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Non-Coding Nucleic Acid Sequences and Female Infertility

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ABSTRACT

Female infertility is one of the least investigated forms of reproductive dysfunction. This review presents promising molecular factors associated with infertility and analyzes the mechanisms involved in its manifestation and progression. Globally, up to 17.5% of couples experience infertility, which can negatively affect individual health and society as a whole. Female-related factors account for approximately 37% of cases. The presence of numerous factors associated with chronic inflammatory diseases of the reproductive system, including genetic and environmental influences, pose significant challenges for treatment of this patient population. Epigenetic mechanisms represent promising targets for regulation. MicroRNAs (miRNAs) are short non-coding RNA sequences that are approximately 18–25 nucleotides long. They regulate a wide range of various physiological processes within the cell, including cell growth, signal transduction, apoptosis, and pathological processes. Several miRNAs, including miR-324, miR-155, miR-335-5p, miR-9119, miR-23a, miR-27a, and miR-146b-5p, may be associated with female infertility. The role of long non-coding sequences influencing the activity of key targets involved in granulosa cell maturation is also highlighted. These factors have been shown to act as regulatory RNAs and mediate the decidualization of stromal cells. Particular attention is given to circulating miRNAs such as let-7b, miR-29a, miR-30a, miR-140, and miR-320a.

Keywords: non-coding nucleic acid sequences; female infertility; microRNA.

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Роль некодирующих последовательностей нуклеиновых кислот в развитии женского бесплодия

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АННОТАЦИЯ

Женское бесплодие относится к одной из наименее изученных форм репродуктивной патологии. В обзоре представлены перспективные молекулярные факторы, связанные с развитием бесплодия, проанализированы механизмы, участвующие в манифестации и прогрессировании данной патологии. До 17,5% пар в мире сталкиваются с проблемами бесплодия, что может негативно сказаться на здоровье самих пар и общества в целом. Женские факторы — причина примерно 37% случаев бесплодия. Наличие большого количества факторов, ассоциированных с развитием хронических воспалительных заболеваний репродуктивной системы, в т. ч. генетических, а также факторов внешней среды, является существенной сложностью в лечении данной категории пациентов. Эпигенетические механизмы представляют собой перспективные мишени для регуляции. МикроРНК — короткие последовательности некодирующей РНК примерно от 18 до 25 нуклеотидов. Они также оказывают глубокое воздействие на различные физиологические процессы внутри клетки, включая клеточный рост, передачу сигналов, апоптоз и патологические процессы. miR-324, miR-155, miR-335-5p, miR-9119, miR-23a**,** miR-27a и miR-146b-5p могут быть ассоциированы с развитием женского бесплодия. Обозначена роль длинных некодирующих последовательностей, влияющих на активность ключевых мишеней, определяющих созревание гранулёзных клеток. Показано, что данные факторы способны выступать в качестве регуляторной РНК и опосредовать децидуализацию стромальных клеток. Выявлено, что особое значение придаётся циркулирующим микроРНК let-7b, miR-29a, miR-30a, miR-140, miR-320a.

Ключевые слова: некодирующие последовательности нуклеиновых кислот; женское бесплодие; микроРНК.

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BACKGROUND

Infertility is a disease of the reproductive system defined as the inability to achieve a clinical pregnancy after ⩾12 months of regular unprotected sexual intercourse [1]. Up to 17.5% of couples experience infertility worldwide, which can negatively affect both individuals and society as a whole. Female factors account for approximately 37% of infertility cases [2].

In developed countries, the most common causes of female infertility are ovulatory disorders, occurring in 24.8% of cases of female infertility [1]. Ovulatory disorders include hypothalamic amenorrhea, polycystic ovary syndrome (PCOS), hyperprolactinemic anovulation, and thyroid dysfunction [3].

Globally, approximately 15% of couples of reproductive age—at least 48.5 million—encounter difficulties conceiving [3]. At present, this public health issue affects 20%–30% of women of reproductive age. Approximately 10%–15% of couples aged 20–45 years experience infertility [4–6]. According to the World Health Organization, infertility may affect nearly 80 million women worldwide [7].

Infertility can become a hopeless challenge for couples, leading to stress. Couples facing infertility are at higher risk for developing serious mental health conditions, such as anxiety and depression, than healthy couples [8, 9].

Female infertility is described as infertility primarily caused by female factors such as ovulatory dysfunction, diminished ovarian reserve, reproductive tract disorders, and chronic diseases [7]. Primary female infertility is diagnosed in women who have never given birth and secondary infertility in those who have previously had a live birth or miscarriage but are currently unable to achieve clinical pregnancy. In addition to physiological and age-related factors, conditions associated with the pathophysiology of the reproductive organs and other factors such as environmental exposures and lifestyle contribute to female fertility [10].

MOLECULAR AND BIOLOGICAL MECHANISMS OF INFERTILITY

Currently, various factors are associated with impaired oocyte maturation, including genetic causes and environmental influences [11]. However, recently, the condition of the immune system has been of greatest interest to researchers [12]. For example, in the peritoneal fluid of women with endometriosis, increased levels of tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, and IL-8 have been observed [12]. In the uterine cavity, cytokines stimulate prostaglandin production by endometrial cells, leading to overexpression of other inflammatory cytokines. Moreover, these cytokines initiate inflammatory responses, promote angiogenesis, and participate in tissue injury and regeneration. Excessive levels of cytokines may impair follicular steroidogenesis and development, ovulation, and implantation, adversely affecting the possibility of achieving a natural pregnancy [12].

Furthermore, lipid peroxidation plays a crucial role in infertility-associated processes [2]. Physiological levels of reactive oxygen species are critical for essential regulatory functions in folliculogenesis, oocyte maturation, endometrial cycling, luteolysis, implantation, embryogenesis, and pregnancy maintenance via various signaling pathways.

Infertility is a heterogeneous condition, with genetic factors accounting for approximately 50% of all cases [10]. Next-generation sequencing, including whole-genome sequencing and whole-exome sequencing (WES), has accelerated the identification of potentially pathogenic variants (population polymorphisms) and private mutations [13].

In their study, Wang et al. [14] identified the genetic causes of oocyte maturation arrest (OMA), a disease that leads to female infertility and is a major cause of in vitro fertilization failure. OMA can occur at different stages of meiosis, and several genes involved in key processes, such as homologous recombination, spindle assembly, zona pellucida formation, and translational repression, have been implicated in its development [3].

Feng et al. (2016) conducted WES of five members of a four-generation family, three of whom experienced infertility due to oocyte meiotic arrest at meiosis I [15]. Then, Sanger sequencing of the candidate gene *TUBB8* was performed on DNA from these individuals, additional relatives, and members of 23 other unrelated families affected by OMA. Consequently, seven mutations in the primate-specific *TUBB8* gene were identified, which were responsible for meiosis I arrest in 7 of 24 families. *TUBB8* expression is unique to oocytes and early embryos, wherein it represents nearly all β-tubulin expressions. These mutations impair chaperone-mediated folding and α/β-tubulin heterodimer assembly, disrupt microtubule behavior in cultured cells, alter microtubule organization in vivo, and lead to severe spindle assembly defects and maturation arrest when manifested in mouse and human oocytes. *TUBB8* mutations induce dominant-negative effects that impair microtubule behavior, meiotic spindle assembly, and maturation in oocytes, resulting in female infertility [15].

Subsequently, Feng et al. (2016) sequenced *TUBB8* in oocytes arrested during maturation [16]. Seven heterozygous missense mutations and two homozygous mutations were determined. These mutations caused in vitro folding defects, varying degrees of microtubule disruption when expressed in cultured cells, and impaired meiotic spindle assembly in mouse oocytes at different extents. Some of the newly identified *TUBB8* mutations led to phenotypic variability. For example, oocytes carrying one of the three missense mutations (i.e., I210V, T238M, and N348S) extruded the first polar body. Moreover, these oocytes could be fertilized, although the resulting embryos exhibited developmental arrest. The patient-derived oocytes were homozygous. Mutations that prevent the expression of a functional *TUBB8* polypeptide contain identifiable spindles. Thus, Feng et al. expanded the phenotypic spectrum of oocyte dysfunction associated with *TUBB8* mutations, emphasizing the independent nature of meiosis

and human oocyte differentiation and broadening the group of genetic disorders classified as tubulinopathies [16].

Chen et al. revealed a homozygous mutation in *PATL2* in a consanguineous family with OMA at the prophase I stage and biallelic *PATL2* mutations in members of four additional families. Furthermore, they attributed the phenotypic variability in these patients to the extent of *PATL2* dysfunction, with more severe impairment resulting in oocyte arrest at earlier stages [17].

A research team from the American College of Medical Genetics and Genomics hypothesized that genetic disorders predispose individuals to infertility and subsequent medical conditions. The exomes of 197 women with unexplained infertility were sequenced to detect pathogenic and potentially pathogenic gene variants. In four women (2%), pathogenic or potentially pathogenic variants in *BRCA1* or *BRCA2* were found, indicating a high risk of breast or ovarian cancer [18].

In a study, Huang (2014) described a form of infertility with autosomal recessive inheritance characterized by abnormal oocytes lacking the zona pellucida. A homozygous frameshift mutation in ZP1 was observed in six family members. In vitro studies showed that defective ZP1 and normal ZP3 proteins were distributed throughout the cell and were not expressed on the cell surface. This indicated that aberrant ZP1 causes ZP3 sequestration in the cytoplasm, preventing the formation of the zona pellucida around the oocyte [19].

These findings were confirmed using mouse models with the same mutations generated with the CRISPR/Cas9 gene-editing system, allowing to conclude that *ZP* mutations exhibit dosage effects that may cause female infertility in humans [20].

Further research focused on identifying candidate genes that may cause meiotic arrest in mice when ablated but have not yet been definitively associated with human infertility. Mutations in numerous genes may lead to OMA. One such candidate is poly(A)-binding protein cytoplasmic 1-like (PABPC1L), which encodes a protein that binds to the elongated poly(A) tail to stabilize polyadenylated messenger RNAs (mRNAs). Female mice deficient in Pabpc1l are infertile; their oocytes are dysmorphic, which fail to complete maturation due to impaired translational activation of maternal mRNAs [13].

Currently, noncoding nucleic acid sequences are gaining attention [21]. Study of microRNAs provides new opportunities for the diagnosis, treatment, and prevention of disease. Inhibited proliferation of granulosa cells (GCs) contributes to abnormal follicular maturation [3]. It has been shown that lnc-MAP3K13-7:1-dependent inhibition of DNA methyltransferase 1 regulates *CDKN1A*/p21 gene expression and suppresses cell proliferation [22].

Extracellular Nucleic Acids and Their Role in the Pathogenesis of Reproductive Organ Disorders

MicroRNAs (miRNAs) are short noncoding RNA sequences approximately 18–25 nucleotides in length. Although they do not act as templates for protein synthesis, miRNAs are crucial in gene expression regulation, influencing nearly half of all protein synthesis processes. Additionally, they induce significant effects on various intracellular physiological functions, including cell growth, signal transduction, apoptosis, and pathologic processes [23].

MiRNAs can be detected within cells and in extracellular fluids such as serum, plasma, urine, follicular fluid, and cerebrospinal fluid. These molecules change in response to various cellular states and may be biomarkers for screening and predicting a wide range of diseases [24].

MiRNAs are present in various cells of the female reproductive system; thus, dysregulation of their activity may impair female reproductive potential [23]. They play a regulatory role in the uterine endometrium during the menstrual cycle. Moreover, increasing evidence demonstrates a key role of miRNAs in the proliferation and apoptosis of GCs, oocyte maturation, and oocyte apoptosis [25]. Table 1 presents the role of noncoding nucleic acid sequences in the development of infertility. It highlights the involvement of miR-324 and miR-155 [26]. Notably, miR-155 expression was found to be increases in the tissues of patients with PCOS. It has been shown that miR-155 enhances the proliferation, migration, and invasion of KGN-derived GCs [26, 27].

Studies have shown differences in the number of expressed microRNAs between women with normal and those with impaired reproductive function [27]. Additionally, dysregulation of microRNAs has been observed in various gynecologic malignancies and female disorders associated with infertility, such as PCOS, primary ovarian insufficiency, and endometriosis [26].

Moreover, microRNAs may be useful for determining the implantation window and improving outcomes of assisted reproductive technologies. Patients with PCOS exhibit lower miR-335-5p levels than those without PCOS. MiR-335-5p downregulates SGK3 expression and stimulates granulosa cell proliferation [28].

Upregulation of miR-9119 and miR-135a in the GCs of patients with PCOS may induce apoptosis [29]. In turn, miR-23a and miR-27a induce granulosa cell apoptosis in vitro by activating the SMAD5-mediated FasL–Fas signaling pathway [30].

Liu et al. reported that miR-146b-5p is involved in the development of PCOS in mice by γH2A phosphorylation suppression and Dab2ip/Ask1/p38-MAPK signaling pathway inactivation [20]. However, the role of miR-146b-5p in patients with PCOS remains unclear. Decreased miR-146b-5p expression has been observed in patients with PCOS [20].

The long noncoding RNA NEAT1 is retained in the nucleus, where it comprises a core structural component of subnuclear organelles called paraspeckles [30]. It may regulate transcription of numerous genes, including those involved in cancer progression. The antisense long noncoding RNA GNG12-AS1, located at the *GNG12* gene locus, is considered a regulator of G protein-mediated signaling pathways. Studies have shown that GNG12-AS1 may influence signaling cascade activity such as the AKT/GSK-3β/β-catenin pathway, thereby affecting cell proliferation and migration [32]. It is believed

Table 1. Non-coding nucleic acid sequences associated with infertility

Type of sequence	Mechanism of action	Source
	MicroRNA	
miR-324	Regulate proliferation of KGN cells in PCOS.	[25]
miR-155	Enhance proliferation, migration, and invasion of granulosa cells.	[26, 27]
miR-335-5p	Decrease *SGK3* expression and promote proliferation of granulosa cells.	[28]
miR-9119	May induce apoptosis in granulosa cells of patients with PCOS.	[29]
miR-23a miR-27a	Induce apoptosis in granulosa cells in vitro via activation of the SMAD5-mediated FasL-Fas signaling pathway.	[30]
miR-146b-5p	Involved in PCOS pathogenesis in mice by suppressing γH2A phosphorylation and inactivating the Dab2ip/Ask1/p38-Mapk pathway.	[20]
	Long noncoding nucleic acids	
NEAT1	Produces long noncoding RNA (lncRNA), transcribed from the multiple endocrine neoplasia locus. This lncRNA is retained in the nucleus and is a structural component of paraspeckles. It may regulate transcription of numerous genes, including those involved in cancer progression.	[31, 32]
GNG12-AS1	Modulate the AKT/GSK-3β/β-catenin signaling cascade, crucial for cell division and migration. Localized in extracellular exosomes.	
ZEB2-AS1	Produce a spliced long noncoding RNA as a natural antisense transcript corresponding to the 5' UTR of zinc finger E-box binding homeobox 2 (*ZEB2*). This transcript regulates *ZEB2* expression and contributes to bladder cancer progression.	
LINC473	Participate in transcription, DNA matrix mediates decidualization of stromal cells through transcriptional regulation of *PRL, IGFBP1, PGR, FOXO1, HOXA10, HOXA11*, and *WNT4*.	[33]
STAT3	Functions as a transcription factor. Its expression markedly increases in endometrial stroma during decidualization, indicating its role in embryo implantation.	
	Circulating nucleic acids	
let-7b	Expressed in granulosa and cumulus cells of mammalian and human ovaries; may predict blastocyst formation and growth.	[35]
miR-29a	Highly expressed in rat uterus during embryo implantation. Expression is regulated by blastocyst activation and uterine decidualization (regulatory role).	
miR-30a	Overexpression of miR-30a in cultured human granulosa cells enhances *BCL2A1*, *IER3*, and cyclin D2 expressions by suppressing *FOXL2*.	
miR-140	Functions as a tumor suppressor, downregulated in breast cancer via ERα-mediated signaling.	
miR-320a	Reflects the quantity and quality of mature oocytes; its intrafollicular expression may vary with the quality of ovarian response in IVF patients.	

Note: PCOS, polycystic ovary syndrome; IVF, in vitro fertilization.

to participate in G protein-coupled receptor-mediated signaling cascades and has been detected in extracellular exosomes. ZEB2-AS1 encodes a spliced long noncoding RNA that is a natural antisense transcript complementary to the 5' untranslated region(5'-UTR) of the zinc finger E-box binding homeobox 2 (*ZEB2*) gene. This transcript regulates *ZEB2* expression and may contribute to bladder cancer progression [31].

LINC473 functions as an RNA scaffold and mediates stromal cell decidualization by regulating *PRL, IGFBP1, PGR, FOXO1, HOXA10, HOXA11*, and *WNT4* transcription [31]. STAT3 is a transcription factor whose expression in the endometrial stroma markedly increases during decidualization owing to its critical role in embryo implantation [33]. Human endometrial epithelial cells provide a molecular environment for blastocyst attachment by regulating the expressions of integrins, cadherins, and other adhesion molecules, contributing to the formation of a receptive endometrium [34].

Another class of markers includes circulating microRNAs [34]. For example, let-7b is expressed in granulosa and cumulus cells of mammalian ovaries, including those of humans, and may be a predictor of blastocyst formation and development [35]. MiR-29a is highly expressed in the rat uterus during embryo implantation; its expression is regulated by blastocyst activation and uterine decidualization, indicating a regulatory role [34]. Moreover, miR-30a is crucial in oocyte maturation. Its overexpression in cultured human GCs

promotes the expression of *BCL2A1*, *IER3*, and cyclin D2 by suppressing *FOXL2* [35]. MiR-140 functions as a tumor suppressor and is downregulated in breast cancer by ERα signaling. MiR-320a reflects the quantity and quality of mature oocytes, and its intrafollicular expression may be modulated by the quality of ovarian response in patients undergoing in vitro fertilization [35, 36].

CONCLUSION

Some noncoding nucleic acid fragments may play a critical role in the development of female infertility. Investigating the functions of these fragments and microRNAs in the context of infertility may improve understanding of the molecular mechanisms underlying this condition. Further studies on the role of microRNAs in the development of infertility may lead to novel diagnostic and therapeutic approaches.

ADDITIONAL INFORMATION

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. M.M.A. — концептуализация, анализ, редактирование рукописи, общее руководство; М.Е.Д. — методология, валидация, исследование, создание черновика; С.Л.В. — редактирование рукописи, общее руководств. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.
Этическая экспертиза. Неприменимо.
Источники финансирования. Отсутствуют.
Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.
Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Доступ к данным. Редакционная политика в отношении совместного использования данных к настоящей работе не применима, новые данные не собирали и не создавали.
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Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали два внешних рецензента, член редакционной коллегии и научный редактор издания.

REFERENCES

1. Męczekalski B, Niwczyk O, Battipaglia C, et al. Neuroendocrine disturbances in women with functional hypothalamic amenorrhea: an update and future directions. *Endocrine*. 2023;84(3):769–785. doi: 10.1007/s12020-023-03619-w EDN: XLBEHI
2. Mihalas BP, Redgrove KA, McLaughlin EA, Nixon B. Molecular mechanisms responsible for increased vulnerability of the ageing oocyte to oxidative damage. *Oxid Med Cell Longev*. 2017;2017:4015874. doi: 10.1155/2017/4015874
3. Gordon CM, Ackerman KE, Berga SL, et al. Functional hypothalamic amenorrhea: an endocrine society clinical practice guideline. *J Clin Endocrinol Metabol*. 2017;102(5):1413–1439. doi: 10.1210/jc.2017-00131 EDN: SVDBOH
4. Canipari R, De Santis L, Cecconi S. Female fertility and environmental pollution. *IJERPH*. 2020;17(23):8802. doi: 10.3390/ijerph17238802 EDN: RDOMJG
5. Vitagliano A, Petre GC, Francini-Pesenti F, et al. Dietary supplements for female infertility: a critical review of their composition. *Nutrients*. 2021;13(10):3552. doi: 10.3390/nu13103552 EDN: VZBVHW
6. Łakoma K, Kukharuk O, Śliż D. the influence of metabolic factors and diet on fertility. *Nutrients*. 2023;15(5):1180. doi: 10.3390/nu15051180 EDN: PPPGUO
7. Silvestris E, Lovero D, Palmirotta R. Nutrition and female fertility: an interdependent correlation. *Front Endocrinol*. 2019;10:346. doi: 10.3389/fendo.2019.00346 EDN: LZOGAB
8. Panth N, Gavarkovs A, Tamez M, Mattei J. The influence of diet on fertility and the implications for public health nutrition in the United States. *Front Public Health*. 2018;6:211. doi: 10.3389/fpubh.2018.00211
9. Simionescu G, Doroftei B, Maftei R, et al. The complex relationship between infertility and psychological distress (Review). *Exp Ther Med*. 2021;21(4):306. doi: 10.3892/etm.2021.9737 EDN: TRWKUA
10. Skoracka K, Ratajczak AE, Rychter AM, et al. female fertility and the nutritional approach: the most essential aspects. *Adv Nutr*. 2021;12(6):2372–2386. doi: 10.1093/advances/nmab068 EDN: BQCFOD
11. Munro MG, Balen AH, Cho S, et al; FIGO Committee on menstrual disorders and related health impacts, and FIGO committee on reproductive medicine, endocrinology, and infertility. The FIGO ovulatory disorders classification system†. *Hum Reprod*. 2022;37(10):2446–2464. doi: 10.1093/humrep/deac180.;PMCID EDN: BPEQCK
12. Sasaki H, Hamatani T, Kamijo S, et al. Impact of oxidative stress on age-associated decline in oocyte developmental competence. *Front Endocrinol*. 2019;10:811. doi: 10.3389/fendo.2019.00811
13. Ding X, Schimenti JC. Female infertility from oocyte maturation arrest: assembling the genetic puzzle. *EMBO Mol Med*. 2023;15(6):e17729. doi: 10.15252/emmm.202317729 EDN: RRRYTY
14. Wang W, Guo J, Shi J, et al. Bi-allelic pathogenic variants in PABPC1L cause oocyte maturation arrest and female infertility. *EMBO Mol Med*. 2023;15(6):e17177. doi: 10.15252/emmm.202217177 EDN: RWDJKO
15. Feng R, Sang Q, Kuang Y, et al. Mutations in TUBB8 and human oocyte meiotic arrest. *N Engl J Med*. 2016;374(3):223–232. doi: 10.1056/NEJMoa1510791
16. Feng R, Yan Z, Li B, et al. Mutations in TUBB8 cause a multiplicity of phenotypes in human oocytes and early embryos. *J Med Genet*. 2016;53(10):662–671. doi: 10.1136/jmedgenet-2016-103891

17. Chen B, Zhang Z, Sun X, et al. Biallelic mutations in PATL2 cause female infertility characterized by oocyte maturation arrest. *Am J Hum Genet*. 2017;101(4):609–615. doi: 10.1016/j.ajhg.2017.08.018
18. Dougherty MP, Poch AM, Chorich LP, et al. Unexplained female infertility associated with genetic disease variants. *N Engl J Med*. 2023;388(11):1055–1056. doi: 10.1056/NEJMc2211539 EDN: FSBJSH
19. Huang HL, Lv C, Zhao YC, et al. Mutant ZP1 in familial infertility. *N Engl J Med*. 2014;370(13):1220–1226. doi: 10.1056/NEJMoa1308851
20. Liu W, Li K, Bai D, et al. Dosage effects of ZP2 and ZP3 heterozygous mutations cause human infertility. *Hum Genet*. 2017;136(8):975–985. doi: 10.1007/s00439-017-1822-7 EDN: DFYPZF
21. Fontana L, Garzia E, Marfia G, et al. Epigenetics of functional hypothalamic amenorrhea. *Front Endocrinol*. 2022;13:953431. doi: 10.3389/fendo.2022.953431 EDN: BKBEVO
22. Geng X, Zhao J, Huang J, et al. lnc-MAP3K13-7:1 Inhibits Ovarian GC Proliferation in PCOS via DNMT1 Downregulation-mediated CDKN1A promoter hypomethylation. *Mol Ther*. 2021;29(3):1279–1293. doi: 10.1016/j.ymthe.2020.11.018 EDN: JTBOTQ
23. Bahmyari S, Jamali Z, Khatami SH, et al. MICRORNAS in female infertility: an overview. *Cell Biochem Funct*. 2021;39(8):955–969. doi: 10.1002/cbf.3671 EDN: SRRPYC
24. Guo Y, Sun J, Lai D. Role of microRNAs in premature ovarian insufficiency. *Reprod Biol Endocrinol*. 2017;15(1):38. doi: 10.1186/s12958-017-0256-3 EDN: ZQDWQN
25. Yuanyuan Z, Zeqin W, Xiaojie S, et al. proliferation of ovarian granulosa cells in polycystic ovarian syndrome is regulated by MicroRNA-24 by targeting wingless-type family member 2B (WNT2B). *Med Sci Monit*. 2019;25:4553–4559. doi: 10.12659/MSM.915320 EDN: DXAWRG
26. Xia H, Zhao Y. miR-155 is high-expressed in polycystic ovarian syndrome and promotes cell proliferation and migration through targeting PDCD4 in KGN cells. *Artif Cells Nanomed Biotechnol*. 2020;48(1):197–205. doi: 10.1080/21691401.2019.1699826
27. Wang L, Chen Y, Wu S, et al. miR-135a Suppresses granulosa cell growth by targeting Tgfbr1 and Ccnd2 during folliculogenesis in mice. *Cells*. 2021;10(8):2104. doi: 10.3390/cells10082104 EDN: WFRBWD
28. Yao L, Li M, Hu J, et al. MiRNA-335-5p negatively regulates granulosa cell proliferation via SGK3 in PCOS. *Reproduction*. 2018;156(5):439–449. doi: 10.1530/REP-18-0229
29. Ding Y, He P, Li Z. MicroRNA-9119 regulates cell viability of granulosa cells in polycystic ovarian syndrome via mediating Dicer expression. *Mol Cell Biochem*. 2020;465(1–2):187–197. doi: 10.1007/s11010-019-03678-6 EDN: MPFXUM
30. Nie M, Yu S, Peng S, et al. miR-23a and miR-27a promote human granulosa cell apoptosis by targeting SMAD51. *Biol Reproduct*. 2015;93(4). doi: 10.1095/biolreprod.115.130690
31. Dong L, Xin X, Chang HM, et al. Expression of long noncoding RNAs in the ovarian granulosa cells of women with diminished ovarian reserve using high-throughput sequencing. *J Ovarian Res*. 2022;15(1):119. doi: 10.1186/s13048-022-01053-6 EDN: DFHTBN
32. Xiang Z, Lv Q, Chen X, et al. Lnc GNG12-AS1 knockdown suppresses glioma progression through the AKT/GSK-3β/β-catenin pathway. *Biosci Rep*. 2020;40(8):BSR20201578. doi: 10.1042/BSR20201578
33. Aljubran F, Nothnick WB. Long non-coding RNAs in endometrial physiology and pathophysiology. *Mol Cell Endocrinol*. 2021;525:111190. doi: 10.1016/j.mce.2021.111190 EDN: GVVWEV
34. Takamura M, Zhou W, Rombauts L, Dimitriadis E. The long noncoding RNA PTENP1 regulates human endometrial epithelial adhesive capacity in vitro: implications in infertility. *Biol Reproduct*. 2020;102(1):53–62. doi: 10.1093/biolre/ioz173
35. Scalici E, Traver S, Mullet T, et al. Circulating microRNAs in follicular fluid, powerful tools to explore in vitro fertilization process. *Sci Rep*. 2016;6(1):24976. doi: 10.1038/srep24976
36. Galimov ShN, Galimova EF, Gilyazova IR, et al. Expression of exosomal microRNAs miR-34a and miR-210 in male infertility: relationship with morphokinetic parameters and sperm DNA fragmentation. *Urology Herald*. 2024;12(4):34–42. doi: 10.21886/2308-6424-2024-12-4-34-42 EDN: FAFNXQ

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