytical workflows, robust normalization approaches, independent cohort validation, and integration of lncRNA data with semen parameters, hormonal profiles, genomic variants, and other non-coding RNA classes.

In conclusion, lncRNAs represent a biologically meaningful and potentially clinically useful component of the molecular landscape of male infertility. Their incorporation into multiparametric diagnostic models may support a transition from conventional phenotype-based evaluation toward more precise, non-invasive, and individualized reproductive medicine.

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